THE ROLE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PREMATURE EJACULATION

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ABSTRACT

Premature ejaculation is a very common male sexual medical illness worldwide. Amongst several biological risk factors, the disturbance of central serotonin neurotransmission is one important cause. Various research has allowed a better understanding of the development of this disorder, as well as allowing for improved treatment options in order to decrease the significant morbidity associated with this condition; among the more recent treatments, selective serotonin reuptake inhibitors are believed to be one of the best. During this review, the action and role of serotonin reuptake inhibitors at different levels will be discussed, along with their relevance and effectiveness in the treatment of premature ejaculation.

Keywords: Dapoxetine, fluoxetine, premature ejaculation (PE), selective serotonin reuptake inhibitors (SSRI), serotonin, 5-HT receptors.

INTRODUCTION

Premature ejaculation (PE) was once considered to be a psychosomatic disturbance.[1] This sexual disorder is more common than some estimate and is responsible for significant emotional and psychological issues.[2] Researchers have faced difficulties studying PE and physicians still do not know the most effective treatments, since patients are often unwilling to divulge personal information.[3,4] According to Guiliano and Hellstrom,[5] lack of knowledge of aetiology and lack of approved treatments may be responsible for under-diagnosis and under-treatment of PE. PE can be a lifelong condition (PE present since the onset of sexual maturity) or acquired (PE is secondary to other conditions such as chronic prostatitis, diabetes mellitus, and hyperthyroidism). On treating the underlying pathology, it is possible that acquired PE can be reversed.[6]

Although many definitions of PE have previously been described, and the definitions given in the Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Association (APA) were largely accepted by the medical community with little discussion, these definitions have no evidence-based medical support.[7] The first evidence-based unified definition for both acquired and lifelong PE was given by the first Ad Hoc Committee of the International Society for Sexual Medicine (ISSM) for the Definition of Premature Ejaculation. The committee stated that lifelong PE was a male sexual dysfunction that was determined by the presence of three criteria: i) ejaculation always (or nearly always) occurring either prior to vaginal penetration or within 1 minute; ii) inability to delay ejaculation in all (or nearly all) vaginal penetrations; and iii) negative personal consequences for the affected individual, including distress, frustration, bother, and/or avoidance of sexual intimacy. This definition was then expanded upon in 2013 by the second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation. The committee noted that an additional characteristic by which acquired PE could be defined was the presence of a clinically significant and bothersome reduction in latency time (to about 3 minutes or less).[7]

EJACULATION AND THE EJACULATORY NEURAXIS

Ejaculation is a complex sexual response consisting of two sequential phases: emission (deposition of seminal fluid and sperm in the posterior urethra) and expulsion (propulsion of the ejaculate out of the urethra). The whole process occurs through the interaction of supra-spinal, spinal, and peripheral neural pathways. The spinal part is a result of a reflex, requiring sympathetic, parasympathetic, and somatic efferent pathways.[8] The cell bodies of primary sensory neurons innervating peripheral anatomical structures participating in ejaculation are located in lumbar dorsal root ganglia, and their central projections terminate in the medial dorsal horn and the dorsal grey commissure (Lamina VII and X) of the T10–L2 spinal cord segments.[9] In humans, functional magnetic resonance imaging studies revealed that in cases of PE, the brain responses and functional integration in certain brain areas were impaired.[10] The hindbrain nucleus paragigantocellularis (nPGi) projects bilaterally to the lumbosacral motor neuron pools that innervate the genital musculature. nPGi lesions facilitate ejaculation, proving that nPGi is the source of descending inhibition to genital reflexes.[11,12] When men are sexually stimulated, neurological signals are sent to the spinal cord and brain. At a certain level of excitement, signals are then sent from the brain to the reproductive organs.[13] This causes semen to be released through the penis. Pharmacological delay of ejaculation can be achieved either by inhibiting excitatory or reinforcing inhibitory pathways from the brain or from the periphery to the spinal cord.[8]

Many neurotransmitters and receptors are found at the ejaculatory neuroaxis including dopamine, nitric oxide, and 5-hydroxytryptamine (5-HT), also referred to as serotonin.[8,9] Dopamine causes excitation of the ejaculatory neuroaxis, and inhibition occurs by serotonin and nitric oxide.[9] All serotonin receptors are located post-synaptically, except for 5-HT1A, 5-HT1B, and 5-HT1D which are pre-synaptic and involved in negative feedback.[9] These 5-HT receptors are found throughout the central and peripheral nervous system, from the brainstem, hypothalamus, nPGi, and the dorsal horns of the spinal cord, as well as in structures involved in ejaculation, including the seminal vesicles, vas deferens, urethra, and prostate. Serotonin induced contraction of urogenital organ smooth muscle could regulate the emission of urine and/or semen.[9,14-16] Disturbance of the central (spinal and supra-spinal) serotonergic neurotransmission is principally responsible for ejaculation. Presynaptic 5-HT1B and postsynaptic 5-HT2C receptor stimulation is thought to increase ejaculation latency time and 5-HT1A receptor stimulation is also known to play a role in ejaculation.[17]

