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European Association of Urology

Update on Pathophysiology of Premature Ejaculation: The Bases for New Pharmacological Treatments

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Article info

Keywords:
Ejaculation
Erection
Premature ejaculation
Erectile dysfunction
Impotence

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Abstract

Even though premature ejaculation is the most widespread pathology of sexual behavior, it is still considered a psychological disease. Organic etiologies are only now becoming more evident.

Premature ejaculation is largely under-diagnosed and under-treated, while erectile dysfunction has received great scientific and clinical attention in recent years. There are plenty of reasons for this: (i) PE is classically considered as psychogenic in nature; (ii) it is traditionally treated with behavioral psychotherapies; (iii) clear and accepted clinical definition(s) are lacking; (iv) the etiologies are largely unknown; (v) the pathogenesis is still obscure – there is a lack of awareness and acknowledgement of PE as a symptom of medical disease; (vi) lacking a medical presence in the field, requests for help from patients are low. Finally, erectile and ejaculatory dysfunctions frequently overlap. For all these reasons, an update on pathophysiology of premature ejaculation is to be considered the base for new pharmacological treatments.

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1. Introduction

Are new pathophysiological insights able to change current therapeutic approaches to the most diffuse male sexual symptom, premature ejaculation (PE)? Medical sexology and sexual medicine are young, developing disciplines, rapidly changing a scenario that, in the immediate past, was substantially stationary. Thanks to the development of the first effective oral treatment of impotence, this effort is clearly much more evident in the field of erectile dysfunction (ED). However, after the pioneering efforts of some researchers, who are the bibliographical framework of this review article, PE, a symptom previously considered exclusively psychogenic in nature, entered in the categories of the evidence based medicine.

1871-2592/$ – see front matter © 2006 European Association of Urology and European Board of Urology. doi:10.1016/j.eeus.2006.05.002

Table 1 – The five pathogenetic causes of premature ejaculation

Mechanism of action	Etiology
Psychorelational	Anxiety, relational problems
Neurobiological	Serotonin hyperactivity, penile hypesensitivity (multiple sclerosis)
Urological	Prostate inflammation
Hormonal	Hyperthyroidism
Andrological	Erectile dysfunction

For humans, a species with a symbolic and cultural sexual behavior, the timing of ejaculation has become an important feature of a couple's sexual health. As one of the principal aims of human sexuality is pleasure, men have learned to control ejaculation and to enhance their own and their partners' enjoyment so that the ejaculation control is not to be considered *natural*, but, on the contrary, almost completely *cultural*. For this reason lack of ejaculatory control has a profound psycho-relational basis and its treatment is susceptible to male and/or couple's psychotherapy. In other animals, sexual intercourse is in fact a brief episode. By an adaptive mechanism (*coitus citus*), male genitalia are in fact designed to ejaculate quickly.

Premature ejaculation was rarely described in classic sexology. Only after the advent of reliable contraceptives, the sexual and feminist revolution of the mid 1960s, and the ''discovery'' of the female orgasm, did PE become important in the cohort of symptoms connected with male sexual performance [1].

Aim of this article is to describe the five pathophysiological aspects of PE leading to different therapies (Table 1).

2. Definition, diagnosis, and epidemiology

Some authors define PE on the basis of time: ejaculation from 1 minute up to 7 minutes after penetration has been considered as pathological. Others consider the number of penile thrusts, suggesting from 8 to 15 thrusts as a criterion for PE, Masters and Johnson suggested that a man experienced PE if he was unable to delay his ejaculation until his partner was sexually satisfied in at least 50% of their sexual relations, while Kaplan considered it as the persistent or recurrent inability to voluntarily delay ejaculation (see [2] for bibliography). A simple, objective method to define PE was proposed by Waldinger et al. in 1994 [3]. The ''intravaginal ejaculation latency time'' (IELT) is the time from the start of vaginal intromission to the start of intravaginal ejaculation. For research purposes, but also for clinical assessment and therapeutic monitoring, this method may be considered the most objective in the evidence-based sexual medicine.

