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REVIEW

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Fortacin™ spray for the treatment of premature ejaculation

Hartmut Porst, Andrea Burri

Private Institute for Urology, Andrology and Sexual Medicine, Hamburg - Germany

ABSTRACT

Premature ejaculation (PE) is a common complaint of male sexual dysfunction affecting men and their partners and consequently causing significant personal and interpersonal distress. Increased sensitivity of the glans penis and abnormalities of the afferent-efferent reflex pathway within the ejaculatory process are involved in the occurrence of PE. Drugs that either selectively reduce penile sensitization or modify the afferent-efferent reflex are well established therapeutic options for PE. Fortacin™ is the first topical treatment to be officially approved for the treatment of primary PE in adult men, and is mentioned as an experimental aerosol (as TEMPE) in the current European Association of Urology guidelines. It was approved for use in the European Union and launched in the United Kingdom in November 2016. Fortacin™ is a eutectic-like mixture of lidocaine 150 mg/mL and prilocaine 50 mg/mL that meets the requirements of an ideal treatment for PE because it is fast acting (within 5 minutes), has durable effects, can be easily used "on-demand", and shows minimal side-effects. The metered-dose spray delivery system allows the desensitizing agents to be deposited in a dose-controlled, concentrated film onto the glans penis consequently reducing its sensitivity. This is translated into a delaying of the ejaculatory latency time without adversely affecting the sensation of ejaculation and orgasmic pleasure. The efficacy and safety of Fortacin™ have been proven by means of increased ejaculatory latency, control, and sexual satisfaction in large scale studies demonstrating the significant benefits for both patients and their partners.

Keywords: Fortacin™, Intravaginal ejaculatory latency time, Lidocaine/Prilocaine, Premature ejaculation, Topical anesthesia

Introduction

Premature ejaculation (PE) is a frequent complaint of male sexual dysfunction and a major source of sexual distress (1). Increased sensitivity of the glans penis and abnormalities of the afferent-efferent reflex pathway within the ejaculatory process are implicated in the occurrence of PE and may contribute to penile hypersensitivity and PE (2). Therefore, a reduction in penile sensitivity is anticipated to prolong intravaginal ejaculation latency time (IELT) without affecting the sensation of ejaculation and orgasmic feelings (3).

There are several definitions of PE and how to accurately capture the phenomenon remains a major debate. Although there is little consensus amongst different organizations and societies regarding the definition and classification of PE, most include the three main accepted dimensions of this condition: short IELT, inability to control ejaculation, and both personal and interpersonal distress.

In 2014, the International Society for Sexual Medicine (ISSM) introduced a new definition of lifelong and acquired PE, representing the first evidence-based, in contrast to purely expert-based, definition (4). According to this definition, PE (lifelong or acquired) is a male sexual dysfunction characterized by: (1) ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration starting at time of the first sexual experience (lifelong PE) or a clinically significant and bothersome reduction in IELT, often to about 3 minutes or less (acquired PE); (2) the inability to delay ejaculation during all or nearly all vaginal penetrations; and, (3) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy (4, 5).

Epidemiology of PE and quality of life

PE is more than just a short time to ejaculation and the determinants of PE are complex and multifactorial (6). IELT, control over ejaculation, and the sexual satisfaction of the man and his partner have been identified as important interrelated determinants of PE (7). By causing significant personal and interpersonal distress for both the patient and partner, a vicious cycle can develop where the emotional reactions to

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Corresponding author:
Hartmut Porst
Private Institute for Urology
Andrology and Sexual Medicine
Neuer Jungfernstieg 6a
20354 Hamburg, Germany
Porst20354@aol.com

