EFFICACY OF TYPE 5 PHOSPHODIESTERASE (PDE-5) INHIBITORS AND SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN TREATMENT OF PREMATURE EJACULATION

Ibrahim Fathi Rashed1, Mostafa Kamel Ahmed2, Ahmed Mohamed Nabil3, Ibrahim Mohammed Ibrahim4

1,2,3,4Urology Department, Faculty of Medicine, Zagazig University Zagazig, Egypt.

Email: ivrahemrashed.elshiheby@gmail.com

ABSTRACT

Premature ejaculation (PE) is very common disease that affect more than 20% of men and the most common self-reported male sexual disorder. Five–Hydroxytryptamine 2C (5HT2C) hyposensitivity, 5-Hydroxytryptamine 1A (5-HT1A) hypersensitivity and peripheral penile hypersensitivity, all are suggestive causes of life long premature ejaculation.

Key words: Premature Ejaculation, Type 5 Phosphodiesterase (PDE-5) Inhibitors, Selective Serotonin Reuptake Inhibitors.

I. TREATMENT OF PREMATURE EJACULATION

Premature ejaculation (PE) is very common disease that affect more than 20% of men and the most common self-reported male sexual disorder. Five–Hydroxytryptamine 2C (5HT2C) hyposensitivity, 5-Hydroxytryptamine 1A (5-HT1A) hypersensitivity and peripheral penile hypersensitivity, all are suggestive causes of life long premature ejaculation. The pharmacological treatment of PE includes using local anesthetic agents, antidepressants, and currently dapoxetine is the only short-acting selective serotonin reuptake inhibitor that is licensed for PE treatment. The systemic side effects and the recurrence of premature ejaculation post withdrawal are the main limitation for these options.

1-Topical Anesthetics:

A number of creams and gels are available that desensitize the penis and may in effect delay orgasm in men with PE. After a man applies one of these agents to his penis, he proceeds to sexual activity with or without use of a condom. If he removes the condom, he should wash the penis to remove any remaining compound, thus reducing or avoiding the chances of desensitizing or numbing his partner’s genitalia. The use of topical anesthetic ointments is probably the oldest treatment for delaying ejaculation, but only a few controlled studies gave been reported. In one study, the results of lidocaine-prilocaine cream 10 minutes before intercourse were described (1). Also, an aerosol formulation of lidocaine-prilocaine is effective in prolonging IELT and in improving sexual satisfaction in men with PE and their partners. The main drawback of topical anesthetics is their potential to cause a reduction in penile sensation and vaginal numbness in his partner.

In Korea, positive results were reported with SS-cream, a regionally manufactured agent consisting of the extracts of nine natural herbal products proposed to decrease penile hypersensitivity and or hyper excitability (2).

These investigators examined the efficacy of SS-cream in a double blind, randomized, placebo-controlled study in 106 men with lifelong PE. During the screening phase of the study, the men’s mean IELT was 1.37 ± 0.12 minutes and both the men, and their partners reported being dissatisfied with their sexual lives (2).

During the treatment phase, which consisted of 6 separate applications (one of which was a placebo), the men applied the cream to the glans penis 1 hour before intercourse.

After treatment the men’s mean IELT increased to 2.45 ± 0.29 minutes with placebo and to 10.92 ± 0.29 minutes with use of SS-cream. Side-effects included local burning and mild pain, which was reported in 18.49% of the
530 active treatment applications, but these symptoms disappeared in less than 1 hour. No adverse effects on sexual function or systemic side-effects were noted.

2-SSRIs:
SSRIs are widely used pharmacotherapeutic agents. This group showed that the tricyclic antidepressant clomipramine prolonged ejaculatory latency in rats by blocking central serotonin reuptake. However, as postsynaptic 5-HT1C receptors are minimally stimulated after a few hours of SSRI administration, it can be predicted that on-demand SSRI treatment will have only a slight ejaculation-delaying effect (3).

The absence of a significant ejaculation delay after acute SSRI administration has been demonstrated in animal sexual behavioral studies (4).

Although, many studies have been published on the use SSRIs in the treatment of PE, Waldinger et al. were the first to evaluate these studies methodologically in light of evidence-based criteria (3). The results revealed that from 79 publications on drug treatment of PE, 35 studies involved serotonergic antidepressants. He clearly documented that in both single-blind and open-design studies, as well as studies using a questionnaire or subjective report on ejaculation time, there was a high variability, and that there was over-estimated responses in the degree of ejaculatory delay. Only 8 studies (18.5%) fulfilled all criteria of evidence-based medicine, e.g., double-blind studies prospectively using real-time stopwatch assessments at each intercourse both at baseline and during the drug trial (3).

