

## AUA GUIDELINE ON THE PHARMACOLOGIC MANAGEMENT OF PREMATURE EJACULATION

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### INTRODUCTION

The three major forms of male sexual dysfunction are ejaculatory dysfunction, erectile dysfunction (ED), and decreased libido (hypoactive sexual desire disorder). While survey findings vary considerably, most epidemiological studies suggest that premature ejaculation (PE) (also known as early ejaculation or rapid ejaculation) may be the most common male sexual disorder. Data from the National Health and Social Life Survey have revealed a prevalence of 21% in men ages 18 to 59 in the United States.<sup>1</sup> Using various definitions, other studies report prevalences ranging from less than 5%<sup>2</sup> to greater than 30%.<sup>3–5</sup>

A universally accepted definition of PE has yet to be established. Masters and Johnson proposed one of the earliest definitions that focused on the inability to delay ejaculation long enough for the woman to achieve orgasm fifty percent of the time, assuming that PE is the sole cause of the female anorgasmia.<sup>6</sup> Kaplan first suggested that PE is primarily a problem of voluntary control over timing of ejaculation, a concept on which the current definition is based.<sup>7</sup> *The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders* (4th ed, text revision) (DSM-IV TR) (2000) defines PE with an added emphasis on the emotional and interpersonal impact of ejaculation that occurs earlier than the male desires.<sup>8</sup> Premature ejaculation has been subclassified into two forms: a primary (lifelong) form that begins when a male first becomes sexually active and a secondary (acquired) form.<sup>9,10</sup> The present guidelines and recommendations are based on the following definition, which assumes the absence of partner sexual dysfunction: Premature ejaculation is ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.

The exact etiology of PE is unknown. Psychological/behavioristic and biogenic etiologies have been proposed. Consequently, the treatment of PE has encompassed psychological, behavioral, and pharmacologic interventions. Current treatments are largely based upon logical solutions (decreasing sensory input), behavior modification therapies, and observations of drug side effects (those with serotonin reuptake inhibiting activity). This guideline will address only pharma-

cologic therapies, as other therapies are not routinely prescribed by our target audience.

To facilitate informed treatment decisions by physicians and their patients, recommendations on the use of medications currently available in the United States are provided. The majority of the recommendations contained herein are based on a consensus of expert opinion following review of the literature. In some cases, expert consensus is supplemented with a focused review of the limited data. This guideline does not preempt physician judgment in individual cases. Variations in patient subpopulations, physician experience, and available resources necessarily will influence choice of clinical strategy. Adherence to the recommendations presented in this document cannot assure a successful treatment outcome.

For ease of review, the recommendations are bolded and followed by supporting text. The evidence supporting the recommendations is summarized in Appendices 1 to 3 ([www.auanet.org](http://www.auanet.org)).

### METHODS

The Erectile Dysfunction Guideline Update Panel (the Panel) of the American Urological Association (AUA) was convened in April 2000 at the request of the AUA Board of Directors. The Practice Guidelines Committee of the AUA selected the panel co-chairmen, and the full panel roster was assembled by invitation to experts in the field. The panel evaluated several topics for possible guideline development. Premature ejaculation was selected because of its high prevalence and the availability of a defining body of literature.

Using the MEDLINE® database with MeSH headings related to ejaculatory dysfunction, initial literature searches were performed limiting papers to reports of human studies published in English language journals between 1966 and January 2001. Only a small number of articles provided outcomes data on PE. Additional studies were identified from references cited in these articles and from recommendations of individual panel members. The MEDLINE® search was last updated in October 2002. Even after the final literature search was completed, however, the panel continued to scrutinize key references that were identified up until the peer review process.

