

BJUInt Minireview: The link between penile hypersensitivity and premature ejaculation.

ABSTRACT

Objectives

This review attempts to determine if there is a correlation between penile hypersensitivity and premature ejaculation (PE), as defined by the criteria identified by the International Society of Sexual Medicine (ISSM). The determination of whether penile hypersensitivity is directly relevant to the aetiology of PE is based on the historical clinical neurophysiological data and the clinical efficacy of the topical desensitising agent PSD502 in the treatment of PE. PSD502 is a eutectic-like mixture of two local anaesthetics - lidocaine and prilocaine - and, as such, the primary action is to reduce neuronal conduction in sensory afferents.

Methods

Historical neurophysiological data was reviewed, together with data from the recent PSD502 clinical trials, the first published double-blind clinical trial data evaluating a topical desensitising agent in a population of men with PE, as per the new ISSM definition. The clinical profile of PSD502, based on its local anaesthetic properties, is used as a surrogate index of the role of sensory afferents in the ejaculatory reflex.

Results

The literature does not support unequivocally that penile hypersensitivity is directly relevant to the aetiology of PE. Interpretation of the literature is hampered by the variability of the population described as having PE across studies. Data from the PSD502 clinical trials show that PSD502 increases ejaculatory latency, and improves control and sexual satisfaction when applied topically to men with PE five minutes before intercourse, enabling subjects to delay ejaculation up to six times longer than those who used a placebo.

Conclusion

Although not all the literature supports the hypothesis that PE results from penile hypersensitivity, the clinical profile of PSD502 lends considerable credibility to this hypothesis. The predominant action of local anaesthetics is to reduce neuronal firing in sensory afferents; the clinical profile of PSD502, which demonstrated improvement of ejaculatory function in the reduction of general penile desensitisation, can most readily be explained on the basis of an underlying hypersensitivity in PE patients.

Keywords

Premature ejaculation (PE); hypersensitivity; topical desensitising agents; PSD502.

INTRODUCTION

PE is the most common sexual problem experienced by men, thought generally to affect around 30% [1] of the world's male population, although some studies have had this figure as high as 75% [2].

The determination of the prevalence of PE was hampered until recently when the International Society of Sexual Medicine (ISSM) generated an evidence based definition: "Premature ejaculation is a male dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and, an 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" [3].

While there has been a proliferation of men diagnosed – and self-diagnosing [3] – with PE over the last decade, there still remains a dearth of clear, evidence-based research as to its causes. Penile hypersensitivity has been implicated as one of a variety of potential contributing factors in the aetiology of PE, warranting its own targeted research. However, data from such research into the link with hypersensitivity and other potential aetiologies has been conflicting and lacking in definitive conclusions. One potential reason for the confusion is that all research studies pre-dated the ISSM definition of PE and, as such, the definitions of 'normal' and PE are somewhat arbitrary and variable across study centres. This review attempts to determine if there is a correlation between penile hypersensitivity and PE, as defined by the criteria identified by the ISSM.

Physiology of ejaculation

Ejaculation consists of emission and expulsion as two distinct but coordinated sequential neurological reflexes, stimulated by sensory input to the penis (Figure 1). Pudendal sensory nerve fibres provide information from nerve endings in the glans penis to the sacral cord and sensory cerebral cortex. The ejaculatory reflex is modulated by the brain and also at the lumbosacral spinal cord level, although it is not dependent upon central neural control as it remains intact in patients with complete spinal cord transaction who (depending on the location of the lesion) are able to ejaculate with powerful vibratory stimulation of the penis (reviewed in [4]).