Several definitions have been proposed for PE (see [4] for references), considering the partner, the timing, the presence of distress. On the basis of all this, we recently proposed a new definition of PE, which is diagnosed on the basis of the pathological IELT, as measured by the stop-watch method, with a feeling of loss of voluntary control and distress or relational disturbances. From this definition, two different forms of PE arise: ''Objective PE'' (which is defined ''Severe'' when ejaculation occurs before penetration or with a IELT $\leq$ 15 s, ''Moderate'' with a IELT $\leq$ 1 min, and ''Mild'' with a IELT $\leq$ 2 min), and ''Subjective or Relational'' PE, when the loss of voluntary control is experienced with distress by the male or both partners [4].

The simplest way to subclassify PE is to consider whether the symptom begins when a male first becomes sexually active (primary, lifelong), or occurs after a period of normal ejaculatory control (acquired). Premature ejaculation can be absolute (irrespective of partners or context, permanent) or relative (to a partner and/or context, situational). Ejaculation may take place before penetration (*ante portas*) or suddenly during coitus (*intra moenia*). It can be found in the absence (simple) or presence (complicated) of other sexual symptoms that can be cause or caused of/by PE [2].

Premature ejaculation is the most diffuse male sexual disorder [2]. It has been anecdotally reported as affecting from 5% to 40% of sexually active men, depending on age. It is widespread in adolescents, young adults, and other sexually naive males. Despite its very high prevalence, PE is rarely a reason for medical or sexological consultation. This is probably due to both cultural reasons and the erroneous belief that effective pharmacological treatments for PE do not exist. The USA National Health and Social Life Survey and Global Study of Sexual Attitudes and Behaviors both reveal a prevalence of 21% for PE [5]. Although some authors found the same global prevalence across all age groups [6], in a selected population of 755 Italian subjects attending an outpatient clinic for sexual dysfunction, PE was confirmed as being age-dependent. Patients reporting PE were younger and showed a higher prevalence of anxiety symptoms when compared to the rest of the sample [7].

Table 2 – Psychosocial factors involved in premature ejaculation

- GUILT (belief that the sexual activity is sinful, e.g. premarital or extramarital sex)
- FEAR (of pregnancy, sexually transmitted diseases, being discovered)
- ANXIETY (general or related to sexual performance)

3. The psychorelational pathogenesis

While for impotence the list of etiological causes is large and growing, for PE it is still quite short (Table 1), being the psychological causes the most studied (Table 2). For this reason, the psychophysiological model has been applied to the study of ejaculatory response for well over four decades. This approach illustrates the complex relationship emerging among cognitive, affective, and physiological components of ejaculation control [8]. Distortions of belief and false convictions about sexuality are established in childhood as a consequence of adverse influences on sexual behavior. This, in a Freudian perspective, may lead to sexual dysfunction such as PE. Classic psychoanalytic theories identified a sadistic or narcissistic behavior in PE. For other psychoanalysts, however, men who ejaculate prematurely are typically passive and masochistic in their marriage and obsessive-compulsive in character [9]. These theories were the basis of Helen S. Kaplan's first idea, that PE is the result of an unconscious hatred of women [10]. By ejaculating quickly, a man symbolically and physically ''steals'' the woman's orgasm. However, the same researcher rejected her own theory when she found that men with PE do not have any particular neuroses or personality disorders.

Premature ejaculation has been considered frequent, if not normal, during early sexual experiences. Kaplan's original etiologic explanation is also connected with the role of early experiences: the man with PE has not allowed himself to receive the sensory feedback of those sensations occurring immediately before orgasm which would enable him to bring his ejaculatory reflex under voluntary control [10]. She compares this etiologic mechanism to the control of enuresis obtained when a child recognizes the sensation of a full bladder. In the same way, lack of awareness of pre-ejaculatory sensations may lead to PE (Table 3).

Table 3 – Personality characteristics of men with premature ejaculation

A) INSECURE and ANXIOUS	with aggressive and castrating women
B) COMPETITIVE	always demonstrating their virility
C) YOUNG and NAIVE	at their first sexual experiences

Finally, the role of anxiety (for sexual performance generally, but also for other, extra-sexual reasons) has been frequently raised as a cause [11]. This is in keeping with Kaplan's theory: anxiety may block pre-ejaculatory sensations. It should be noted however that anxiety may also be the effect rather than the cause of PE (Fig. 1, panel A).

4. Sexological therapies for PE

The cognitive feedback from PE can lead to a 'performance anxiety', which may combine with other conditions to further impair ejaculatory control. Performance anxiety acts as a positive feedback in a vicious circle described in Fig. 1, panel A. For these reasons, a psychological approach is always useful in PE treatment.

