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### FAST TRACK

**SSRIs significantly  
delay ejaculation  
compared with  
placebo**

## What's the best drug treatment for premature ejaculation?

### Evidence-based answer

Antidepressants—specifically clomipramine, fluoxetine, paroxetine, and sertraline—are best and have been shown to improve symptoms of premature ejaculation (strength of recommendation [SOR]: **A**, meta-analysis of randomized controlled trials [RCTs]). The topical application of prilocaine-lidocaine cream (trade name EMLA) improves intravaginal ejaculatory latency time (IELT), but penile numbness and loss of erection may occur (SOR: **B**, based on several small RCTs).

There is no evidence that phosphodiesterase type 5 (PDE5) inhibitors—such as sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)—decrease instances of premature ejaculation in otherwise healthy men. There is limited evidence, however, that PDE5 inhibitors reduce symptoms of premature ejaculation for men with concomitant erectile dysfunction (SOR: **B**, systematic review of RCTs of variable quality).

### Clinical commentary

#### Overcome any reluctance to discuss premature ejaculation

Family physicians should be comfortable diagnosing and treating premature ejaculation because of their unique and long-term relationship with the patient. But that's not always the case. Premature ejaculation is underdiagnosed and undertreated because of a reluctance to discuss it, by both patient and physician.

A thorough medical history, including pertinent sexual history and physical examination, can often establish the diagnosis of premature ejaculation. Effective treatments can improve sexual satisfaction and quality of life for both the men and their partners.

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### Evidence summary

Premature ejaculation is the most common male sexual dysfunction, but there is no universally accepted definition or validated screening instrument. The pathophysiology and etiology remain incompletely understood.<sup>1</sup> Based on surveys, prevalence rates for premature ejaculation are approximately 20% to 30%.<sup>1</sup>

Studies in male rats have demonstrated that serotonin with various 5-HT receptor subtypes are involved in the ejaculatory process.<sup>2</sup> Based on these studies, it's been suggested that lifelong premature ejaculation is a neurobiological phenomenon related to decreased central serotonergic neurotransmission, 5-HT<sub>2c</sub> receptor hyposensitivity, or 5-HT<sub>1a</sub> receptor hypersensitivity.<sup>3</sup>

## Antidepressants delay ejaculation

The introduction of selective serotonin reuptake inhibitors (SSRIs) revolutionized the treatment of premature ejaculation.<sup>4</sup> In 1994, the first study of SSRIs in men with premature ejaculation demonstrated a delaying effect with paroxetine (Paxil).<sup>5</sup> Since that time, SSRIs have been repeatedly investigated for their propensity to delay ejaculation. Certain SSRIs and the tricyclic antidepressant clomipramine (Anafranil) have become the agents of choice for the treatment of premature ejaculation.<sup>6</sup>

A meta-analysis<sup>6</sup> of 35 treatment studies with serotonergic antidepressants from 1943 to 2003 shows that, despite major differences in design and drug dosing, clomipramine, fluoxetine (Prozac), paroxetine, and sertraline (Zoloft) significantly delay ejaculation compared with placebo. The percentage increase in IELT was the primary outcome measured. The rank order of efficacy was:

- 1) paroxetine (1492% IELT increase; 95% confidence interval [CI], 918–2425)
- 2) sertraline (790% IELT increase; 95% CI, 532–1173)
- 3) clomipramine (512% IELT increase; 95% CI, 234–1122)
- 4) fluoxetine (295% IELT increase; 95% CI, 172–506).<sup>6</sup>

Of the 35 studies used in the previous meta-analysis, 8 studies (N=263) were prospective, double-blind, real-time stopwatch studies that were separately analyzed in a subsequent meta-analysis. These 8 studies evaluated clomipramine, fluoxetine, paroxetine, sertraline, citalopram (Celexa), fluvoxamine (Luvox), mirtazapine (Remeron), and nefazodone (Serzone) against placebo. Paroxetine (783% IELT increase, 95% CI, 499–1228), clomipramine (360% IELT increase, 95% CI, 200–435), sertraline (313%, 95% CI, 161–608), and fluoxetine (295%, 95% CI, 200–435) exerted a significant delay in the IELT compared with placebo.<sup>6</sup>

## EMLA cream: “Improvement” and “cure” seen

EMLA cream, a topical anesthetic, has been evaluated as a treatment option for premature ejaculation. One double-blinded RCT<sup>7</sup> (N=29) showed significant improvement in the IELT (measured by stopwatch by the subject’s partner) from baseline compared with placebo (8.45 min vs 1.95 min;  $P<.001$ ) at 2 months.

Another RCT<sup>8</sup> (N=84) compared EMLA cream applied 15 minutes prior to intercourse, sildenafil 50 mg orally 45 minutes prior to intercourse, EMLA cream plus sildenafil, and placebo. In the sildenafil-plus-EMLA group, 32% of the patients reported “improvement” and 54% reported “cure,” which was defined as ejaculation delayed until the patient wished it. In the EMLA-only group, 27% of the patients reported “improvement” and 50% reported “cure.” This was a statistically significant difference when compared with the placebo and sildenafil-only groups (number needed to treat [NNT]=3). There was no significant difference in reports of “improvement” or “cure” between the placebo and sildenafil-only groups.

One small RCT<sup>9</sup> (N=24) compared placebo with the application of EMLA cream 20, 30, and 45 minutes prior to sexual intercourse. Improvement was seen in IELT in the 20- and 30-minute group, but penile numbness and erection loss increased in the 30- and 45-minute group.

## PDE5 inhibitors: No convincing evidence

A review<sup>10</sup> of 14 clinical trials concluded that there is no convincing evidence for PDE5 inhibitors in the treatment of men with lifelong premature ejaculation and normal erectile function. One RCT<sup>11</sup> found no increase in IELT from baseline in men taking sildenafil when compared with placebo, although patients reported overall sexual satisfaction and confidence based on a questionnaire.

### FAST TRACK

**Topical prilocaine/lidocaine cream (EMLA) improves intravaginal ejaculatory latency time**

CONTINUED

## FAST TRACK

**There is no good evidence that PDE5 inhibitors treat premature ejaculation effectively**

However, a study by Li et al<sup>12</sup> treated 45 men with premature ejaculation and comorbid erectile dysfunction with sildenafil. Eighty-nine percent reported improved erectile function, and 60% reported decreased severity of premature ejaculation.

### Recommendations from others

The American Urological Association<sup>13</sup> recommends antidepressants as first-line systemic therapy for premature ejaculation, specifically the SSRIs fluoxetine, paroxetine, sertraline, and the tricyclic clomipramine. Topical EMLA cream is also recommended, but the reduction of penile sensation may limit the acceptability of this treatment option.

The British Association for Sexual Health and HIV Special Interest Group for Sexual Dysfunction<sup>14</sup> also recommends SSRIs and clomipramine as they have the strongest evidence for their efficacy. The group emphasizes the importance of combining behavioral and pharmacologic therapies as the management approach should be tailored to the individual patient. ■

### Acknowledgments

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US Government.

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