Safety and Efficacy of Escitalopram in the Treatment of Premature Ejaculation A Double-Blind, Placebo-Controlled, Fixed-Dose, Randomized Study

THESIS

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Dermatology, Andrology& STDs
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LIST OF ABBREVIATIONS

5-HT	5- Hydroxytryptamine
APA	American Psychateric Association
AUA	Area Under the curve
BNSTpm	Posteromedial Bed Nucleus of Stria Terminalis
CNS	Central nervous system
DA	Dopamine
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-Fourth edition-Text revision.
ED	Erectile Dysfunction
EE	Early Ejaculation
ELT	Ejaculation Latency Time
FDA	Food and Drug Association
FMRI	Functional Magnetic Resonance Imaging
GABA	Gamma Amino Byuteric Acid
GSSAB	The Global Study of Sexual Attitudes and Behaviours.
ICD	International Classification of Diseases
IELT	Intravaginal Ejaculatory Latency Time
ISSM	The International Society of Sexual Medicine
L-NMMA	N-Monomethyl-L-arginine

Lst	Lumbar Spinothalamic
Me Apd	Posterodorsal medial amygdaloid nucleus
MPOA	Medial Preoptic Area
mRNA	Messenger ribonucleic acid
NMDA	N methyl-D-aspartate
NO	Nitric oxide
nPGI	Nucleus paragigantocellularis
PCA	P-chloroamphetamine
PDE-5	Phosphodiestrase type 5
PDPn	Posterodorsal preoptic nucleus
PE	Premature ejaculation
PEPA	The premature ejaculation prevalance and attitudes
PET	Positron emission tomography
PLC	Plethora solution holdings
PROs	Patient reported outcomes
PVN	Paraventricular nucleus of the hypothalamus
RE	Rapid ejaculation
SPFP	Parvocellular part of the subparafasicular thalamus
SSRIs	Selective serotonin reuptake inhibitors
TEMPE	The topical eutectic mixture for premature ejaculation
VTA	Ventral tegmental area

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INTRODUCTION

AND

AIM of THE WORK

Introduction

From an epidemiological perspective, premature ejaculation (PE) has been reported as the most common male sexual dysfunction with overall prevalence rates estimated at around 30% **(Laumann et al, 1999).**

PE is defined by the Diagnostic and Statistical Manual of Mental Disorders (revision IV) (DSM-IV-TR) as 'the persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it' **(American Psychiatric Association, 1994).**

International Society of Sexual Medicine (ISSM) Definition of premature ejaculation is a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy **(www.issm.info).**

Premature ejaculation has been associated with erosion in sexual self-confidence and low sexual satisfaction in men and their female partners **(Byers and Grenier, 2003).**

Behavioural therapy and psychological counselling are the historically initial approaches in the treatment of PE. However,

there is no evidence that non-drug therapy is able to guarantee long-term cure or improvement of PE **(Rosen, 2004).**

These techniques require active involvement of the patients and their partners and the benefits are generally short-lived, and patients usually relapse. In addition, these therapies may not be applicable for some cultural and socioeconomic groups. Therefore, some pharmacological agents have been proposed for the treatment of PE **(Rosen, 2004).**

The serotoninergic system has an inhibitory effect on the ejaculatory reflex. Selective serotonin reuptake inhibitors (SSRIs) (paroxetine, fluoxetine, sertraline, citalopram) are reported to be effective for treating PE **(Rosen, 2004; Safarinejad & Hosseini, 2006).** Psychopharmacological studies suggest that PE might be due to decreased serotonergic neurotransmission through pathways that control ejaculation (**Waldinger et al, 1998).**

Ejaculation delay induced by SSRIs is due to alterations in specific serotonin receptors in the central nervous system. The ejaculation-retarding effect of 5-hydroxytryptamine (5-HT, serotonin) has been attributed to the activation of 5-HT1B and 5-HT2C receptors. By contrast, stimulation of 5-HT1A receptors has a facilitator effect on ejaculation **(Giuliano, 2007).** The net effect of on-demand SSRI administration is only a mild increase of 5-HT neurotransmission and mild stimulation of the various post-synaptic serotonin receptors (**Waldinger et al, 2005)b.** In contrast, chronic SSRI administration is associated with more 5-HT (serotonin) release into the synapse, stronger increase of 5-HT

neurotransmission, and as a result durable activation of post-synaptic 5-HT receptors (**Blier et al, 1988).**

Escitalopram, one of the SSRIs, has been claimed to have the highest selectivity for the human serotonin transporter relative to the noradrenaline or dopamine transporters (**Owens et al, 2001)** This might be associated with greater clinical efficacy. Most adverse events reported by escitalopram-treated patients are mild and transient **(Lepola et al, 2003).**

Aim of the work

1- The aim of this study to assess the efficacy of escitalopram (10 mg / day) in treatment of premature ejaculation.

2- To evaluate the side effect of the drug (escitalopram).