The groundbreaking work of Masters and Johnson is at the origin of behavioral therapies, which have been modernized with the so-called *new* sexual therapy of Kaplan, who offered a psychodynamic, or transactional, account of the dyadic causes of sexual dysfunction. While behavioral therapies can be considered as the first effective treatment of sexual symptoms, they need further research and validation.

Basically, the method is a non-demanding genital stimulation, which may proceed to erection but not to orgasm (stop-and-start, squeeze). Following this, a brief intromission is allowed in the female on top position. During this exercise, the woman inserts the penis into her vagina, thrusts a few times, and then dismounts before any anxiety is built up. Finally, after several weeks of these first steps, the couple is free to copulate in any position. The limitation of genital activity should reduce the pressure to ''perform'' [10,12]. In addition, the patients learn to (i) evaluate pre-orgasmic pleasure, (ii) be aware of the ''orgasmic point of no return'', (iii) prolong the *plateau* phase, and (iv) distinguish between excitation and orgasm.

Unfortunately, therapeutic success in sex therapy is often unpredictable [13], and is more frequent in highly motivated couples with a good relationship, in young age, in sexual dysfunction of recent onset, and in relationship of recent onset. Behavioral therapies for PE, although revealing some immediate gains, remain beneficial to only a minority of men three years after treatment ends. There are many reasons for therapy failure. The most important is probably the ''sticking to the symptom''. In couples with a long term sexual problem (such as PE, or ED) vicarious mechanisms are structured to

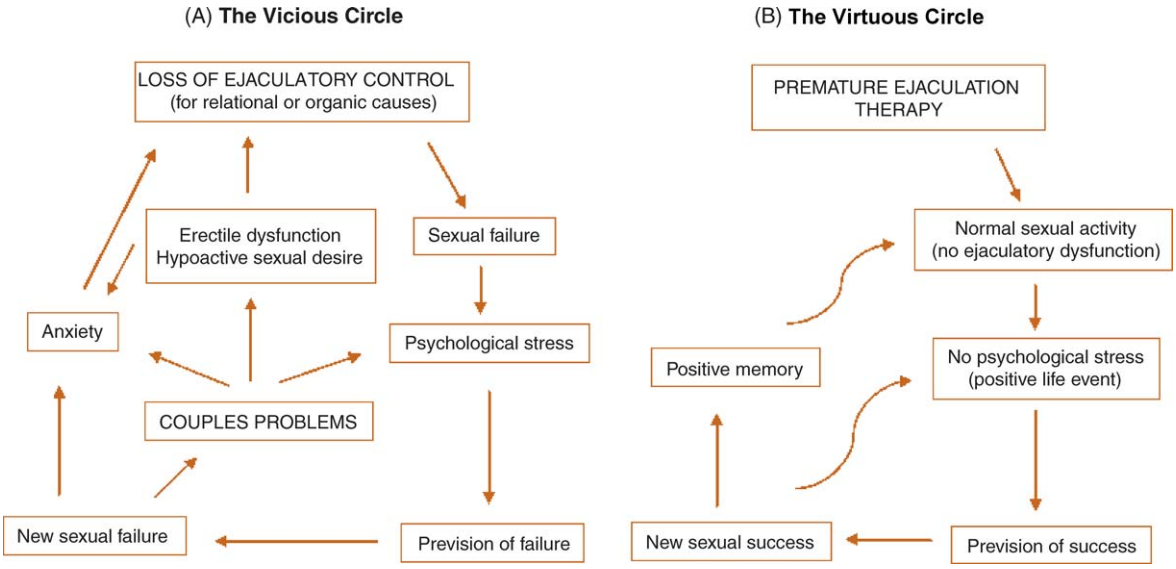

Fig. 1 – The vicious and the virtuous circle of premature ejaculation.

overcome the absence of sexual happiness. These are couples that are still together, despite their problem. Even if they strongly desire recovery, they may subconsciously fear that cure might destroy their relationship. This is a frequent condition in which the help of sexual therapist may be decisive.