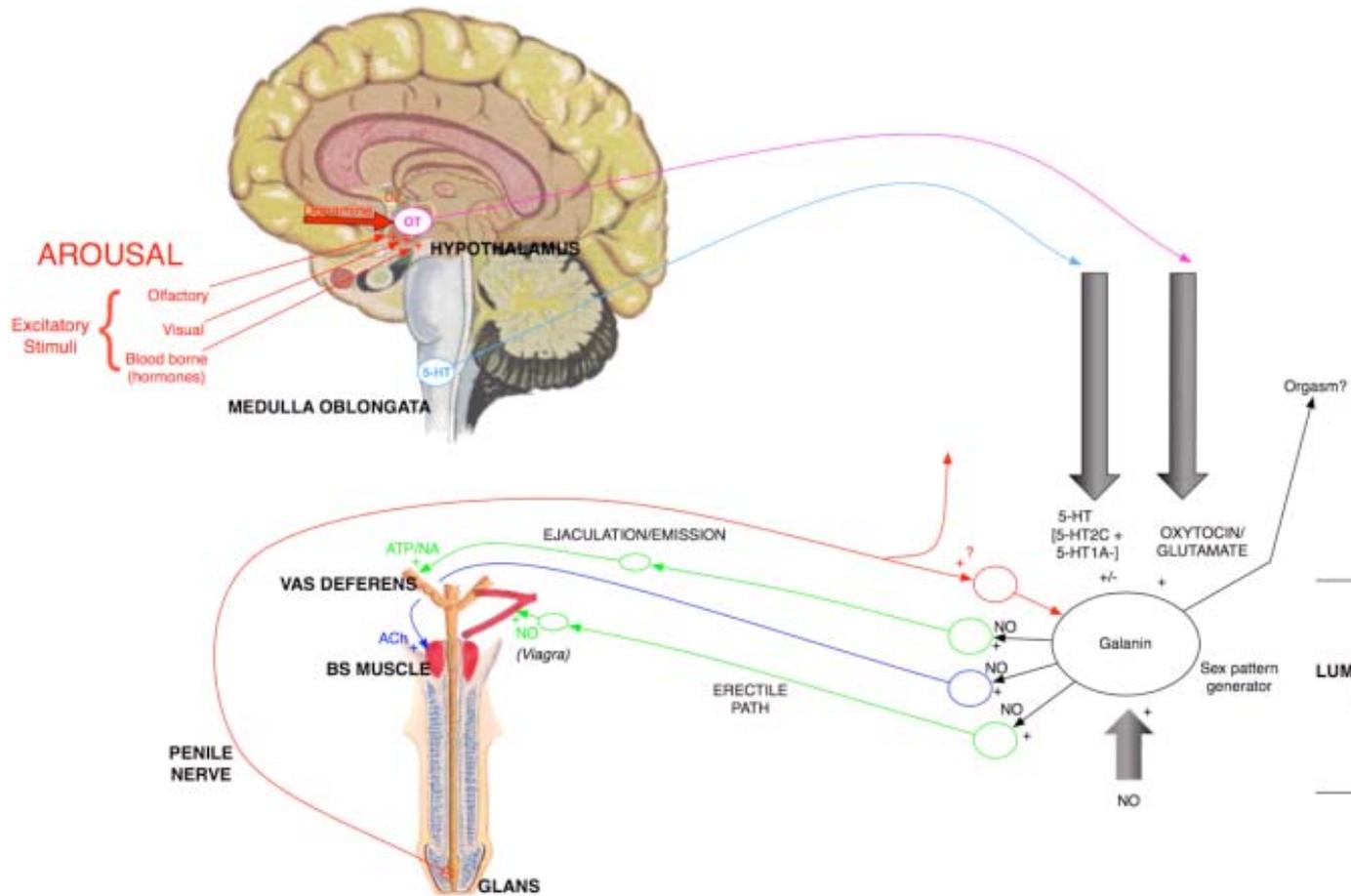


FIGURE 1. NEUROPHYSIOLOGY OF EJACULATION

Aetiology of PE

No organic disease has been firmly associated with PE, although there is perhaps some evidence that prostatitis or hyperthyroidism might have a role in the aetiology of PE in some men [5, 6].

There are many overlapping theories on the aetiology of PE. One contemporary view is that primary PE (being present since the onset of sexual activity) is part of the normal biological variability of ejaculatory latency in men, with a possible familial genetic vulnerability [7, 8].

The large natural variation in ejaculatory latency in men might be due to differences in penile sensitivity, with hypersensitivity causing - or contributing to - the very short latency experienced by men with PE. Should this be the case, drugs which selectively produce some degree of penile desensitisation, or which act within the afferent-efferent reflex arc, should be effective therapy for PE.