From a review of abstracts, the panel chairs selected articles with potentially usable information. Selected papers were reviewed in detail, and relevant data on efficacy and adverse events were extracted and listed in evidence tables (Appendix 1, [www.auanet.org](http://www.auanet.org)). Only papers with outcomes data that were relevant to PE, involving pharmacologic treatments generally available in the United States, were included in the evidence tables. If the study was seriously flawed, the article was not considered. Summary tables of adverse event rates and effects of various treatments on latency were created to supplement the data captured in the evidence tables (see Appendices 2 and 3, [www.auanet.org](http://www.auanet.org)). A complete list of the 51 references that met all inclusion criteria is available in Appendices 4 and 5 ([www.auanet.org](http://www.auanet.org)). The full panel reviewed the evidence and summary tables at successive meetings.

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Three major limitations were encountered in the evaluation of the evidence that precluded the ability to combine outcomes data and to perform study outcomes comparisons:

- The lack of standardization in studying PE. Clinical trials employ a variety of definitions, entry criteria, physiological measurements and psychometric instruments for evaluation.
- The lack of agreement in quantifying the amount of stimulation that patients experienced. Time to ejaculation is a function of many factors, not the least of which is the nature of the stimulation. The same stimulus may be excessive for one man but elicit little excitement in another. Furthermore, the lack of a consistent stimulus (partner variables, nature of sexual activity, presence or absence of foreplay, preference for single or multiple stimuli) precludes a rigorous experimental design.
- The lack of consistency and accuracy in measurements of time to ejaculation and other outcomes. The most common outcome parameter, time to ejaculation, is either recorded at the time or documented later by recall. These measurements lack accuracy but generally are useful when applied consistently within a single study. Application across multiple studies in a meta-analysis is problematic because any methodological differences will compromise the ability to make a valid comparison. Other common outcome measures concern patient and partner satisfaction. A variety of assessment tools are used, and there is no assurance of comparability between studies.

The panel determined that a meta-analysis was inappropriate due to the disparate outcome measures and populations in the existing studies. The amount of variation between studies also made other less rigorous forms of outcome estimation inaccurate. The panel's recommendations were developed either solely by consensus or by consensus combined with a review of the available, though limited, evidence. Unless otherwise noted, the statistics cited in this document are derived from the evidence tables.

After this guideline was written, it was reviewed and approved by each member of the panel and submitted for peer review by 53 physicians. Based on the results of peer assessment, revisions were made and the guideline was forwarded to the panel again, to the Practice Guidelines Committee and to the Board of Directors of the AUA, all of which rendered approval.

#### EVALUATION OF THE PATIENT WITH PREMATURE EJACULATION

Premature ejaculation is a self-reported diagnosis. A sexual history in which the patient uses language that explicitly communicates the circumstances of the condition is the fundamental basis of assessment with time to ejaculation as the most important feature. The opinion of a partner can provide a significant contribution to clinician understanding. A complete description is essential in distinguishing PE from ED, ie the inability to attain or maintain an erection, because these conditions frequently coexist. Moreover, some men are unaware that loss of erection after ejaculation is normal and, thus, they may erroneously complain of ED when the actual problem is PE.

**Recommendation 1: The diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints (based on panel consensus).**

When obtaining the patient's history, several important sexual and psychological characteristics should be assessed: frequency and duration of PE, relationship to specific partners, occurrence with all or some attempts, degree of stimu-

lus resulting in PE, nature and frequency of sexual activity (foreplay, masturbation, intercourse, use of visual clues, etc), impact of PE on sexual activity, types and quality of personal relationships and quality of life, aggravating or alleviating factors, and relationship to drug use or abuse. Laboratory or physiological testing is not required unless the history and a physical examination reveal indications beyond uncomplicated PE.

**Recommendation 2: In patients with concomitant PE and ED, the ED should be treated first (based on panel consensus).**

Another priority of assessment should be determining whether ED is a concurrent problem. Many patients with ED develop secondary PE, perhaps due to either the need for intense stimulation to attain and maintain an erection or due to the anxiety associated with difficulty in attaining and maintaining an erection. Premature ejaculation may improve in patients when concomitant ED is effectively treated.