For daily treatment, a rank order of efficacy of the SSRIs was established, with clomipramine being the best, followed by paroxetine, sertraline, and fluoxetine.

In a double-blind stopwatch study in men with lifelong PE associated with an IELT of less than 1 minute, Waldinger et al. (3) found that on-demand treatment with 20 mg paroxetine exerted only a 1.41-fold increase in IELT at a drug coitus interval time (DCIT) of 5.30 hours (3). The calculated 1.41-fold increase means that on-demand treatment with 20 mg paroxetine induced only a 40% ejaculation delay. The degree of ejaculation delay in this study was considered as clinically insignificant by the men and their female partners. On the other hand, on-demand treatment with 25mg clomipramine with a mean DCIT of 5.15 hours led to a 4.05-fold increase in the IELT, which was considered as clinically relevant by the couples, and confirmed earlier reports on the efficacy of on-demand clomipramine treatment (3).

Interestingly, other studies on paroxetine on-demand use for PE demonstrated stronger ejaculatory-delaying effect. In the first study, Abdel-Hamid et al. (5) reported a 4-fold ejaculation delay with on-demand 20 mg paroxetine, administered 3-4 hours prior to coitus. Similarly, McMahon and Touma (6), using a single-blinded design, reported an 11-fold ejaculation delay without remarkable serotonergic side-effects, with 20 mg paroxetine administered 3-4 hours before coitus.

However, such a strong delay with on-demand treatment in the absence of serotonergic side-effects does not seem likely, as this implies better effects with on-demand treatment than previously reported daily treatment with 20 mg paroxetine (3).

As an absence of ejaculation delay with acute SSRI administration has been demonstrated in a number of animal sexual behavioral studies and based on current knowledge with conventional SSRIs, it is unlikely that on-demand use of SSRIs will delay ejaculation within 1-2 hours of intake (4; 3). Based on animal studies, Waldinger et al. (3) postulated that on-demand treatment of PE with conventional SSRIs will only be successful when an SSRI is combined with a 5-HT1A receptor antagonist, or another serotonergic intervention that acutely stimulates serotonergic release.

On demand Dapoxetine:
Although SSRIs are intended for chronic use in the treatment of depression and are designed to have pharmacokinetic profiles that would allow them to provide constant systemic concentration with long-term administration, they may need days to weeks to reach a maximum steady-state concentration in order to exhibit efficacy (7).
Therefore, SSRIs are commonly used in a daily dosing schedule for the treatment of PE. In addition to the potentially desirable side-effect of delaying ejaculation, this dosing regimen for long-acting SSRIs is associated with a number of undesirable side-effects, such as decreased libido and ED (8).

With the success of daily SSRI use in delaying ejaculation, it has been suggested that on-demand treatment with SSRIs possessing a short half-life and short $T_{\text{max}}$ would be equally effective, more convenient, and exhibit fewer serotonergic side-effects than observed with daily treatment (3). Therefore, an ideal compound for the treatment of PE should exhibit pharmacokinetic profiles having rapid absorption, adequate availability to establish therapeutic exposure at the target site, and rapid elimination to reduce total drug exposure and minimize the incidence of side-effects (9).

Table (1): Doses and adverse effects of selective and nonselective serotonin reuptake inhibitors for treatment of PE (10)

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Recommended dose</th>
<th>IELT increase from baseline (=1 minutes)</th>
<th>Side effects</th>
<th>% side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine (Anafranil®)</td>
<td>25–50 mg/d or 25 mg 4–24 hours pre-intercourse</td>
<td>3–6 minutes</td>
<td>Dry mouth, drowsiness, reduced potency, nausea, vomiting, other</td>
<td>60%</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®, Sarafem®)</td>
<td>5–20 mg/d</td>
<td>2–9 minutes</td>
<td>Drowsiness, dry mouth, an ejaculation, reduced potency, nausea</td>
<td>35%</td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td>10–40 mg/d or 20 mg 3–4 hours pre-intercourse</td>
<td>3–10 minutes</td>
<td>An ejaculation, nausea, reduced libido, anorexia, drowsiness, sensory confusion</td>
<td>15–65%</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td>25–200 mg/d or 50 mg 4–8 hours pre-intercourse</td>
<td>3–6 minutes</td>
<td>Drowsiness, dry mouth, an ejaculation, reduced potency, nausea</td>
<td>30%</td>
</tr>
</tbody>
</table>

*: The compounds are ordered alphabetically.

Dapoxetine hydrochloride is a water-soluble powder with a molecular weight of 341.88 and has a pKa of 8.6 and is mainly charged at a physiological pH. These pharmacological characteristics allow for rapid distribution in the body and are different from the pharmacokinetics observed in conventional SSRIs.