The distribution of intravaginal ejaculation latency time (IELT) in the male population has been found to follow a skewed distribution, and the question of where to draw the line that defines a particular IELT as being premature or not has been largely academic as definitions of PE in use until recently generally did not include such cut-off points. As a result, the population of men with PE in many clinical trials and neurobiological evaluations have been

largely self-diagnosed, somewhat heterogeneous and, in many cases, poorly defined, making comparative evaluations difficult.

This paper will attempt to re-evaluate the theory of penile hypersensitivity as a possible aetiology of PE in the light of its contemporary definition, which includes an IELT of 'about one minute' as one of the features defining PE.

HISTORICAL DATA

Possible motor pathway impairment

The bulbocavernosus reflex (BCR) is a sharp contraction of the bulbocavernosus and ischiocavernosus muscles (internal and external anal sphincter) when the glans penis is suddenly compressed or tapped. This reflex can also be tested electrophysiologically by stimulating the penis and recording evoked potentials (the electrical potential produced as a result of the external stimulus) from the anal sphincter [9]. In healthy males, the evoked potential appeared simultaneously in the bulbocavernosus muscle and in the anal sphincter, with an average latency of 45 msec. In men with PE (undefined), an average delay of 15 msec was reported between the response in bulbocavernosus and the anal sphincter [10].

Based on this evidence, Vignoli [10] suggested that in men with PE the shortening of the latency in the bulbocavernosus muscle could be due to a shunting in the reflex arc, possibly mediated by facilitatory impulses from supraspinal centres. However, it is not clear whether this physiological parameter represents a consequence or cause of PE, and the value of the study, in the absence of information defining the patient population, is limited.

A similar, larger study (85 men with undefined PE) found no differences in the latencies of the evoked responses, although they did demonstrate significantly higher amplitudes of evoked responses in men with PE than in controls [11]. The authors suggest that the results indicate that men with PE have a reflex hyperexcitability, or an impaired 'modulation' of the motor neurons of the pudendal nucleus by the regulating upper centres. PE was not clearly defined in this study and there was no mention of IELT having been measured.

Possible somatosensory impairment

Somatosensory evoked potentials (SEPs) are recorded from the cerebral cortex to give a cortical representation of the sensory stimuli arising from the genital area.

Amplitude of SEPs

The amplitudes of the SEPs in the cortical area were found to be significantly higher in men with (undefined) PE than in the normal controls [11, 12], suggesting a greater cortical representation of the sensory stimuli from the genital area (penile shaft and glans).

The authors suggest that patients with PE have a greater cortical representation of the sensory stimuli from the glans penis, indicating that excessive excitation from the glans penis to the ejaculation centres has a role in rapid, uncontrolled ejaculation [11, 12]. Perretti

et al. [13] reported the opposite finding, at least for the SEPs in the dorsal nerve, which they found to be significantly smaller in the men with PE (n=14, IELT <3 min, range 0-2.7 min) than the controls [13].

Latency of SEP

The mean latency of both the dorsal nerve and the glans penis SEP was found to be shorter in the PE group (mean IELT 1.2 min, range 0.5 – 3.0 min) than in the control group, although both were within normal limits [12]. In addition, in normal subjects the mean latency of the SEP from the glans was prolonged by 0.99 msec, compared to that in the dorsal nerve; postulated by the authors to be related to the longer distance from the glans penis compared to the penile shaft, as well as the different distribution of nerve fibres. In men with PE this was reversed, with the mean latency from the glans penis shorter by 4.30 msec than that in the dorsal nerve [12].

The authors suggested a peripheral cause of primary PE, hypothesising that either a thickening of the glans penis nerves, increased myelination and an increased ratio of the thicker and faster A nerve fibres compared with the C nerve fibres; or that the sensory stimuli in patients with primary PE could be conducted by a pathway different from the dorsal nerve. Neither hypothesis has been demonstrated.