#### TREATMENT OF PREMATURE EJACULATION

**Recommendation 3: The risks and benefits of all treatment options should be discussed with the patient prior to any intervention. Patient and partner satisfaction is the primary target outcome for the treatment of PE (based on panel consensus).**

As outlined above, the treatments for PE range from psychological and behavioral therapies to pharmacologic therapies. While pharmacologic therapies are the focus of this guideline, other types of interventions may be considered. The patient plays a central role in determining the need for treatment. The patient and possibly his partner can be reassured that PE is a common and treatable disorder. Information on the risks and benefits of all therapeutic options should be presented to the patient (and partner) so that an educated treatment choice may be made by the patient in consultation with the physician. Premature ejaculation is not a life-threatening condition and, therefore, safety should be a primary consideration. Some treatments, such as neurectomy and penile prosthesis implantation, have risks that far outweigh their benefits. In addition, none of the medical therapies currently employed in the management of PE has been approved by the U.S. Food and Drug Administration (FDA) for this specific indication. Thus, doses and dosing regimens frequently deviate from that employed for FDA-approved indications, and this difference should be considered in the risk-versus-benefit assessment of pharmacologic therapy.

*Efficacy of proposed treatments.* The preponderance of evidence together with panel consensus strongly suggests that patients can benefit from the use of several oral or topical medications. At the dosages used in the management of PE, these treatments have been shown to have safety profiles that generally are appropriate to support their use.

**Recommendation 4: Premature ejaculation can be treated effectively with several serotonin reuptake inhibitors (SRIs) or with topical anesthetics. The optimal treatment choice should be based on both physician judgment and patient preference (based on panel consensus and review of data).**

*Oral medication: antidepressants.* Several antidepressants known to cause anorgasmia and delayed ejaculation have been evaluated in the management of PE. These antidepressants include SRIs, the majority of which are selective (SSRIs)—fluoxetine, paroxetine, and sertraline—and the tricyclic antidepressant clomipramine (see table). The SRIs have been successfully utilized in the management of PE. As a group, in clinical trials, the SRIs have provided significant benefit over placebo. Studies have suggested that nefazodone, citalopram, and fluvoxamine are ineffective for the treatment of PE and may be more suitable than other SSRIs

*Medical therapy options for the treatment of premature ejaculation*

| Oral Therapies                                          | Tradenames*       | Recommended Dose†                                         |
|---------------------------------------------------------|-------------------|-----------------------------------------------------------|
| Nonselective serotonin reuptake inhibitor: clomipramine | Anafranil®        | 25–50 Mg/day or 25 mg 4–24 hrs pre-intercourse            |
| Selective serotonin reuptake inhibitors:                |                   |                                                           |
| Fluoxetine                                              | Prozac®, Sarafem® | 5–20 Mg/day                                               |
| Paroxetine                                              | Paxil®            | 10, 20, 40 Mg/day or 20 mg 3–4 hrs pre-intercourse        |
| Sertraline                                              | Zoloft®           | 25–200 Mg/day or 50 mg 4–8 hrs pre-intercourse            |
| Topical therapies                                       |                   |                                                           |
| Lidocaine/prilocaine cream                              | EMLA® cream       | Lidocaine 2.5%/prilocaine 2.5% 20–30 mins pre-intercourse |

This list does not reflect order of choice or efficacy.

\* Tradenames listed may not be all-inclusive.

† Peak plasma concentrations occur 2 to 8 hours post-dose, half-lives range from 1 to 3 days and titrate doses from low to high based on response.

for treatment of depression in men *not* wanting ejaculatory impairment.

**Dosing:** Various doses and dosing regimens of the SRIs have been evaluated in efficacy and safety studies of PE. Some studies have employed continuous daily dosing while others use a situational dosing regimen whereby the medication is only taken prior to sexual activity. Different situational dosing regimens also have been assessed, varying timing of the dose prior to sexual activity to the time of peak plasma concentrations of the prescribed agent. The limited data on situational dosing suggest that this regimen may be of use to some men because of the theoretical advantage that less of the drug will be used. In general, though, these SRIs have been designed for continuous usage, and their benefits in the treatment of depression are better established after a period of consistent drug administration. Conversely, continuous administration may foster a problem with patient compliance.