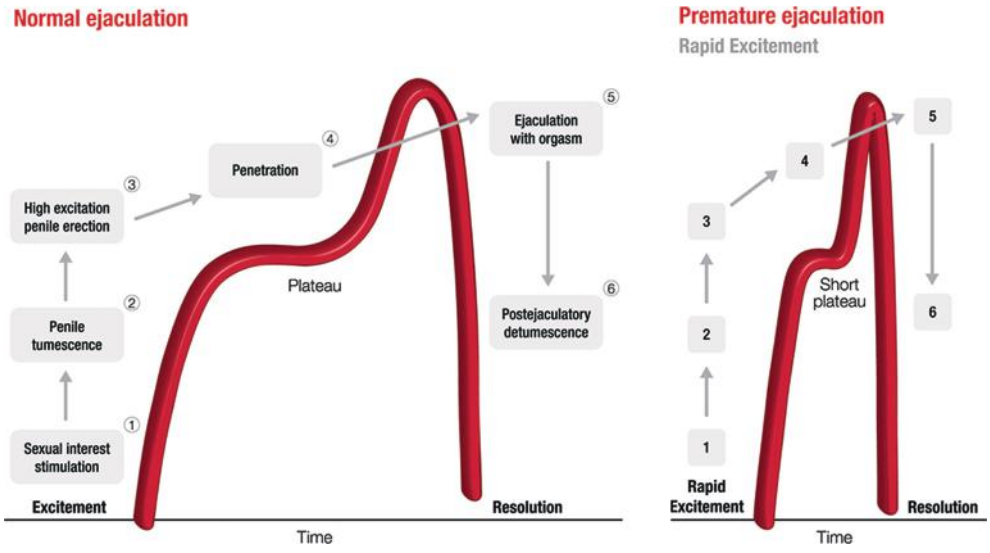

Fig. 1 - Normal male sexual response compared with premature ejaculation. Figure adapted from Kirby 2014 (11).

PE by both parties can exacerbate or perpetuate the problem (6). Indeed, men with PE report having more interpersonal difficulties and higher levels of personal distress than men without PE, and partners of men with PE report having higher levels of relationship problems compared with partners of men without PE (5). Importantly, men with PE feel they are "letting their partner down" and that the quality of their relationship would improve without PE (8).

Apart from interpersonal friction and distress, PE is also associated with significant sexual and psychological comorbidities. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey (9), a comprehensive Internet-based survey conducted on 12,133 men aged 18-70 years in the United States, Germany, and Italy, for example, found that the percentage of men self-reporting comorbid conditions including sexual dysfunctions (e.g., anorgasmia, low libido, erectile dysfunction) and psychological disturbances (e.g., depression, anxiety, excessive stress), was significantly higher in men with PE (22.7% of the total sample) than in men without PE (all $p<0.05$) (9). In the survey, men were classified as having PE based on self-reporting of low or absent control over ejaculation, resulting in distress for them, their sexual partner, or both, with similar prevalence rates among the participating countries (United States 24%, Germany 20.3 %, Italy 20%).

Despite the fact that PE can have serious effects on the psychological well-being and overall quality of life of the sufferer and his partner, only a minority of men seek professional help. The PEPA survey, for example, showed that only 9% of men with self-reported PE had consulted a doctor (9). Embarrassment and a belief that there is no effective treatment available are the main reasons for not discussing PE with their physician (10).

Neurophysiology of ejaculation

The male sexual-response cycle consists of four phases: desire, arousal (erection), orgasm (ejaculation), and resolution (Fig. 1) (11). The process of ejaculation is classified by two distinct phases, "emission" and "expulsion". Sympathetic, parasympathetic, and somatic nervous systems are involved in the ejaculatory response and are coordinated by the spinal ejaculatory generator (SEG) (12, 13). Sensory afferents received by the SEG are coordinated with inhibitory and excitatory influences from supra-spinal sites, as well as biochemical or mechanical information from the accessory sex organs (14). The ejaculatory process starts with the emission of semen into the posterior urethra, induced by increased activity of the sympathetic efferent fibers causing sequential contractions of the epididymis, vas deferens, seminal vesicles, and prostate, alongside the closure of the bladder neck (15). Emission of the semen with dilation of the posterior urethra results in the forceful expulsion of semen out of the urethral orifice induced by activation of the somatic pudendal nerve with subsequent contractions of the bulbospongiosus, bulbocavernosus, and perineal muscles (16). The rhythmical expulsion is mainly influenced by the somatic nervous system and represents an involuntary spinal cord reflex (13). Various neurotransmitters also play a major role in the control of ejaculation, such as the excitatory role of dopamine and the inhibitory role of serotonin or nitric oxide (13).

Although numerous preclinical and clinical studies in recent years have been able to provide a better understanding of the ejaculatory process, many details remain unknown regarding the exact physiology of the ejaculatory process. At present, it is commonly accepted that PE is the result of a dysregulation of the normal ejaculatory process with either over-activation of ejaculation stimulatory or inhibition of ejaculation delaying 5-HT (serotonin) receptors, leading to an involuntary lack of control over ejaculation (17). Clearly, a more in-depth understanding of the normal physiological ejaculatory reflex (Fig. 2) is essential in order to determine the exact underlying pathophysiology of PE.