In another study, no significant difference was found in the mean latency values of the dorsal nerve SEPs between PE patients (n=14, IELT <3 min, range 0-2.7 min) and controls. Only three patients underwent glans penis stimulation but, in contrast to the earlier study, [12] the glans penis SEP latency in all cases was longer than that from the penile shaft [13].

Individual differences in the neurophysiological properties of penile receptors and effectors may partially account for the speed of the ejaculatory reflex.

Vibratory thresholds

The sensory perception threshold of the penis can be evaluated and measured using penile biothesiometry, in which a fixed frequency variable amplitude vibration is used. The test evaluates the afferent somatic dorsal pathway and has also been used to quantify penile sensory levels in patients with PE.

Rowland *et al.* [14] tested empirically whether penile sensitivity to physical stimulation might distinguish premature ejaculators from men with normal sexual function by measuring penile vibrotactile stimulation in four small groups of men: primary PE (IELT 0-2 min); secondary PE and ED (IELT 0.5 – 2 min); ED alone (IELT 5-7 min); and controls with normal sexual function (IELT 7-10 min). A biothesiometer, modified with variable amplitude, was used to determine the sensory thresholds at various locations on the flaccid penis (without retraction of the foreskin).

Penile sensory thresholds varied in the four groups, with the highest threshold in the control group followed by the PE, PE+ED and ED groups, in descending order. However, the difference between the control and PE group (as defined in this small study) was not significant and the authors conclude that the study indicates that subjective threshold to

vibrotactile stimulation of the penis in men with PE does not differ from that of sexually functional men [14]. However, interpretation of these results in the light of contemporary definitions of PE is somewhat different, as the PE group was small and included men who would not fit the contemporary definition (for example, IELT was >1 min for some men and was estimated rather than measured).

The study did find a strong correlation between the self-reported IELT and penile sensory threshold, with low thresholds related to short latencies; this is independent of the definition of PE used and is still relevant today. It can be concluded, therefore, that the study does provide some evidence that ejaculation latency is related to penile sensitivity. Ejaculation is a phenomenon that occurs during penile erection and in one study [15] was used as a surrogate of penile sensitivity in PE patients in the erect state [15]. They used a high kind precision digital vibrometer to evaluate the penile sensitivity thresholds of 18 men with primary PE (defined as an IELT of <1 min) and 15 controls with normal sexual function, at a range of locations on the penis when flaccid, and also with an 'artificial' erection following injection of PGE₁ 10 µg.

No significant difference was found between the two groups in vibratory threshold at the glans penis, dorsum of the penile shaft or frenulum of the penis, in either the flaccid or erect state. Also, in contrast to other studies, no difference was seen in penile vibratory thresholds between the flaccid and erect state in the PE or control group. The authors acknowledge that these negative results might be related to the small number of subjects and variations caused by age differences [15]. However, the authors point out that penile sensitivity as evaluated by many researchers, including themselves, does not represent the sensory threshold that finally induces ejaculation [15]. Little is known about the intensity of stimulus required to induce ejaculation, or the modulating influence of the cerebral cortex on the ejaculatory reflex.

A different approach was employed in one of many studies by Xin *et al.* [16]: a biothesiometer was placed on the index finger, right and left lateral aspects of the penile shaft, glans penis and mid scrotum of 120 men with primary PE (with an average IELT of 1.1 min; range 0-3 min) and 66 controls with normal sexual function [16]. The patients were asked to inform the examiner of the first sensation of vibration as the amplitude of vibration was slowly increased, or the disappearance of the sensation as the amplitude was decreased.

There was a statistically significant decrease in vibratory threshold on the glans penis and penile shaft in patients with PE ($p < 0.001$), but not at other sites such as the index finger or scrotum [16]. In the normal control group, but not the PE group, the vibratory threshold at the glans penis and penile shaft showed a significant age-dependent increase in vibratory threshold [16]. It has been suggested that this study was subject to possible bias as the vibrator was handheld (allowing possible variation in the pressure applied) and that the stimuli were presented in a non-random order [17], which might be important given that men with PE often believe themselves to have genital hypersensitivity [17].

