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Review – Sexual Medicine

Serotonin and Premature Ejaculation: From Physiology to Patient Management

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Abstract

Introduction: Premature ejaculation (PE), whose pathophysiology is still not clearly identified, is the most common male sexual dysfunction, yet it remains underdiagnosed and undertreated. The aims of this paper are to provide a scientific and pharmacologic rationale, and to discuss to what extent selective serotonin reuptake inhibitors (SSRIs) can help patients with PE.
Materials and Methods: A comprehensive evaluation of available published data included analysis of published full-length papers that were identified with Medline and Cancerlit from January 1981 to January 2006. Official proceedings of internationally known scientific societies held in the same time period were also assessed.
Results: The central ejaculatory neural circuit comprises spinal and cerebral areas that form a highly interconnected network. The sympathetic, parasympathetic, and somatic spinal centers, under the influence of sensory genital and cerebral stimuli integrated and processed at the spinal cord level, act in synergy to command physiologic events occurring during ejaculation. Experimental evidence indicates that serotonin (5-HT), throughout brain descending pathways, exerts an inhibitory role on ejaculation. To date, three 5-HT receptor subtypes (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C}) have been postulated to mediate 5-HT's modulating activity on ejaculation. Pharmacologic manipulation of the serotonergic system has been performed in rats, with the antidepressant selective serotonin reuptake inhibitors (SSRIs) exhibiting the greatest efficacy in delaying ejaculation. The mechanism of action by which SSRIs modulate central 5-HT tone has been studied in depth, but gaps in this knowledge prevent an explanation of the efficacy of acute treatment in delaying ejaculation. Emerging clinical evidence indicates chronic and on-demand dosing of SSRIs has a beneficial effect for the treatment of men with PE, at least for paroxetine. On-demand dapoxetine, and SSRI with a short half-life, recently has been shown to significantly increase intravaginal latency time and PE patient-related outcomes in phase 3 clinical trials.
Conclusions: Nowadays there is no doubt that PE can be treated effectively by SSRIs. Nevertheless their mechanism of action is not yet well understood and deserves more research. In particular it is not understood why all the SSRIs are not equal in terms of their ability to delay ejaculation. Therefore, there is a need for more research to better characterize the mechanism of action of SSRIs as well their clinical benefit in patients affected by PE.

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1. Introduction

Sexual medicine has evolved greatly in the past several years, to a large extent because of the introduction of the phosphodiesterase-5 inhibitor sildenafil followed by tadalafil and vardenafil as highly effective oral therapies for erectile dysfunction (ED) [1]. Conversely, despite some substantial progress in medical and scientific knowledge in other areas of sexual medicine including ejaculation disorders and female sexual dysfunctions, there is still a need for the development of a clinically effective treatment for these sexual symptoms.

According to the epidemiologic studies conducted so far, premature ejaculation (PE) is the most common male sexual dysfunction in younger men (<30 years) [2]; its prevalence is higher than that of ED, and varies from 9% and up to 31% of the male population [3]. PE recently has been reported to be associated with significant effects on sexual functioning and satisfaction [4]. Nevertheless according to the National Health and Social Life Survey conducted in the United States, it is noteworthy that men with ED and low sexual desire experienced diminished quality of life, but those with premature ejaculation were not affected [5]. Accordingly it must be kept in mind that the level of bother attributable to PE is likely less than that caused by ED, and the number of men currently seeking medical assistance for PE is likely less than that for ED. Another striking difference between PE and ED is the fact that, conversely to ED, PE patients have no impairment of the physiologic process that leads to the forceful expulsion of sperm at the urethral meatus. Actually in such patients, there is an inadequate timing for ejaculation to occur as well as a self-reported lack of voluntary control associated more or less with personal distress. It is currently unknown whether peripheral and/or central mechanisms are involved in the pathophysiology of PE.

The *Diagnostic and Statistical Manual of Psychiatry, Fourth Edition* (DSM-IV) defines PE as ''persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it,'' which is associated with ''marked distress or interpersonal difficulty'' [6]. More recently during the 2nd International Consultation on Sexual Dysfunctions, premature ejaculation, also referred to as rapid or early ejaculation, was defined according to three essential criteria: (1) brief ejaculatory latency, (2) loss of control, and (3) psychologic distress in the patient and/or partner. Ejaculatory latency of 2 minutes or less may qualify a man for the diagnosis of PE, which should include consistent inability to delay or control ejaculation and marked distress about the condition. All three components should be present to qualify for the diagnosis [7].

The aetiology of PE is uncertain in almost all cases, and might include a combination of organic and psychogenic factors. Negative conditioning and penile hypersensitivity are the most frequently cited aetiological factors in PE, although neither mechanism has received adequate experimental support to date [7]. Accordingly from a scientific perspective, it is fair to state that PE pathophysiology is largely unknown.

Since the first publications of clomipramine [8] and paroxetine [9] for the treatment of PE, numerous other studies have confirmed the efficacy of selective serotonin reuptake inhibitors (SSRIs) antidepressants as well as clomipramine in the treatment of lifelong PE [10–12].

The rat is the most widely used animal for the study of sexual behaviour, and the data presented below refer to this animal species unless specified otherwise. At first glance, human copulatory behaviour does not resemble the copulatory behaviour in rats. However, when looking at greater details, some common features emerge (for review see [13]) that allow animal studies-based development of relevant strategies for the treatment of sexual dysfunctions in human.

The aims of this paper are to provide a scientific and pharmacologic rationale, and to discuss to what extent SSRIs can help patients with PE.

2. Neurophysiology of ejaculation

2.1. *Spinal network*

The thoracolumbar sympathetic as well as the sacral parasympathetic and somatic (Onuf's nucleus) spinal ejaculatory centres play a pivotal role in ejaculation, because they integrate peripheral and central signals, and send coordinated outputs to pelviperineal anatomic structures that allow a normal ejaculatory process to occur. Integrity of these spinal nuclei is necessary and sufficient for the expression of ejaculation as demonstrated by the induction of the ejaculatory reflex after peripheral stimulation in animals with spinal cord transection and in patients after spinal cord lesion [14,15]. The conversion of sensory information into secretory and motor outputs involves spinal interneurones that have been recently characterised in rats [16]. The presence of these cells, named lumbar spinothalamic (LSt)