Rationale for the use of topical anesthetics

The use of drugs that selectively reduce penile sensitization or which modify the afferent-efferent reflex could provide effective therapy for PE, as has been shown with the off-label use of topical desensitizing creams (2). Due to the variable nature of sexual intercourse, spontaneity is an important factor in the treatment of PE. The ideal treatment

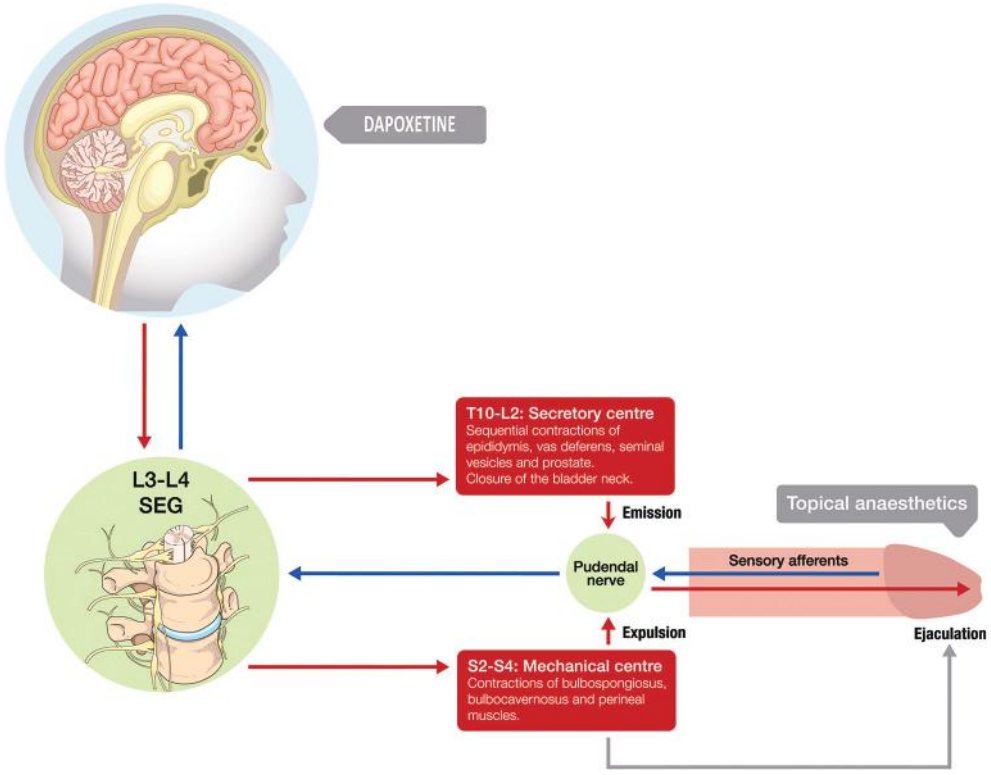

Fig. 2 - The physiological ejaculatory reflex. Ejaculation results from coordinated contractile activity organized by the spinal ejaculatory generator (SEG). Sensory afferent information is received by the SEG which, alongside supra-spinal information arising from specific brain regions, triggers the ejaculatory mechanism during sexual activity. Topical anesthetics applied to the glans penis inhibit penile sensory receptors. Figure adapted from Saitz and Serefoglu 2015 (12).

for PE should therefore be characterized, among others, by a rapid on-set of action, which is effective for "on-demand" use from the first dose, and which is reversible (18). An ideal PE medication should also demonstrate high efficacy on IELT reflected in patient-reported outcomes and, in addition, should show a good safety profile with minimal side-effects and no undesirable effects on the sexual partner.

The use of topical anesthetics to reduce sensitivity of the glans penis has been shown to improve ejaculatory latency without having any adverse effects on the sensation of ejaculation and impairment of orgasmic capacity (19, 20). Unlike the majority of systemic treatments for PE, topical treatments can be used "on-demand" and are unlikely to have systemic side-effects (20). There are, however, a number of disadvantages to some topical treatments including difficult dosing with the potential of either over- or under-dosing causing either erectile difficulties or lack of efficacy, which may interfere with spontaneity (20). Some topical treatments may also need to be used with a condom or washed off prior to intercourse, and again may potentially interfere with spontaneity and arousal.

The paucity of approved pharmacological treatments for PE, has led to an increased "off-label" use of oral antidepressants and local anesthetics.

Clearly, an approved treatment that can be used "on-demand" and which is effective from first use with minimal systemic side-effects is essential (2, 21).