Correlation between penile sensitivity and ejaculatory latency (ELT) in normal men

In men without PE, i.e., presumably 'normal' men, no correlation has been found between penile sensitivity at any of the penile surface areas and intravaginal, masturbatory or laboratory ELTs [18], indicating that ELT variability in normal men cannot be explained by differences in penile sensitivity. However, the authors recognise that this does not exclude the possibility that penile sensitivity might have a role in a lowered ejaculatory threshold in men with PE.

Summary

Some electrophysiology studies have found that men with PE appear to have a heightened sensory response to penile stimulation, with a vibration threshold significantly lower than that of normal men, as well as other abnormal autonomic reflex pathways for the ejaculatory process, including shorter bulbocavernosal latency time and higher bulbocavernosal evoked potentials. However, other studies have shown no significant difference between these variables in men with PE and normal controls. In many studies, confounding variables such as age and circumcision complicate interpretation. The problem is that PE is not defined sufficiently in most studies to determine whether patients fit the contemporary definition of PE. Correlation between IELT and vibratory thresholds are more useful as they are independent of self-diagnosis or the application of arbitrary IELT cut-offs. This has only been evaluated in one study to date where a significant correlation was seen between IELT (albeit estimated) and penile sensory threshold [14].

The major problem in these studies is that most were undertaken in the absence of a precise diagnosis of PE or normality. In fact, in many studies patients could be classified as suffering with PE with IELTs three to four times outwith the ISSM definition. Under these circumstances, even if the clinical and clinical neurophysiological data strongly supportive or strongly refuted the link with penile hypersensitivity, the evidence would be of little value.

DATA FROM CLINICAL TRIALS EXPLORING DRUG TREATMENTS

Oral Therapies

Electrophysiological studies

Treatment with daily fluoxetine or clomipramine in two independent studies significantly increased penile sensory thresholds in men with PE [19, 20] although, in both cases, no change was observed in either the amplitude or latencies of sacral evoked response and cortical SEP (in contrast to the decrease in amplitude of SEP reported following the use of SS cream [21]). Increased penile sensory thresholds might, therefore, be a relevant mechanism for the effectiveness of SSRIs in increasing IELT in men with PE.

Topical therapies for PE on electrophysiology

SS-cream consists of extracts of nine natural products of herbal and animal origin, several of which are reported to have a local desensitising effect [22]. Evaluation of penile biothesiometry and SEP in men with PE showed that SS-cream increased penile sensory

perception threshold, prolonged the latencies of SEP and decreased amplitudes of SEP [21, 23], suggesting that SS-cream has a local desensitising effect on penile hypersensitivity and/or hyperexcitability in patients with PE.

The same group investigated the effect of various doses of SS-cream or placebo (double-blind) on the vibration threshold of the glans penis of 53 men with primary PE (estimated IELT of >3 min, mean IELT 1.45 ± 0.57 min) one hour after application of the cream [24]. After a total of 153 tests with various doses of the cream there was a significant dose-dependent increase in the mean vibratory threshold of the glans penis from baseline. The authors concluded that SS-cream can increase the penile sensory threshold [24].

Clinical Studies in PE patients

Several clinical studies on EMLA have shown that the local anaesthetic-containing medication can prolong ejaculation latency time [25]. The issue in these relatively small studies is if this can be achieved in the absence of a generalised penile 'numbing' or hypoaesthesia.

Late in 2008, phase III data emerged on the use of a new aerosolised topical form of lidocaine-prilocaine, PSD502 [26]. The study was conducted on three hundred men with an average age of 35 who were clinically diagnosed with PE across 32 investigational centres in the UK, Czech Republic, Hungary and Poland.

Data from the study showed that PSD502 produced a highly clinically and statistically significant increase from baseline in all three co-primary study endpoints, and also in all secondary endpoints. The IELT for PSD502 was four minutes, compared with one minute in placebo ($p < 0.0001$). There was a seven-point difference between PSD502 and placebo in Ejaculatory Control ($p < 0.0001$), and a six-point difference between PSD502 and placebo in Sexual Satisfaction ($p < 0.0001$), where a two-point difference in a 16-point range is considered clinically significant. There was a three-point difference between PSD502 and the placebo in the Index of Premature Ejaculation domain for distress ($p < 0.0001$).