Sexological therapies are still used without substantial modification of the original definitions and format. The field of psycho-sexology has only recently taken seriously the task of scientifically demonstrating the efficacy of sex therapies [14]. Following this way, talking therapies will continue to play a pivotal role in sexology, not as an alternative to, but probably in conjunction with medical treatments. However, some points need to be addressed by a new research effort. While the central role of couple dynamics in the genesis and continuation of many ejaculatory disorders cannot be ignored, no single theoretical approach adequately incorporates the totality of intra- and interpersonal dynamics [15]. Behavioral therapies require the active participation of the partner, but often, for socioeconomic or cultural reasons, this is not possible. The experience of the past 40 years suggests that North American patients agree more easily than Europeans to behavioral treatment and its ''gymnastic'' aspects. Behavioral therapies are inappropriate for subjects in whom profound personal or relationship problems underlie sexual disorders. Furthermore, the behavioral approach is designed for the couple. These methods therefore cannot be easily proposed to single males with multiple or occasional partners, who may not collaborate with the sexologist. It should be noted that this is a frequent condition of young men in western societies. Additionally, the success rate of behavioral therapies has been difficult to duplicate and verify in controlled studies.

Medical therapies, with some limitations, are emerging and scientific production on this is continuously growing. This suggests three possible scenarios for the future: (i) the decline of the sexual therapist without medical training, (ii) the development of new roles for sex therapists and medical sexologists, and (iii) integration of the diagnostic and therapeutic roles of medical and non-medical practitioners. To obtain the last possibility, a renewed effort must be made to validate psycho-sexological therapies.

5. The neurobiological pathogenesis

Little information, which in any case mostly relates to animals, has been produced on central ejaculation control. In humans, by positron emission tomography, it has been measured an increase in regional cerebral blood flow (rCBF) during ejaculation in several mesodiencephalic structures as well in other brain regions such as neocortex [16]. The serotoninergic system acts as a suppressor of the ejaculatory reflex. In fact, both serotonin reuptake inhibitors and serotonin agonists determine the extension of ejaculatory latency [17]. In contrast, the dopaminergic pathway may act as an ejaculation stimulator [18] through the D_2 receptors [19]. Efferent innervation is somatic through the parasympathetic sacral outflow, originates at S2-S4 and

runs through the pudendal nerve, causing clonic contractions of the striated male genital tract muscles.

Among peripheral neurobiological causes, major neurological disorders are rare (multiple sclerosis, spina bifida, tumor of the spinal cord). The roles of short frenum of prepuce, penile hypersensitivity and reflex hyperexcitability have been investigated in different studies [20,21] using penile biothesiometer or cortical and sacral somatosensory evoked potentials, and showing that this condition could be an important contributing factor to PE. In fact, patients with PE may have penile hypersensitivity, providing further evidence for an organic basis.

On the basis of the role of the serotoninergic system in the ejaculation control, the researcher who gave the best recent scientific production in the field, Dr. M. Waldinger, wrote that PE is not a psychological disorder but a neurobiological phenomenon due to a chronic – possibly genetic in nature – serotoninergic hypoactivity [22]. This is a very interesting pathophysiological explanation, although some of the arguments sustaining this thesis seem to be weak. The fact that various psychological hypotheses and psychotherapies, as above discussed, have not been adequately investigated does not demonstrate that they are false. Animal studies, demonstrating the role of serotoninergic system in ejaculation, cannot be easily extrapolated to human sexual behavior. The effectiveness of serotoninergic antidepressants demonstrates that central neurotransmission is involved in ejaculatory control, but not that serotonin hypoactivity is the cause of PE. In fact, many psychological disturbances (such as stress) provoke a neuroendocrine imbalance. On the other hand, the classic psycho-sexological approach affirms apodictically that PE is a psychosexual disorder which is ''all in the mind'', with a psychogenic etiology and pathogenesis that must be treated with psychotherapy [23]. Both positions are extreme, and also dangerous for the growth of sexology and patient well-being.

6. Neurobiological therapies for PE

Although off-label, drugs increasing serotonin levels (such as antidepressants) are largely prescribed in PE. The effectiveness of tricyclic antidepressants [24] and selective serotonin reuptake inhibitors (SSRIs) (see for references [25]) is probably due to their effect of increasing penile threshold without changing the amplitude and latency of sacral evoked response and cortical somatosensensory evoked potential.

In drug treatment research of PE it has been recommended to use a randomized double-blind prospective design, the use of the IELT, the use of a stopwatch at each coitus both during a baseline period and during drug treatment and a definition of PE as an ejaculation that occurs within 1 min after vaginal penetration [26]. However, current methods and measures utilized to assess treatment outcome in PE are standardized with some difficulty [27]. Antidepressant drugs are generally effective in restoring ejaculatory control. However, as these drugs may significantly worsen erectile dysfunction, they are strongly contraindicated for patients suffering from both PE and impotence (see later).