Dapoxetine is a fast-acting compound that attains its peak plasma concentration in about 1.5 hours after dosing, which is much faster than fluoxetine, paroxetine, or sertraline (11).

After oral administration, dapoxetine is readily absorbed, followed by a rapid decline in plasma concentrations. These pharmacokinetic properties make dapoxetine an excellent candidate for on-demand dosing, which avoids the potential disadvantages of continuous pharmacotherapy (12).

Dapoxetine is a potent inhibitor of the 5-HT reuptake transporter, in which it binds to 5-HT, norepinephrine, and dopamine reuptake transporters and inhibits 5-HT, norepinephrine, and dopamine uptake with an order of potency: 5-HT > norepinephrine dopamine (13).

A double-blind, randomized, placebo-controlled, crossover, 3-period phase II US study of dapoxetine for the treatment of PE, comparing the safety and efficacy of on-demand dapoxetine 60 mg versus 100 mg versus placebo was presented (14). Each of the three 2-week treatment periods was separated by a 72-hour washout period.

The patients enrolled in the study were all heterosexual men aged 18–65 years who had been involved in a stable, monogamous relationship for at least 6 months and whose baseline IELT was under 2 minutes, as measured by the partner using a stopwatch. The primary endpoint was IELT, as well as patients’ satisfaction control over ejaculation.
A total of 130 men with PE completed the study. The mean baseline IELT increased from 1.01 minutes to 2.94 minutes with 60 mg dapoxetine, 3.20 minutes with 100 mg dapoxetine, and 2.05 minutes with placebo (p < 0.0001 vs placebo).

Patients who received the 60-mg dose of dapoxetine reported significant increases in their control over ejaculation from baseline (p < 0.0001) and significant benefits in their sexual satisfaction (with their sexual intercourse episodes).

Nausea, the most common reported adverse effect, occurred in 5.6% of patients who received 60 mg, 16.1% of those who received 100 mg, and 0.7% of those who received placebo (Table 3) (14). Of the 10 patients who discontinued the study because of side-effects, 9 were receiving the 100-mg dose of dapoxetine and 1 patient was receiving placebo.

Another two-phase II clinical trials investigated the efficacy and tolerability of 20, 40, 60, and 100 mg dapoxetine in order to determine the appropriate on-demand doses of dapoxetine for further study in large-scale phase III clinical trials (14). Both double-blind, multi-center, randomized, placebo-controlled, 3-period cross-over phase II studies enrolled men with PE, based on DSM-IV-TR criteria and IELT.

Subjects were instructed to take study drug prior to the anticipated sexual intercourse (1–3 hours prior in study 1, and 1–2 hours prior in study 2) and to attempt sexual intercourse ≥ twice weekly.

The primary endpoint was IELT measured with a stopwatch held by the female partner. In study 1, 128 of 157 patients (20 mg and 40 mg dapoxetine), and in study 2, 130 of 166 (60 mg and 100 mg dapoxetine) randomized subjects completed the trials. All four doses of dapoxetine documented statistically significant improvements in IELT over placebo.

<p>| Table (2): Pharmacokinetic characteristics of dapoxetine compared with paroxetine and sertraline (12). |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Dose (mg)</strong></th>
<th><strong>Dapoxetine</strong></th>
<th><strong>Paroxetine</strong></th>
<th><strong>Sertraline</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>386.0</td>
<td>19.0</td>
<td>22.7</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.5</td>
<td>6.83</td>
<td>6.4</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.03</td>
<td>3.93</td>
<td>3.57</td>
</tr>
<tr>
<td>Accumulation</td>
<td>1.3</td>
<td>2.45</td>
<td>2.68</td>
</tr>
</tbody>
</table>

C<sub>max</sub>: is the maximum serum concentration that drug achieves in a specified compartment.

T<sub>max</sub>: the time needed to reach peak plasma volume of a certain drug.

T<sub>1/2</sub>: the time needed for drug to reduce from its peak concentration in plasma into half.