The number of patients in the PSD502 group who rated the quality of their orgasm as good or very good increased from 20% at baseline to 62% after treatment. In comparison, the number of placebo-treated patients with this rating decreased from 21% to 19%.

PSD502 was well tolerated and there were no serious adverse effects, with only 2.6% of patients reporting treatment-related adverse effects in the PSD502 group, compared with 1% in the placebo group. Of these localised adverse effects, one patient who received PSD502 (0.5%) reported temporary numbness of the penis, which was described as mild. The incidence of systemic side effects such as headache was less than 1%.

An additional phase Ibis/III clinical trial has recently been completed and preliminary data is available (Carson/Wyllie SMSNA abstract 2009). In general, a qualitatively and quantitatively similar picture emerged; there were clinically and statistically significant changes in the IELT

and all domains. Adverse side effects during this study indicated that four patients (2.4%) reported hypoaesthesia of the reproductive system.

DISCUSSION

Until recently, there was no unequivocal evidence that penile hypersensitivity was the underlying aetiology for PE. This was due in part to the methodology involved, as well as the definition of normality of PE used in the analysis of the data. All studies were completed prior to the ISSM definition. The clinical profile of PSD502 does, however, provide substantial additional, albeit circumstantial, evidence.

The clinical profile of PSD502, i.e. prolongation of ejaculation latency without penile desensitisation (in all but one patient), must arise from the local anaesthetic actions of the ingredients (lidocaine and prilocaine). Local anaesthetics interact on sodium channels within sensory nerve endings [27] to alter axonal conduction to spinal and supra-spinal centres (Figure 1).

The nerve receptor density of the glans penis is higher than in any other part of the body and has a high tactile threshold [28], therefore it is more sensitive than most other parts of the body [29]. It stands to reason, then, that topical treatments providing local anaesthetic, and thus reducing the sensitivity of the glans penis, should offer a level of efficacy in assisting the delay of ejaculation. In other dysfunctions there are clinical parallels as to why this can be achieved without a generalised 'numbing' or hypoaesthesia. In hypertension, most effective drugs only restore the status quo, i.e. the patient becomes normotensive without becoming hypotensive [30]. It is assumed, therefore, that PSD502 acts to address the imbalance in PE (i.e. hypersensitivity without producing the clinically effective dose range of hypoaesthesia). It is possible, however, that the selectivity of the effect is a result of the localised administration of the spray.

Although animal research may give some clues, the precise mechanism of the ejaculatory reflex in man is unclear, but will undoubtedly involve a variety of peripheral afferent-efferent reflexes and spinal and supra-spinal pathways (Figure 1). The underlying patho-physiology of PE is likewise unclear. The clinical benefit of off-label SSRIs and dapoxetine is likely to arise from the ability of these drugs to rectify a central imbalance in serotonergic systems within the brain. The action of desensitising creams such as EMLA is peripheral by an action on sensory afferent pathways, thereby altering signal transmission to the brain; a selective sensory 'dampening' action at this level would, in theory, be effective independent of the aetiology of PE [31].

Overall, although circumstantial, the clinical profile of PSD502 is consistent with penile hypersensitivity being a major contributor in the manifestation of PE. In essence, PSD502 is assumed to act by restoring normal levels of penile sensitivity. If there were no underlying hypersensitivity, a generalised hypo-aesthesia 'glandular numbing' would have occurred.

CONCLUSION

The literature provides some degree of circumstantial evidence that penile hypersensitivity may be an underlying cause of PE. Much additional support comes from the clinical profile of

PSD502, where ejaculation latency is achieved in the absence of generalised penile desensitisation. A direct association remains to be demonstrated. The major problem in these studies is that most were undertaken in the absence of a precise diagnosis of PE or normality. Indeed, in many studies, patients could be classified as suffering with PE with IELTS three to four times outwith the ISSM definition. Under these circumstances, even if the clinical and clinical neurophysiological data strongly supported or strongly refuted the link with penile hypersensitivity, the evidence would be of little value. Prospective studies using the ISSM to stratify patients and volunteers will be required to resolve the debate.

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