DISCUSSION

Action of Selective Serotonin Reuptake Inhibitors in Premature Ejaculation

Serum 5-HT levels could be used as a diagnostic tool for PE and as an indicator in PE treatment.[18] Selective serotonin reuptake inhibitors (SSRI), such as paroxetine, fluoxetine, and sertraline, are used to treat depression and mental health disorders and can cause delayed or blocked ejaculation as a side effect in men. Clinical studies have shown that after treatment with SSRI, intravaginal ejaculation latency time gradually increased. Therefore, SSRI have opened a new potential avenue for PE treatment.[19]

Due to their pharmacokinetic profile and pharmacodynamic activity, these agents are intended for chronic use. SSRI actively block presynaptic membrane 5-HT transporters and thus inhibit the 5-HT (serotonin) reuptake and breakdown; this results in availability of higher levels/activity of serotonin in the synaptic cleft. Increased synaptic availability of serotonin facilitates its binding to 5-HT receptors, leading to a delayed ejaculation.[17] SSRI induced inhibition of ejaculation may be mediated by the serotonergic ventrolateral periaqueductal gray nPGi pathway.[20]

Dapoxetine Treatment

Dapoxetine is a short acting oral SSRI, purely created for the on-demand treatment of PE.[8] Dapoxetine cannot permanently cure PE but has increased in importance due to fewer side effects, as a result of its rapid absorption, fast action, and fast excretion. Dapoxetine inhibits the reuptake of serotonin, dopamine, and noradrenaline transporters. Nausea, dizziness, and headache were the most commonly reported side effects.[21-23] However, the US Food and Drug Administration (FDA) issued a non-approval letter for dapoxetine in 2005, and approval is still anticipated.[24]

Dapoxetine has a much lower ejaculation-delaying effect compared with traditional SSRI. Fold increase in mean geometric intravaginal ejaculation latency time with dapoxetine on-demand treatment was

approximately three-fold, versus an estimated nine-fold increase with daily paroxetine, five-fold increase with daily clomipramine, and four-fold increase with daily sertraline and fluoxetine. Chronic treatment with SSRI does, however, produce unwanted, adverse sexual effects as well as withdrawal symptoms upon abrupt discontinuation. The activation of presynaptic 5-HT1A auto-receptors and chronic 5-HT1A auto-receptor desensitisation may be a contributing factor to an increase in the number of side effects and withdrawal symptoms.[5] In young adults, suicidal thoughts and behaviour were also seen, which limits their use. There are also a few case reports indicating that these sexual side effects may continue beyond cessation of SSRI treatment; these would, theoretically, be reduced by on-demand use of SSRI (such as dapoxetine). While discontinuation syndrome was more common with short half-life SSRI, dapoxetine treatment was associated with a low incidence of discontinuation syndrome. The safety profile of dapoxetine is good but the safety of its long-term use is currently unknown.[17,25-27] The American Urological Association (AUA) guidelines state that the relative effectiveness of daily dosing SSRI and on-demand SSRI in the treatment of PE is inconclusive. The lowest possible therapeutic doses of oral antidepressants are compatible and successful at helping to treat PE. According to the European Association of Urology (EAU) guidelines, daily treatment with SSRI has become the first-choice treatment in PE.[17]

It is postulated that on-demand (acute) treatment with SSRI, such as dapoxetine, will not produce an ejaculation delay equivalent to daily long-term (chronic) treatment of SSRI, such as fluoxetine and paroxetine. This may be due to the discontinuous use of on-demand SSRI, which does not produce a continuous elevated level of serotonin in testis and accessory reproductive organs[28-30] and can produce histological changes in such reproductive organs in the form of proliferation of seminal vesicle mucosal crypts, narrowing of lumen, and change in mucosal lining from secretory mucosa to non-secretory low cuboidal and to flat cells.[28] Due to there not being any physiological impairment as a result of PE, any pharmacological agent with either a central or peripheral mechanism of action that delays ejaculation could therefore be a potential therapeutic drug candidate for the treatment of PE.[8]

CONCLUSION

The benefits of any pharmacotherapy should, as always, be weighed-up against their safety and efficacy. SSRI appear to be the most important therapeutic drug for PE with regard to their multiple sites of action in the regulation of the complex mechanisms involved in ejaculation. There is a need for further experimental and clinical studies to fully understand whether the histological changes produced by low doses of chronic SSRI in seminal vesicles are permanent and responsible for relieving or curing the symptoms of PE; it may be that these doses of SSRI could be curative for PE sufferers. Use of low to moderate therapeutic daily doses of SSRI for chronic use/long duration for the treatment of PE could reduce the frequency and severity of adverse PE events.

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