Many well-designed clinical studies conducted with SSRIs and antidepressants support Level 1 evidence on the efficacy of Paroxetine (20–40 mg), Clomipramine (10–50 mg), Sertraline (50–100 mg), Fluoxetine (20–40 mg). Meta-analysis of all drug treatment studies has demonstrated that paroxetine exerts the strongest ejaculation delay (mean IELT fold increase of 8.8) [28].

While pharmacological treatment of PE has been demonstrated to be reliable and efficacious, its therapeutic window is frequently localized to the period of drug assumption. In fact, after therapy, PE once more affects most patients who obtained good ejaculatory control. This is in keeping with the evidence that antidepressants are a symptomatic therapy.

The best outcome is obtained when drugs are used for a short period (60 days, in our experience) during which sexual therapy with the couple is also performed. The pharmacological aid, delaying the emission phase, allows the patient to understand what is happening in his body before the point of no return. In this way, the ability to control ejaculation creates a ''positive memory'' of sexual success, which will help the patient overcome the problem (Fig. 1, panel B).

Dapoxetine may represent the first of a new category of SSRIs [29]. It is a short-acting not useful for depression therapy, but, for this reason, functional for on-demand therapy of PE. Although this drug has pharmacological similarities to other drugs of the same class, its efficacy after acute administration sets it apart and suggests a different mode of action [30]. Its physicochemical and pharmacokinetic properties and its clinical efficacy make dapoxetine a hope for on-demand treatment of PE.

Finally, topical agents such as anesthetics [31] and herbal products [32] have been studied in neurobiological PE due to penile hypersensitivity. The use of these products, however, is not diffuse.

7. The urological pathogenesis and therapy

It has been demonstrated that there is a high prevalence of chronic prostatitis in premature ejaculators when compared to an age-matched control group, suggesting that a prostatic infection and/or inflammation is a predisposing condition for PE [33]. Evaluating segmented urine specimens before and after prostatic massage and expressed prostatic secretion specimens from 46 patients with PE and 30 controls by bacteriological localization studies, prostatic inflammation was found in 56.5% and chronic bacterial prostatitis was demonstrated in 47.8% of subjects with PE. Considering the role of the prostate gland in the mechanism of ejaculation, we suggest a role of chronic prostate inflammations in the pathogenesis of some cases of PE. Interestingly, our findings have been fully confirmed in Chinese [34] and Egyptian [35] large cohorts of patients with PE.

For all these reasons, we suggest to include in the diagnostic protocol of PE the prostate evaluation by transrectal ultrasonography and the standardized Meares & Stamey protocol.

In a case report, a 31-year-old patient with an inflamed prostate gland and, unknown to his doctor, PE, both of which were treated successfully by the antibiotic ciprofloxacin [36].

8. The hormonal pathogenesis and therapy

We recently showed that PE had a significant correlation with suppressed TSH values, a marker of thyroid hyperfunction, in a selected population of andrological and sexological patients [7]. We later demonstrated that hyperthyroid patients show a very high prevalence of PE, which is reverted when euthyroid status is achieved [37].

As the relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, three possible sites of action have been hypothesized: the sympathetic nervous system, the serotoninergic pathway and the endocrine/paracrine system.

Most of manifestations of thyrotoxicosis and sympathetic nervous system activation overlap. This may suggests a similar action of both systems on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma cathecolamines and their urinary metabolites are usually normal in hyperthyroidism. On the other hand, there are studies showing that thyroid hormones augment sensitivity to β-adrenergic agonists by increasing the β-adrenoceptor density and G_s/G_i protein ratio with an overactivation of adenylate cyclase. This leads to an increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may precipitate both PE and ED, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability.

Considering the neuropsychic reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, emotional lability), PE may be a nonspecific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotoninergic pathway, leading to diminished ejaculation control. In animals with experimentally-induced hypothyroid states, increased serotonin turnover in the brainstem is consistently reported and thyroid hormones replacement is associated with increased cortical 5-HT concentrations and augmentation of serotonergic neurotransmission by desensitization of the 5-HT inhibitory 5-hydroxytryptamine$_{1a}$ autoreceptor (auto-inhibition). Finally, thyroid hormone receptors have been described in the animal and human testis, and may also be present in other male genital tract structures triggering ejaculation [38].

