Management of ejaculatory/orgasmic disorders in men: early and delayed

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Premature ejaculation

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Dual Control Model

Excitation

Inhibitory
Excitatory

Dopamine,
Noradrenaline
Oxytocin
Melanocortins

Inhibition

Serotonin
Opioids
Endocannabinoids
Prolactin

Sexual Reflexes

Stimulation

Dopamine
Oxytocin
Melanocortin
Noradrenaline

Inhibition

Serotonin
Opioids
Endocannabinoids

Serotonin

Figure 10: Brain serotonin system. Cells arise from the raphe nuclei in the pons and project caudally to the thalamus, hypothalamus, limbic, and cortical regions. In contrast to the eugenic of opioid reward, the activation of this system produces a generalized sense of alertness, relaxation, and well-being. This system appears to inhibit mesolimbic and mesocorticolimbic DA release mechanisms in limbic and prefrontal cortex, mediated by the modulation of descending inhibitory inputs to the cortical areas. Art: Dallaire.
What is Premature Ejaculation?

Management of ejaculatory/orgasmic disorders in men: early and delayed

Is Premature Ejaculation Common?

The Premature Ejaculation Prevalence and Attitudes Multi-National Survey

What is the normal time of intercourse?

Management of ejaculatory/orgasmic disorders in men: early and delayed

Opioid

Inhibition

Inhibitory

Excitatory

An Evidence-Based Definition of Lifelong Premature Ejaculation: Report of the International Society for Sexual Medicine (ISSM) Ad Hoc Committee for the Definition of Premature Ejaculation

J Sex Med 2004;1:1790-1006

PE is a male sexual dysfunction characterized by: 1) ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and 2) the inability to delay ejaculation on all or nearly all vaginal penetrations, and 3) negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

An Evidence-Based Definition of Lifelong Premature Ejaculation: Report of the International Society for Sexual Medicine (ISSM) Ad Hoc Committee for the Definition of Premature Ejaculation

PE definition: Self-reported ejaculation on last sexual event occurred before or within 2 minutes of penetration

Typical IELT is less than or equal to 2 minutes

Self-reported IELT is longer than 2 minutes but their claim: control over ejaculation is fair or poor,

increased time to ejaculation is a problem for him and/or his partner


The Premature Ejaculation Prevalence and Attitudes Multi-National Survey

Prevalence (%) 18-24 25-34 35-44 45-54 55-64 65-70

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How does the US relate to the median time - “from penetration to ejaculation” – versus Turkey, Netherlands, UK, Spain.

A Five-nation Survey to Assess the Distribution of the Intravaginal Ejaculatory Latency Time among the General Male Population

Is premature ejaculation genetically determined?
The 5-HTTLPR polymorphism is associated with significant effects on the latency to ejaculate in men with lifelong PE.

Men with SS and SL genotypes have 100% and 90% longer ejaculation time, respectively than men with LL genotypes.

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The Premature Ejaculation Prevalence and Attitudes Multi-National Survey

Table 1: Simple logistic regression, odds ratios, and 95% confidence intervals for the associations between independent variables (on %) and distressing sexual dysfunctions occurring rarely (MDC) and occasionally (MDC) in men. Differences (% of the independent variables in their sub-classification)

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What are treatments for Premature Ejaculation?
Sex therapy

1. The stop and start technique - Use distracting mental exercises during sex
2. The breathing technique - breathing deeply and relaxing your body during intercourse can help - especially for premature ejaculation that is caused by anxiety or tension
3. The squeeze technique
4. Masturbate first - Second ejaculatory latency time is increased, second erection is more difficult to achieve with increasing age
5. Different sexual positions – changing positions often gives the man brief pauses

PE TREATMENTS

1. Role of sex therapy
2. Role of desensitizing agent and condom
3. Role of daily vs on demand PDE 5 inhibitor
4. Role of daily vs on demand Tramadol
5. Role of daily vs on demand SSRI
6. Role of penile self-injection therapy
7. Role of treating other medical problems

PSD502 improves ejaculatory latency, control and sexual satisfaction when applied topically 5 min before intercourse in men with premature ejaculation: results of a phase III, multicentre, double-blind, placebo-controlled study