Existing treatments for PE

Of the oral and locally acting topical therapies currently used to manage PE in Europe, only Fortacin™ and dapoxetine have been officially approved for the treatment of PE.

Oral therapies

Dapoxetine, a short-acting selective serotonin reuptake inhibitor (SSRI), was the first oral pharmacological agent developed for the treatment of PE and officially approved for "on-demand" use in adult men aged 18 to 64 years (22). Its mechanism of action in the treatment of PE is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and post-synaptic receptors (23). The recommended starting dose for all patients is 30 mg, taken approximately 1 to 3 hours prior to sexual activity, with no more than one dose taken every 24 hours (23).

Dapoxetine was shown to significantly improve all aspects of PE, including prolonging stopwatch-measured IELT (as primary outcome) and increasing patient-reported outcome measures (i.e. the Premature Ejaculation Profile [PEP] questionnaire and the clinical global impression of change [CGIC] as secondary outcomes), in four randomized, double-blind, placebo-controlled, multicenter, phase III studies of 12-24 weeks' duration in men with PE (n = 4,843) (24-26). A pooled analysis of these studies showed that oral dapoxetine 30 mg or 60 mg (taken as needed) induced significantly greater improvements from baseline in the geometric mean IELT at all time points measured, compared with placebo (27). At week 12, the geometric mean IELT increased from a baseline of approximately 0.8 minutes to 2.0 and 2.3 minutes with dapoxetine 30 mg and 60 mg, respectively, compared with 1.3 minutes for placebo (both $p<0.001$), corresponding to a 2.5-fold and 3.0-fold increase in the geometric mean IELT respectively (vs. a 1.6-fold increase for placebo; $p<0.0001$ for both) (27). Significant improvements in PEP items and CGIC

were also shown with both doses of dapoxetine (all p<0.001 vs. placebo) (27).

Despite its efficacy in the treatment of PE, dapoxetine has also been associated with dose-related systemic adverse effects (AEs), with nausea, dizziness, headache, diarrhea, insomnia, and fatigue as the most frequently reported drug-related adverse events in five randomized, double-blind, placebo-controlled, multicenter, phase III studies in men with PE (n = 6,081) (24-26, 28). Indeed, an integrated analysis of these studies showed that AEs were reported in 47.0% and 60.3% of patients receiving 30 mg and 60 mg dapoxetine, respectively, with AE-related discontinuation occurring in 3.5% and 8.8% of these patients (27). In addition, the Summary of Product Characteristics states that orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine, which should not be used in patients using PDE5 inhibitors due to possible reduced orthostatic tolerance (23).

High discontinuation rates of this drug have also been reported in the setting of real clinical practice. In a study by Mondaini et al. (n = 120), 20% of patients decided not to start dapoxetine with fear of using a "drug" being the most frequently reported reason (29). Moreover, of the 80% who started therapy, 26% stopped taking dapoxetine after 1 month due to side effects and lack of efficacy. Only 10.4% of patients continued the treatment for over one year. The main reasons for discontinuing the treatment were: effect below expectation, costs, side effects, loss of interest in sex, and lack of efficacy.

The off-label use of other SSRIs (including paroxetine, sertraline, and citalopram) in the treatment of PE is based on the side-effect of delayed ejaculation that was observed in depressed patients with normal sexual function who were treated with SSRIs for their depression. This increase in IELT is most likely the consequence of increased concentrations of serotonin in the synaptic cleft, causing an inhibition in the ejaculatory reflex and therefore a delay or even absence of ejaculation (2). Although doses of prescribed SSRIs tend to be generally lower for PE than for depression, the AEs are similar and there is also the potential for serious drug interaction that may result in rare cases of the so-called serotonin syndrome and suicidal ideation (30).

Locally acting topical therapies

Topical therapies that can be applied directly to the glans penis in order to produce some degree of penile desensitization are directed to the hypersensitivity aspect of PE. These topical treatments can be used "on-demand" with minimal systemic effects but may interfere with sexual spontaneity and have dosing difficulties with the potential of either over- or under-dosing, which may either cause penile hypoesthesia with subsequent erectile dysfunction and/or transvaginal transmission resulting in vaginal numbness and anorgasmia or lack of efficacy, respectively (20). Their ease of application and tolerability is further limited by the presence of a number of excipients in the formulation of the majority of creams and topical products causing difficulties in applying the correct measured dose.