Whether continuous or situational dosing is more effective in the management of PE is unclear. The optimal interval for situational dosing before intercourse has not been established and the onset of action of these SRIs for this indication is unknown. However, all panel members utilize a situational dosing regimen in their practices, and some initiate therapy with daily dosing (loading period). The choice of regimen often is based upon the frequency of sexual activity by the patient.

**Duration of Therapy:** Therapy for PE most likely will be needed on a continuing basis. There is no clear consensus as to whether SRIs will effect an eventual cure of PE, allowing for discontinuation of the medication, or whether SRIs will be required for life. The panel members' experience is that PE usually returns upon discontinuing therapy.

**Dosing of Specific Serotonin Reuptake Inhibitors:** Doses of fluoxetine ranging from 5 to 20 mg/day (see table) are reported to be more effective in delaying ejaculation and enhancing patient/partner satisfaction than placebo. A regimen in which the dose is increased after 1 week (to 40 mg or 60 mg/day) also has been used with success.<sup>11, 12</sup> In addition, there is evidence that a clinically beneficial effect may be observed at daily doses as low as 5 mg.<sup>13</sup>

Daily administration of paroxetine at 10, 20 and 40 mg/day and episodic administration at 20 mg 3 to 4 hours prior to intercourse (see table) have been shown to increase ejaculatory latency.<sup>14–16</sup> Due to the limited number of patients evaluated in these trials, the benefit of increasing the dose to 40 mg/day has not been established. The majority of evidence shows effectiveness with 20 mg daily dosing, thus supporting a general suggestion that this dose of paroxetine provides the greatest benefit in remediating PE.

Sertraline, either given in daily doses of 25, 50, 100 or 200 mg or situationally in doses of 50 mg at 5 p.m. (4 to 8 hours before intercourse) (see table), has been shown to increase ejaculatory latency.<sup>17</sup> Higher doses may increase efficacy, but logic suggests that higher doses may be associated with increased frequency of ED and decreased libido. Studies to

date, though, have been too small to substantiate this conclusion about dose-related side effects.

Clomipramine, a tricyclic antidepressant with SRI effects, has improved ejaculatory latency and other measures of PE when prescribed at doses of 25 and 50 mg/day or 25 mg 4 to 24 hours prior to intercourse (see table). Adverse event rates and the beneficial effects of clomipramine appear to be dose-related.<sup>18</sup>

**Adverse Effects:** Although the adverse effects of the SRIs have been well described in the management of clinical depression, the following facts should be considered when weighing the risks of prescribing these agents for the patient with PE:

- First, men being treated for PE often are different from those being treated for depression, and the adverse effects of these medications have not been well assessed in settings other than depression. However, from evidence gathered to date, it appears that the adverse event profiles of the SRIs reported in the treatment of PE are similar to those reported in patients being treated for depression. The type and rate of occurrence of side effects appear to be acceptable to most patients and typically include nausea, dry mouth, drowsiness and reduced libido (see Appendices 1 and 2, [www.auanet.org](http://www.auanet.org)). Isolated cases of more serious complications, such as mania<sup>19</sup> and withdrawal symptoms, and potential drug interactions also have been associated with the use of SRIs. Pharmacodynamic drug interactions resulting in a "serotonergic syndrome" characterized in mild cases by headache, nausea, sweating, and dizziness and in severe cases by hyperthermia, rigidity, delirium, and coma have been reported rarely with concomitant use of monoamine oxidase inhibitors, lithium, sumatriptan and tryptophan. Pharmacokinetic interactions resulting in alterations in drug blood levels have been reported with the concomitant administration of agents that, like the SRIs, also are metabolized by the cytochrome P450 isoenzyme system or are bound to plasma proteins. Clinically significant pharmacokinetic interactions may rarely occur with the use of anticonvulsants, benzodiazepines, cimetidine, tricyclic antidepressants, antipsychotic agents, tolbutamide, antiarrhythmics, and warfarin especially in the elderly patient.
- Second, doses that are effective in the treatment of PE usually are lower than those recommended in the treatment of depression, suggesting that the frequency and severity of adverse events also could be less.
- Third, because two drug administration regimens, continuous daily dosing and situational dosing, are employed in the treatment of PE, adverse event profiles may differ among patients depending on the regimen prescribed.