W. Wallace Dinsmore and Michael G. Wyllie
Australasian Medical Association, and Pfizer Intercourse Ltd, London, UK

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Effects of Phosphodiesterase Inhibitors on the Contractile Responses of Isolated Human Seminal Vesicle Tissue to Adrenergic Stimulation

Suggested that capability of phosphodiesterase 5 (PDE5) inhibitor to retard ejaculatory response may include modulation of contraction of seminal vesicle (SV) smooth muscle

PDE inhibitors can reverse tension of isolated human SV tissue and enhance production of cyclic AMP and cyclic GMP
**Efficacy of Sildenafil Citrate (Viagra) in Men with Premature Ejaculation**

Chris G. McMahon, MB, BS, FACSHM,1* Brown G. A. Bucklay, BA, MBBS, FRACP,2 Morten Andersen, MD, Kenneth Fang, MD, FACP,2 Nancyan Kupferer, MD, FACP,2,3 Scott Haugab, MD,* and Mike Boddie, MD*

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<table>
<thead>
<tr>
<th>Placebo</th>
<th>PDE 5 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you have control over when you ejaculated?</td>
<td>1.45</td>
</tr>
<tr>
<td>How confident were you with your control over ejaculation?</td>
<td>1.89</td>
</tr>
<tr>
<td>How satisfied have you been with your overall sex life?</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Tramadol HCL has Promise in On-Demand Use to Treat Premature Ejaculation

Emad A. Sistem, MD,* Steven K. Wilson, MD,* Nobel K. Bisarda, MD,* John H. Dakil II, MD,* Wayne J. Hallstrom, MD,* and Matos A. Cleves, PhD*

**Tramadol (Ultram)** is a centrally acting synthetic opioid analgesic

Prescribed for years - anti-inflammatory agent; safety profile acceptable

Tramadol’s mode of action - at least two mechanisms:
1) binding of parent and M1 metabolite to mu-opioid receptor agonist
2) inhibition of reuptake of norepinephrine and serotonin which may stand for its effect on delaying ejaculation.

**Single-blind, placebo-controlled, crossover, stopwatch monitored two-period study conducted (n = 60 patients with lifelong PE (IELT <2 minutes 80% of intercourse episodes)**

Tramadol hydrochloride (25 mg) given to one group (n = 30) prior to intercourse and placebo was supplied for the other group (n = 30) for 8 weeks

Drugs were taken 1-2 hours before sexual activity and sexual intercourse was required at least once per week
SSRI's in PE

Delayed ejaculation is a recognised side effect of SSRI treatment in depression.

Studies in PE have mainly measured effects on IELT.

Published studies generally use few subjects.

Most studies have used chronic not prn dosing.

No antidepressants are specifically indicated for PE.
Pharmacologic Erection Program

<table>
<thead>
<tr>
<th>Papaverine HCl</th>
<th>Phentolamine Mesylate</th>
<th>Prostaglandin E1</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg/ml</td>
<td>1 mg/ml</td>
<td></td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>1.5 mg/ml</td>
<td></td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>1 mg/ml</td>
<td>10 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>2 mg/ml</td>
<td>20 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>3 mg/ml</td>
<td>30 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>4 mg/ml</td>
<td>40 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>4 mg/ml</td>
<td>2.5 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>4 mg/ml</td>
<td>5 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>4 mg/ml</td>
<td>7.5 ug/ml</td>
</tr>
<tr>
<td>30 mg/ml</td>
<td>4 mg/ml</td>
<td>10 ug/ml</td>
</tr>
</tbody>
</table>

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Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients


Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients

Delayed or absent ejaculation

Dopamine, Noradrenaline, Oxytocin, Melanocortins

Serotonin, Opioids, Endocannabinoids, Prolactin

Dopamine

Oxytocin

Noradrenaline
Delayed Orgasm, Decreased Pleasure with Orgasm TREATMENTS

1. Role of sex therapy
2. Mechanical devices
3. Treat other medical problems, stop medications
4. Role of testosterone
5. Role of daily vs on demand PDE 5 inhibitor
6. Role of daily vs on demand dopamine agonist
7. Role of oxytocin
8. Role of yohimbine hydrochloride
9. Role of alpha-agonist

