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Current Pharmacological Management of Premature Ejaculation: A Systematic Review and Meta-analysis

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Abstract

Context: Premature ejaculation (PE) is the most prevalent male sexual dysfunction. In the last few years, several pharmacologic approaches for oral or topical treatment of PE have been studied.
Objective: To systematically review the literature on the outcome of pharmacologic interventions for PE on intravaginal ejaculation latency time (IELT) in comparison to placebo.
Evidence acquisition: A systematic literature search of PubMed and Scopus using the term "premature ejaculation" was performed on 10 April 2015. Full-text articles on prospective randomized controlled trials (RCTs) investigating pharmacotherapy were included. The main outcome measure was IELT.
Evidence synthesis: Out of 266 unique records, a total of 22 were reviewed. The majority of RCTs were of unclear methodological quality because of limited reporting of methods. Pooled evidence suggests that selective serotonin reuptake inhibitors (SSRIs), topical anesthetic creams (TAs), tramadol, and phosphodiesterase type 5 inhibitors (PDE5is) are more effective than placebo at increasing IELT (all $p < 0.05$). However, interpretation of the current meta-analyses may be impaired as a result of frequent heterogeneity in the pooled analyses (all $I^2 > 70\%$). Only pooled analyses for dapoxetine 30 mg and 60 mg were characterized by homogeneous data (both $I^2 < 30\%$) while showing a modest but statistically significant improvement in IELT compared with placebo (mean difference 1.39 min, 95% confidence interval 1.23–1.54 min; $p < 0.00001$).
Conclusions: Meta-analysis revealed that treatment with dapoxetine significantly improves IELT in patients with PE but with modest efficacy. The efficacy of SSRIs, TAs, tramadol, and PDE5is remains unclear owing to high heterogeneity of the available RCT data. There is a persisting need for drug research and development in the field.
Patient summary: Premature ejaculation is a condition for which the cause is not well understood. Several types of treatment with medium to low efficacy are available. More research is necessary to identify the ideal treatment.

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1. Introduction

It has been claimed that premature ejaculation (PE) is one of the most commonly reported male sexual complaints, with prevalence ranging between 20% and 30% in the male population according to several epidemiological studies [1]. PE may have a detrimental impact on quality of life for patients and their partners [2].

Despite its high prevalence, a universally accepted consensus on the definition of PE was lacking for many years. This absence of an accepted definition has compromised research on novel PE treatments. In 2008, the International Society for Sexual Medicine (ISSM) [3] proposed a comprehensive evidence-based definition of lifelong PE that has become more universally accepted than its predecessor in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. According to the ISSM, lifelong PE is "an ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all, or nearly all vaginal penetrations, along with negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy." Acquired PE is characterized by gradual or sudden onset over the lifetime of the individual, who describes previous normal ejaculatory performance and ejaculates within approximately 3 min after vaginal penetration [4].

As a result of heterogeneous data and poorly clarified physiology of ejaculation and pathophysiology of ejaculatory disorders (including a mixture of organic, psychogenic, and iatrogenic etiologies), the appropriate approach for PE management was long considered related to the psychosexology field. Notwithstanding, pharmacologic research with selective serotonin reuptake inhibitors (SSRIs) has led to a neurobiological-genetic vision of PE as postulated by Waldinger and colleagues in 1998 [5]. After the first placebo-controlled study of paroxetine, several other SSRIs were investigated and have been used for off-label clinical treatment of PE. SSRIs, topical anesthetics (TAs), and, more recently, tramadol represent the most common on- and off-label pharmacotherapeutic approaches for PE management (Table 1).

The aim of our study was to provide an overview of the efficacy of current pharmacologic treatments for PE (Table 1) in improving intravaginal ejaculation latency time (IELT). IELT represents the most objective criterion for assessing PE improvement according to the latest definition, and is a primary endpoint commonly used in PE studies. To this end, we carried out a systematic review of peer-reviewed randomized controlled trials (RCTs) published in the literature.

2. Evidence acquisition

2.1. Search strategy

A systematic literature review was performed to identify prospective RCTs on PE treatment according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [6]. A literature search of full-text English language publications on clinical trials was performed using PubMed and Scopus on 10 April 2015 with the search term "premature ejaculation".

2.2. Eligibility criteria

The inclusion criteria were prospective RCTs in humans, full-text articles, and English language. Exclusion criteria were the following: (1) articles not in English; (2) articles not reporting on pharmacologic treatment; (3) review or meta-analysis articles; (4) duplicated or updated data; (5) comments, editorials, letters and congress reports; and (6) case reports.

Table 1 – Mode of action of pharmacological treatments for premature ejaculation

Drug	Mechanism of action	Dose	Drug type	Dose regimen
Dapoxetine	Fast-acting SSRI	30–60 mg	Oral tablet	On demand
Sertraline	SSRI	50–200 mg	Oral tablet	Daily or on demand
Fluoxetine	SSRI	20–40 mg	Oral tablet	Daily or on demand
Paroxetine	SSRI	10–40 mg	Oral tablet	Daily or on demand
Citalopram	SSRI	20–40 mg	Oral tablet	Daily or on demand
Tramadol	Mild MOR agonist: (1) MOR stimulation in hypothalamic MPOA; (2) inhibition of 5-HT reuptake	25–100 mg	Oral tablet	On demand
EMLA	TA: decreases sensory-stimulating information reaching the spinal cord after penile anesthesia	2.5% each of lidocaine and prilocaine	Topical cream	On demand
TEMPE	TA: decreases sensory-stimulating information reaching the spinal cord after penile anesthesia	7.5 mg lidocaine + 2.5 mg prilocaine base per actuation	Topical spray	On demand
Sildenafil	PDE5i: reduces contractile response of seminal vesicles and vas deferens	50–200 mg	Oral tablet	On demand
Verdanafil	PDE5i: reduces contractile response of seminal vesicles and vas deferens	10–20 mg	Oral tablet	On demand
Tadalafil	PDE5i: reduces contractile response of seminal vesicles and vas deferens	5–20 mg	Oral tablet	On demand

SSRI = selective serotonin reuptake inhibitor; MOR = μ-opioid receptor; MPOA = medial preoptic area; TA = topical anesthetic.