Creams/ointments that have been frequently used in clinical practice, but that have not been specifically approved for the management of PE, include a local anesthetic cream containing lidocaine and prilocaine (2.5% each) that was developed for the topical anesthesia of intact skin. Although studies have shown some efficacy of lidocaine/prilocaine cream 5% in preventing PE (31, 32), it is slow-acting and cumbersome to use, with genital hypoesthesia reported in both sexual partners (20). In addition, difficulties in applying the cream have been reported along with a decrease in penile and vaginal sensitivity, penile hypoesthesia and loss of erection, and penile irritation (31, 32). Local anesthetic creams may also contain a mixture of base and ionized forms of local anesthetics where only the uncharged base forms are able to penetrate skin or mucous membranes (33).

Fortacin™ (Lidocaine/Prilocaine, Recordati) is the first officially approved topical therapy for PE. It is indicated for the treatment of primary PE in adult men and was approved for use in the European Union in 2013 and launched in the United Kingdom in November 2016 (34, 35). During its clinical development, Fortacin™ was referred to by two separate names, *Topical Eutectic Mixture for Premature Ejaculation (TEMPE)* and *PSD502*, with both names having been used in the published literature. Notably, Fortacin™ (denoted as TEMPE) is mentioned as an experimental aerosol in current European Association of Urology Guidelines (10).

Overview of Fortacin™

Fortacin™ is a metered-dose aerosol spray that delivers topical anesthesia to the glans penis. It contains purely base (uncharged) forms of the local anesthetics lidocaine 150 mg/mL and prilocaine 50 mg/mL, with no excipients except the spray propellant (norflurane) (34). This offers a potential advantage over other existing topical anesthetics in terms of a reduced risk of allergic reaction due to excipients. Although lidocaine and prilocaine are crystalline solids at room temperature, they form a eutectic mixture when mixed together, resulting in an oily liquid that remains in liquid form at temperatures that are lower than their individual melting points (33). Deployment of the metered-dose chamber causes the instant vaporization of the propellant forcing the lidocaine and prilocaine out of the solution and into a eutectic-like mixture. This forms a slightly oily substance that enhances adherence to the penile surface by creating a thin layer of local anesthetic molecules on the glans mucosa. Consequently, the absorption of the active components in their free-base form through the non- or poorly-keratinized tissue of the glans penis can be optimized (33, 36), the extent of neural blockage maximized, and the onset of numbness minimized.

Furthermore, in contrast to the application of creams, the metered-dose spray delivery system allows the desensitizing agents to be deposited in a dose-controlled, concentrated film onto the glans penis (33). Due to its formulation, the uncharged base forms of lidocaine and prilocaine are readily absorbed through the glans penis mucous membrane, but not through normal keratinized skin (i.e. the shaft of the penis); this minimizes absorption through normal skin so that a full sensation can be maintained in the shaft of the penis (33, 36). Furthermore, by reducing the permeability of the neuronal membranes to sodium ions, Fortacin™ produces localized reversible inhibition of nerve conduction (33). The

active substances, lidocaine and prilocaine, block transmission of nerve impulses in the glans penis, reducing its sensitivity, which is then translated into a delaying of the ejaculatory latency time without adversely affecting the sensation of ejaculation and orgasm (34).

Efficacy of Fortacin™

The clinical efficacy of Fortacin™ in the treatment of primary PE in adult men has been evaluated in five studies: one proof-of-concept phase II study (3); one supportive phase II study (37); two pivotal phase III studies (38, 39); and, combined data from the two pivotal phase III studies, including the open-label extension of 5 and 9 months (2, 40).

Positive outcomes in terms of increased IELT, sexual satisfaction, and minimal local AEs were initially shown from the proof-of-concept and supportive phase II studies. In the prospective, open-label, proof-of-concept study, a significant increase in IELT ($p = 0.008$ versus baseline), improved sexual satisfaction, and minimal local AEs were demonstrated in 11 men with self-reported PE who applied Fortacin™ to the glans penis 15 minutes prior to intercourse (3). Similarly, the supportive phase II study (37) conducted on 54 men with PE (according to DSM-IV criteria) also showed positive outcomes with an increased IELT, better ejaculatory control, and improved sexual quality of life compared with the placebo group (41).