The experience with SRIs, as reflected in the evidence tables, and the familiarity of panel members to date with these medications in this clinical setting suggest that the level of adverse effects is acceptable for the benefit derived in the patient with PE.

**Topical anesthetic agents.** Topical anesthetic agents may be applied to the penis prior to intercourse to delay ejaculation. After topical application, these agents have been used either with or without a condom. The condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Lidocaine/prilocaine cream (2.5 gm) applied for 20 to 30 minutes prior to intercourse (see table) has been shown to increase latency time. No significant side effects have been noted. Prolonged application of topical anesthetic (30 to 45 minutes) has been reported to result in loss of erection due to numbness of the penis in a significant percentage of men.<sup>20</sup> The reduction of penile sensation may limit the acceptability of this method of treatment. Diffusion of residual topical anesthetic on the penis into the vaginal wall also may result in numbness in the partner.<sup>21</sup> Topical anesthetics are contraindicated in patients who are either allergic themselves or have partners who are allergic to any component of the product.

**Other pharmacologic therapies.** Other pharmacologic therapies have been described in the treatment of PE in patients without ED. Intracorporal injection of a vasoactive agent, such as alprostadil, and the administration of sildenafil citrate, therapies effective in the management of ED, have been found to increase latency in patients with PE in a few small studies.<sup>22, 23</sup> A recent study of 80 men without concomitant ED found that the administration of a combination of sildenafil citrate and paroxetine on a situational basis enhanced the efficacy of paroxetine alone, although there was an increase in the frequency of the side effects of headache and flushing.<sup>24</sup> Underlying these interventions is the hypothesis that pharmacologic maintenance of a rigid erection reduces the patient's need to rush to orgasm.

Because ejaculation involves the sympathetic nervous system, adrenergic blockade has been proposed as a treatment for delaying or inhibiting ejaculation. One clinical trial did show modest efficacy with alfuzosin and terazosin.<sup>25</sup> Phenoxybenzamine and propranolol also have been studied, but the panel did not believe the evidence was sufficient to support a recommendation for their use.<sup>26–28</sup>

#### FUTURE RESEARCH

Deficiencies and inconsistencies in the design of and lack of reporting standards for clinical studies on PE have hindered attempts to identify best practices. Future research efforts using well-planned and well-executed randomized, controlled trials are needed to:

- Determine ejaculation latency time in the general population
- Develop a consensus on the definition of PE
- Develop standardized, validated instruments to measure outcomes (ie patient/partner satisfaction and bother, ejaculatory latency)
- Determine more precisely the efficacy and risks of drug therapies
- Determine ideal dosing regimens for SRIs (ie, daily versus situational dosing regimens and whether loading is necessary prior to situational dosing),
- Determine the optimal treatment duration and how or whether to discontinue therapy
- Determine the long-term acceptability of therapeutic agents to patients
- Determine the efficacy of combining pharmacologic and behavioral approaches to therapy,
- Identify the age-specific prevalence of PE

Other authors have made recommendations for reporting results in this field that should be considered by investigators studying PE.<sup>29, 30</sup>

#### CONCLUSIONS

A common male sexual disorder, PE traditionally has been treated with psychotherapy or behavioral therapy. This guideline is the first to address the pharmacologic treatment of PE. Although not approved by the FDA for this indication, oral antidepressants and topical anesthetic agents have been shown to delay ejaculation in men with PE and have minimal side effects when used for the treatment of PE. Treatment with oral antidepressants should be started at the lowest possible dose that is compatible with a reasonable chance of success. The choice of additional therapy is based on the patient and partner reports of efficacy, side effects, and acceptance of the therapy as well as on a regular review of alternative approaches. Support and education of the patient and, when possible, the partner are an integral part of PE therapy.

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