9. The andrological pathogenesis and therapy

In many cases, PE is the only sexual complaint presented. Some patients consider it easier and less humiliating to admit to PE caused by ''enthusiasm'' than to other sexual dysfunctions, such as ED. For this reason, the possibility that other sexual problems coexist with the PE should always be investigated.

It could be inferred that PE and ED share a vicious circle, where a man trying to control his ejaculation instinctively reduces his level of excitation (which can lead to ED) and a man trying to achieve an erection basically attempts to increase his excitation (which can lead to PE). Thus, the reduced time to ejaculation cannot be considered as a rare early manifestation of ED, although it may occur with an unstable erection due to fluctuation in penile blood flow. In this case, the subject may ejaculate early to hide the weakness of the erection. On the other hand, some men with PE may express their complaint as an ED, as penile detumescence after ejaculation occurs rapidly. Furthermore, ED may be superimposed on lifelong PE by efforts to minimize sexual excitement. Another linking mechanism is that the lack of ejaculatory control may generate

reactive impotence, due to anxiety arising from poor sexual performance.

In a cohort of 184 subjects attending our Outpatient Clinic for sexual dysfunction 121 claimed to be affected by simple ED, 52 by simple EP, and the remaining 11 by both conditions. However, careful sexological analysis demonstrated the presence of PE prior to ED in 29 subjects with ''simple'' ED, and mild to moderate ED prior to or concomitant with PE in 21 patients with ''simple'' PE. This suggests that ED and PE might be co-morbidities [4].

It has been suggested that type 5 phosphodiesterase (PDE5), the erectolityc enzyme localized in the corpora cavernosa, may play a role in the mechanism of ejaculation, as it is also expressed in the vas deferens [39]. Perfect erection control implies good ejaculation control and *vice versa*, thus the use of PDE5 inhibitors may reduce performance anxiety (a major contributing factor for PE). Furthermore, PDE5 inhibitors may shorten the refractory time, allowing a second intercourse with less pressure.

For patients with erection weakness and PE, treatment with intracavernous medications [40], sildenafil alone [41] or in combination with paroxetine [42,43] has been examined and found effective. Finally, Tadalafil does not affect the pharmacokinetics of dapoxetine, whereas sildenafil increases the dapoxetine AUCinf by 22%; these effects were deemed not clinically important. Dapoxetine did not appear to affect the pharmacokinetics of tadalafil or sildenafil. Thus, this combinations is well tolerated [44].

10. Conclusion

In conclusion, current approaches to treating PE have mixed efficacy and, in all cases, significant drawbacks. The identikit of the ''Holy Grail'' for PE treatment is as follows: effective, practical (oral administration), on demand use, rapid onset, swift elimination, and low incidence of adverse effects.