REVIEW

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Physiology of ejaculation

A normal sexual response cycle comprises four interactive, nonlinear stages: desire, arousal, orgasm and resolution. In males, orgasm usually coincides with ejaculation, but represents a distinct cognitive and emotional cortical event **(Rosen et al, 2003).**

Ejaculation is defined as the expulsion of seminal fluid through the urethra and is closely associated with orgasm, extra genital response and subjective pleasurable feeling in men **(Coolen, 2004).**

There are three basic mechanisms involved in normal ante grade ejaculation: emission, ejection and orgasm **(McMahon et al, 2004).**

I- Emission

It is a pleasurable sensation resulting from spinal cord reflex initiated by genital and/or cerebral erotic stimuli. It involves the sequential contraction of accessory sexual organ and the sensation of emission is due to distention of the posterior urethra. As the sensation of ejaculation inevitability increase, voluntary control progressively decreases until a point at which ejaculation cannot be stopped **(Rampin and Giuliano, 2004).**

II- Ejection

Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. It involves bladder neck closure to prevent retrograde flow, rhythmic contractions of

bulbocavernosous, bulbospongiosus and other pelvic floor muscles, and relaxation of external urinary sphincter to prevent retrograde flow into proximal urethra **(Waldinger et al, 2005)a.**

III- Orgasm

It is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from veromontanum and contraction of the urethral bulb and accessory sexual organs **(McMahon, 2007).**

Central physiology of ejaculation

A tight coordination between sympathetic parasympathetic, and somatic divisions of the nervous system is necessary for normal anterograde ejaculation to occur. The ejaculatory response involves sensory receptors and areas, afferent neural pathways, cerebral sensory and motor areas, spinal motor centers, as well as multiple efferent pathways. The regulation of the ejaculatory reflex handled at the spinal cord level requires neurochemical coordinated interrelationships to take place at different levels of the neural axis **(Giuliano and Clement, 2005a).**

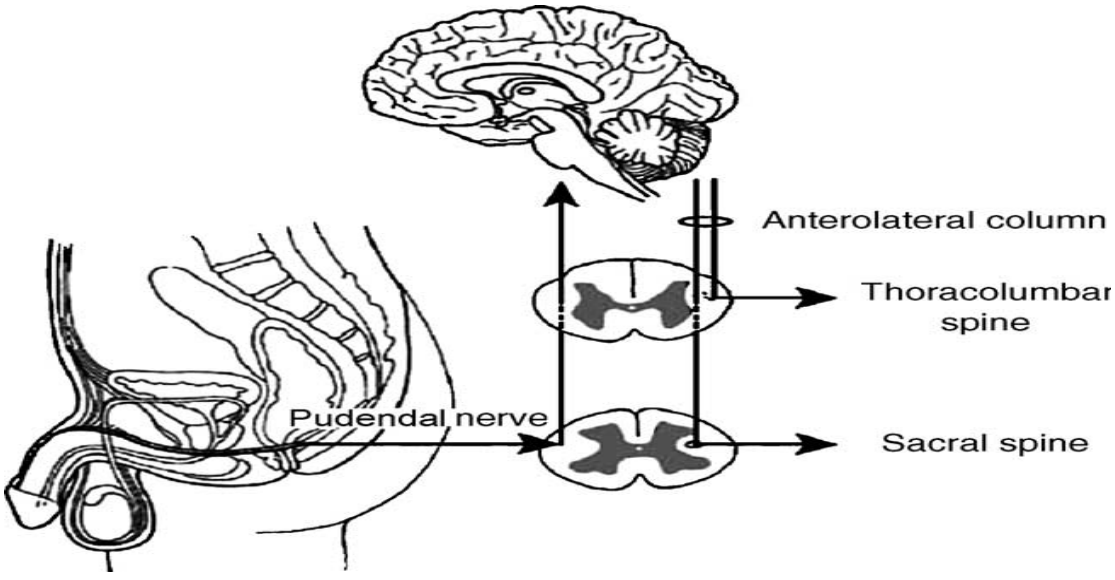
Several neurotransmitter systems are implicated, with the central serotonergic and dopaminergic neurons playing a primary role **(Giuliano and Clement, 2005b; Hull et al, 2004; Paredes and Agmo, 2004)** and other chemical factors including acetylcholine, adrenaline, neuropeptides, oxytocin, GABA and

nitric oxide, intervening secondarily (**Benelli et al, 1995; Filippi et al, 2003; Meston and Frohlich, 2000).**

A relatively clear picture of the spinal and supraspinal pathways as the neurotransmitter network involved in the ejaculatory process is available but a precise description of the dynamic of this physiological process is still lacking **(peeters and Giuliano, 2008)**.

Spinal network

The sympathetic and parasympathetic nervous systems, closely interconnected into the pelvic plexus which represents an integrative peripheral crossroad site, act in synergy to command physiological events occurring during ejaculation. Both sympathetic and parasympathetic tones are under the influence of sensory stimuli from the genitals, as well as cerebral erotic stimuli, and are integrated and processed at the spinal cord level (**Carro-Juarez et al, 2003) Fig. (1).**



(Figure 1) Neural control of ejaculation (**Carro-Juarez et al, 2003).**

Thoracolumbar sympathetic and sacral parasympathetic spinal ejaculatory nuclei are recruited by peripheral and cerebral signals and send coordinated outputs to pelviperineal anatomical structures that lead to a normal ejaculatory process. Integrity of these spinal nuclei is necessary and sufficient for the expression of ejaculation as demonstrated by the induction of ejaculatory reflex by peripheral stimulation of the afferent pathways in animals with spinal cord transection and humans after complete spinal cord lesion **(Brackett et al, 1998; McKenna et al, 1991).**

The conversion of sensory information into secretory and motor outputs involves spinal interneurons which have been recently characterized in rats **(Truitt and Coolen, 2002).**

The presence of these cells, named lumbar spinothalamic (LSt) cells, has been demonstrated in laminae X and VII of the spinal lumbar segments 3 and 4. Immunohistochemical investigations have shown that LSt cells contain galanin, cholecystokinin, and enkephalin. In the rat spinal cord, fibers of the sensory branch of the pudendal nerve innervating the glans and the perineal region terminate close to LSt cells **(McKenna and Nadelhaft, 1986).**

LSt neurons are connected to the spinal sympathetic and parasympathetic preganglionic neurons innervating the seminal tract as well as the motoneurons of the dorsomedial nucleus innervating the bulbospongiosus muscles **(Xu et al, 2005, 2006).** In addition, LSt cells send direct projections to the