Emotional Intelligence and Its Association with Orgasmic Frequency in Women

Andrea V. Buri, MSc, Lynne M. Chtokas, PhD, and Tim D. Spoor, MD
Kings College London St. Thomas Hospital, Men Research and Gender Endocrinology Department, London, UK

Emotional intelligence “the ability to monitor one’s own and others’ feelings and emotions, to discriminate among them and to use this information to guide one’s thinking and actions”

Emotional intelligence “adaptive capacities and abilities to control impulses and cope with stress, as well as interpersonal and interpersonal intelligence (e.g., emotion-related self-perceptions, emotion management, empathy)

Reacting to Events

- No thought given to outcome or consequence of reacting.
- Usually an over-reaction.
- Emotion based response.
- Escalates the tension around the event.
- Creates mental and physical stress in the sexual environment.

Reflecting on Events

- Deliberate thought given to outcome or consequence.
- Usually an appropriate response to an event.
- Reason based.
- Calms emotions and de-escalates tension around the event.
- Creates a high tone sexual environment.

“SOFT” (SCALE OF FEELINGS AND THOUGHTS) SCALE

Love/Appreciation
Empowerment/Freedom
Joy/Passion
Enthusiasm/Eagerness
Happiness/Cheerfulness
Positive expectations/Belief
Optimism/Hopefulness
Contentment/Satisfaction/Pleasure
Resourcefulness/Resilience
Security/Self-Esteem
Laziness/Boredom
Indifference/Apathy
Frustration/Irritation/Impatience
Feeling Overwhelmed/Disagreement
Doubt/Worry/Anxiety
Blame/Sadness/Regret
Anger/Hatred/Rage
Jealousy/Resentment Revenge
Insecurity/Unworthiness/Guilt
Depression/Despair/Grief
Fear/Helplessness/Powerlessness

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Table 2: Self-reported orgasm frequency and emotional intelligence mean scores by category during intercourse and masturbation.

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Low (0-2)</th>
<th>Medium (3-5)</th>
<th>High (6-8)</th>
<th>Very High (9-11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Irritation</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Depression</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Guilt</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Regret</td>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
</tr>
</tbody>
</table>

High Tones

Low Tones
Delayed Ejaculation/Orgasm, Decreased Pleasure with Orgasm TREATMENTS

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Drugs may sedate and impair orgasmic responsiveness:
- alcohol
- recreational drugs
- SSRI antidepressants – fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft)
- alpha-blocking agents
- anti-psychotic agents
- hormone deprivation agents
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Different Testosterone Levels Are Associated with Ejaculatory Dysfunction

Sex Steroid Hormones and Genomic Therapy

Effect of androgens on penile cavernosal nerve structure.

Tissue sections of cavernosal nerves were fixed in glutaraldehyde and stained with toluidine blue to visualize myelinated nerve fibers.

Castrated rats infused with vehicle exhibited decreased nerve fiber density and thinner myelin sheaths when compared to intact rats or castrated rats infused with testosterone.
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Dopamine

1. Bupropion
2. Cabergoline
3. Apomorphine – nasal spray
4. Parkinsons agents – Mirapex, Requip
5. Ritalin
Bupropion Therapy

Effects norepinephrine and dopamine uptake
Increased activity correlates with increased sexual responsiveness and orgasmic capacity
Effect on dopamine - prosexual

Bupropion Treatment for Low Desire

Premenopausal women with low desire
150-300 mg, 400 mg vs. placebo
Increased CSFQ total, pleasure, arousal, orgasm
Multisite single-blind study of premenopausal women
1/3 increased libido
Increased thoughts, arousal, frequency

Bupropion Treatment for Low Desire

Bupropion versus placebo
Increased desire
Frequency of sexual activity correlated with total testosterone, baseline and during treatment
Depressed minority switched from SSRI to Buproprion SR
150-300 mg; CSFQ improved desire, arousal, orgasm


The effectiveness of cabergoline in 50 men was investigated in a 4-month, randomized, placebo-controlled, double-blind study with validated tests
In the cabergoline-treated group, erectile function improved significantly
Sexual desire, orgasmic function, and the patient’s and his partner’s sexual satisfaction were also enhanced


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Sexual Reflexes
Oxytocin has an ultra-short half-life of 2-3 minutes. Use nasal application 20-24 IU during intercourse at the point when orgasm was sought. Patient had orgasms regularly (multiple times per week) after sexual intercourse.