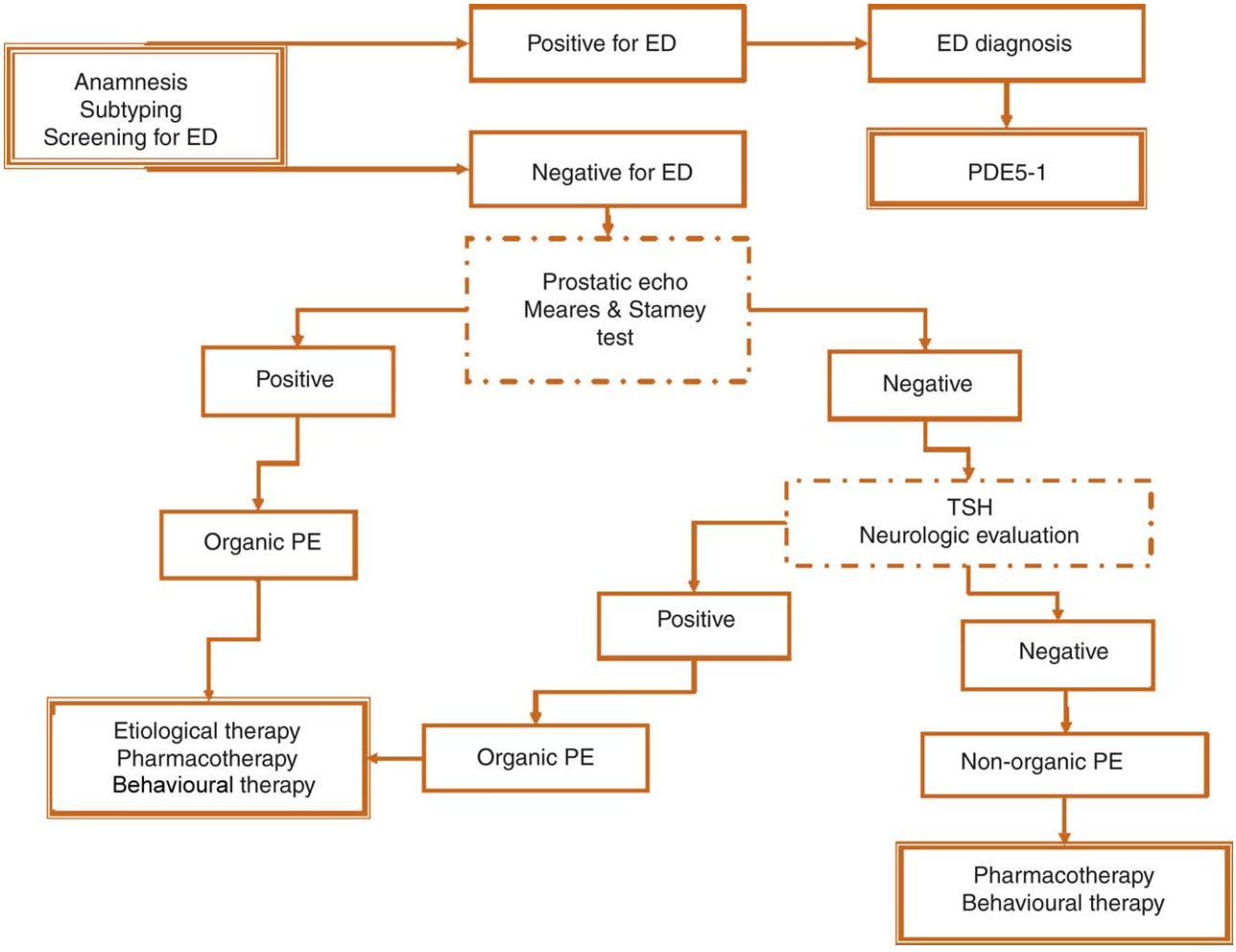

Fig. 2 – Proposal of a practical algorithm for diagnosis and psychosexual and medical treatments of PE (From refs. [1,4], mod.). Dashed lines indicate diagnostic procedures so far not accepted by other guidelines.

Despite the fact that it can be successfully treated with drugs, PE is still under-diagnosed (see in the Fig. 2 a proposal for a diagnostic flowchart) and under-treated. However, increased medical awareness, careful diagnosis and sub-typing, the recognition of the ''specific weight'' of ED and EP in a single patient, together with the forthcoming availability of new drugs specifically designed for EP, will give the andrologist and the medical sexologist a new opportunity to treat the severe suffering of many patients.

Acknowledgments

Our compliments and gratitude to Dr. Rosaria Caruso for adapting their English expertise to our needs. This paper was partially supported by an unrestricted Pfizer grant, by an Italian Ministry of Research and Education grant, by the CIPE grant and by the PRIN 2003 and 2005 grant.

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CME questions

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1. It could be a cause of premature ejaculation:
   A. Psychosis
   B. Prostatitis
   C. Hypothyroidism
   D. Lung cancer

2. The pharmacological therapy of PE is currently based on:
   A. Testosterone
   B. Estrogens
   C. SSRI
   D. Benzodiazepines

3. Between the following SSRIs, which one is more efficacious in IELT prolongation?
   A. Paroxetine
   B. Fluoxetine
   C. Sertraline
   D. Citalopram

4. For the screening of PE is to be considered useful:
   A. Rigiscan test
   B. Meares & Stamey test
   C. Testosterone evaluation
   D. Glucose evaluation

5. Dapoxetine is
   A. An ansiolytic
   B. A hormone
   C. A SSRI with long half life
   D. A short-acting SSRI

6. The IELT is
   A. A test to diagnose PE
   B. A therapeutic tool
   C. An objective way to measure PE
   D. The central neurobiological network controlling ejaculation