<p>| Table (3): Adverse events observed with dapoxetine (60 mg and 100 mg) and placebo (14). |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Adverse effects</strong></th>
<th><strong>Placebo (n = 140)</strong></th>
<th><strong>Dapoxetine 60 mg (n = 139)</strong></th>
<th><strong>Dapoxetine 100 mg (n = 145)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of pts 1 AE</td>
<td>21 (15.0%)</td>
<td>41 (29.5%)</td>
<td>57 (39.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.7%)</td>
<td>8 (5.8%)</td>
<td>24 (16.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>6 (4.3%)</td>
<td>8 (5.5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.7%)</td>
<td>7 (5.0%)</td>
<td>10 (6.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>3 (2.2%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1 (0.7%)</td>
<td>6 (4.3%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>ED</td>
<td>0</td>
<td>0</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (0.7%)</td>
<td>4 (2.9%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.7%)</td>
<td>5 (3.6%)</td>
<td>9 (6.2%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>4 (2.9%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0</td>
<td>5 (3.6%)</td>
<td>5 (3.4%)</td>
</tr>
<tr>
<td>Dropouts</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

**TYPE 5 PHOSPHODIESTERASE (PDE-5) INHIBITORS**
Recently several studies have suggested that sildenafil may be beneficial in the treatment of PE, either as a single agent or in combination with SSRIs. In the study by Abdel-Hamid et al. (5), 31 patients with lifelong PE underwent treatments with clomipramine, sertraline, and paroxetine, the squeeze technique, or sildenafil in a randomized crossover design. Sildenafil was administered as needed 3–5 hours before planned sexual intercourse. The authors reported that sildenafil was superior to all of the SSRIs and the pause–squeeze technique in terms of IELT and sexual satisfaction score. In another study, Chen et al. (15) investigated the efficacy of sildenafil in the treatment of severe PE in 58 men who failed other treatment modalities, such as behavioral therapy, topical lidocaine, tricyclic antidepressants, and SSRIs.

Sildenafil was taken 1 hour before sexual activity in escalating dosing from 25 to 100 mg until satisfactory ejaculation was attained. The authors concluded that sildenafil was useful in the treatment of PE for patients who have failed other remedies. In an extension to the previous study, Chen et al. (15) reported that sildenafil plus paroxetine had a higher success rate (90%) than paroxetine alone in patients with severe PE. The therapeutic protocol involved taking paroxetine 20 mg 7 hours before sexual intercourse and sildenafil 25-100 mg 1 hour before sexual activity.

The most recent combination study compared sildenafil 25-100 mg plus sertraline 50 mg (48 patients) versus sertraline 50 mg alone (51 patients) and sildenafil 50 mg alone (30 patients) in 3 different groups of PE patients (16).

The highest success rate was observed in the group receiving sertraline plus sildenafil (62.5%) followed by those receiving sertraline alone (56.8%), and lastly those who received sildenafil alone (40%)(17).

There are several possible mechanisms that can explain the efficacy of sildenafil in the treatment of PE. Sildenafil may inhibit the contractile responses of the seminal vesicles, vas deferens, prostate, urethra, and even the skeletal muscles. Expression of PDE activity has been reported in the prostate, seminal vesicle, and skeletal muscles (17).

PDE expression in vas deferens has not been studied yet; however, nitrergic innervation and nitric oxide synthase (NOS) activity have been localized to the human vas deferens, seminal vesicle, prostate, urethra, and skeletal muscles (18).

In addition, evidence suggests that nitric oxide (NO) is the predominant inhibitory (relaxatory) neurotransmitter in the genitourinary organs. In male rats, NO and NO-donor agents were reported to inhibit seminal emission (18).

Recently, sildenafil has been documented to exhibit a direct inhibitory action on smooth muscles tone of the human vas deferens, through activation of prejunctional K+ channels (19).

Sildenafil has also been shown to induce a state of peripheral analgesia via activation of the NO/cGMP signaling pathway in animals. This effect could be instrumental in alleviating the penile hypersensitivity that is reported in some patients with PE and may in turn mimic the success of topical anesthetics in the treatment of some PE patients (1).

Other PDE-5 inhibitors (tadalafil and vardenafil) have been evaluated for treatment of PE. Mattos and Lucon (13) evaluated tadalafil alone and in combination with fluoxetine in 84 PE patients without ED. The patients were randomly assigned in a double-blind manner into 4 groups: (1) tadalafil 20 mg and fluoxetine 90 mg, (2) tadalafil 20 mg and placebo, (3) fluoxetine 90 mg and placebo, and (4) two different placebo capsules. Fluoxetine 90 mg or placebo was given once a week, and tadalafil 20 mg or placebo was given in a 36-hour frame of intended sexual intercourse. Mean baseline IELT was 55 seconds with stopwatch and was not different between groups. The greatest increase from baseline IELT was observed in patients in the tadalafil plus fluoxetine group, followed by the fluoxetine only group, and the tadalafil-only group, respectively. This study demonstrates that tadalafil 20 mg once in 36 hours in combination with fluoxetine 90 in a slow-release form taken weekly can significantly increase IELT(13).

REFERENCES


www.turkjphysiotherrehabil.org