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Yohimbine in the treatment of orgasmic dysfunction

Anorgasia might be result of psychological or neurological factors or psychotropic drugs like paroxetine.

Anorgasia has also been treated by psychotherapy or vibrator medications (e.g., dopamine agonist).

Yohimbine, an alpha 2-adrenergic receptor-blocking drug, central action alpha 2-adrenoceptor blockade might possibly lower the threshold for excitability in the forebrain centers.

Yohimbine hydrochloride formulation not well absorbed from the stomach - oral administration poor unless stomach empty. Need to take tablets hours after last meal.

Rapidly cleared, dose is effective only about 30-50 min.

Yohimbine and ED: 5-15 mg daily.

Yohimbine and Ejaculatory Dysfunction: 30 mg for the average man; initial dose of 20 mg.

Side effects: ↑ pulse and blood pressure, tremor, pleasurable tingling, palpitations, malaise, nausea and headache - not a significant deterrent in any patient.

20-mg dose of yohimbine (empty stomach) given to 29 men with orgasmic dysfunction: fertility problems (52%); wanted to experience the pleasure of orgasm (48%).

 Patients were allowed to increase the dose at home (titration) under more favorable circumstances.

Patients classified into three groups of orgasmic dysfunction: primary complete (13), primary incomplete (9), secondary (6).
29 patients completed treatment, 16 (55%) managed to reach orgasm - ejaculate either during masturbation or sexual intercourse.

Further three achieved orgasm, with vibrator

Side effects not sufficient to cause the men to cease treatment.

Conclusion: Yohimbine is a useful treatment option in orgasmic dysfunction.
I've had three attempts since that time, all using the same technique, except I used yohimbine also in one of them. All had fair to good erections. Without yohimbine, I had one mild orgasm, and one time with no orgasm, but an extended mildly pleasurable period. I continue to take 100 mg of bupropion each morning. At your suggestion, I tried a half pill of yohimbine, about 45 minute before sex in the morning. The erection was unusually good, but no orgasm, and after a while I lost the erection totally. An hour or so later, I had the jitters, with some trembling in my fingers, a tight edgy feeling across my shoulders, mild chills, and the runny nose again. These symptoms lasted for several more hours. So far, yohimbine is a bust for me.

Dear Dr. G: You may recall I mentioned that various drugs I have tried for peripheral neuropathy, Lyrica, Neurontin and 2 antidepressants, all caused anorgasmia in doses large enough to make a significant difference on the peripheral neuropathy. I also might add that this is a problem that has never occurred under any other condition. I think I also mentioned reading some loose references to sublingual oxytocin as a way of resolving this. I tried oxytocin and found it actually worked! It worked even when I upped the Lyrica dose. I had been taking a very small dose, 200 mg a day, which helped the pn but only in part. It also slowed but did not prevent orgasm in that dose. However, at 400 mg Lyrica a day, in the past, orgasm was not possible. With the oxytocin 40 units sublingual (whatever the units are) taken 40 minutes before sex things were easier and faster at 400 mg Lyrica than at 200 mg with no oxytocin.

Dr. Goldstein: I want to tell you about my success with Ritalin. I was formerly on 360 mg of Wellbutrin which no longer seemed effective. After switching to Ritalin (10mg daily), I felt an immediate improvement not only affecting my overall therapy of hormones/medications, but also in mood, energy levels and concentration. I don't know if this is a result of having had an undiagnosed adult "attention deficit disorder" or the result of Ritalin's effect on dopamine levels, but for me, it is indeed a great improvement, especially in orgasm quality.

The therapy of yohimbine was also effective, yet the side effects you mentioned were equally present. But my system is slowly adjusting.

Thank you again for the wonderful care you are providing.