Primary evidence for the efficacy of Fortacin™ in the treatment of patients with PE was derived from two pivotal phase III, multicenter, randomized, double-blind, placebo-controlled studies, with open-label follow-up in patients with lifelong PE and their sexual partners (38, 39). In both studies, the 3-month treatment phase with 30 mg Fortacin™ was followed by a 9-month open-label treatment phase in the first study (39) and a 5-month open-label treatment phase in the second study (38). Inclusion criteria for both studies were heterosexual men aged ≥18 years in stable, monogamous relationships with lifelong PE diagnosed according to both the DSM-IV criteria (41) and the ISSM definition (42), and a baseline IELT of ≤1 minute for at least two of the first three sexual encounters during the 4-week screening period. Men taking tricyclic antidepressants, monoamine oxidase inhibitors or short-acting SSRIs, in which the dose had changed within the 4-week screening period or was expected to change, were excluded from the trials, as were those with erectile dysfunction.

Fortacin™ (or matched placebo) was applied to the glans penis (after retracting any foreskin) approximately 5 minutes before intercourse with excess spray wiped off prior to penetration. Patients recorded stop-watch measured IELT during each sexual encounter and completed the Index of Premature Ejaculation (IPE) and PEP questionnaires at study entry and monthly visits.

The 10-item IPE questionnaire assesses subjective aspects of PE, covering three domains: ejaculatory control (four questions), sexual satisfaction (four questions), and distress (two questions) (43). Each question is answered on a 6-point Likert-type scale with final scores for control/satisfaction and distress ranging from 4-20 points and 2-10 points, respectively (38). The PEP questionnaire consists of four questions relating to perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty related to ejaculation. Each question is answered on a 5-point Likert-type scale (44).

Primary efficacy outcome variables for the pivotal studies included the change from baseline to study end in mean IELT and in the IPE questionnaire domains of ejaculatory control, sexual satisfaction, and distress (distress was a primary efficacy variable for the second study only). Secondary efficacy outcome variables included the proportion of patients with a mean IELT of >1 minute and >2 minutes during the 3-month double-blind treatment period, the change in the IPE domain of distress from baseline to month 3 (first study only), and the PEP questionnaire at months 1, 2, and 3. As drug-induced ejaculatory performance has been shown to disclose a positively skewed IELT distribution, the geometric mean IELT and the fold increase of the geometric mean IELT were used in order to avoid overestimation of treatment efficacy (45).

The first pivotal phase III study (n = 290; 191 patients treated with Fortacin™ and 99 with placebo) produced significant, clinically meaningful improvements in ejaculatory latency, control, and sexual satisfaction with active treatment (39). The geometric mean IELT increased from a baseline of 0.6 minutes in both treatment groups to 3.8 minutes in the Fortacin™ group vs. 1.1 minutes in the placebo group at study end after 3 months (Fig. 3). After adjusting for treatment-group imbalances, these numbers effectively represent a 6.3-fold and 1.7-fold increase in adjusted geometric mean IELT, demonstrating a significant between-treatment difference in favor of the active treatment ($p<0.001$), which was also efficacious in restoring control with significantly greater increases from baseline to month 3 for the IPE domain scores of ejaculatory control, sexual satisfaction, and distress (7.0, 5.9, and 2.8 point difference between active treatment and placebo, respectively; all $p<0.001$) (Fig. 4).

Fortacin™ was well received with 65.9% (of 182) patients rating the medication as “good” or “excellent”, as opposed to 14.6% (of 96) patients in the placebo group. In addition, the topical spray improved sexual satisfaction for both patients and their partners at the end of the 3-month double-blind phase, with significantly more patients and partners reporting improvements of at least one point in each of the PEP domains compared with those using placebo ($p<0.001$ for all between-treatment comparisons) (Fig. 5).

The advantageous effects of Fortacin™ were replicated and reinforced by the findings from the second pivotal phase III study (n = 249; 167 patients with active treatment and 82 with placebo) (38). In this study, greater improvements in the geometric mean IELT from baseline to month 3 were observed for the active treatment group compared with placebo (0.56 to 2.6 minutes vs. 0.53 to 0.8 minutes, respectively), with a significant between-treatment difference in the adjusted geometric mean IELT in favor of the active treatment (4.7 vs. 1.5 for placebo; $p<0.0001$) (Fig. 3). Scores for the IPE domains of ejaculatory control, sexual satisfaction, and distress in the active treatment group were also significantly higher than in the placebo group (all $p<0.001$) (Fig. 4) (38). Similarly, significantly more patients and partners reported improvements of at least one point for all four domains of the PEP questionnaire at 3 months with use of the topical spray (all $p<0.0001$ vs. the placebo group) (Fig. 5).

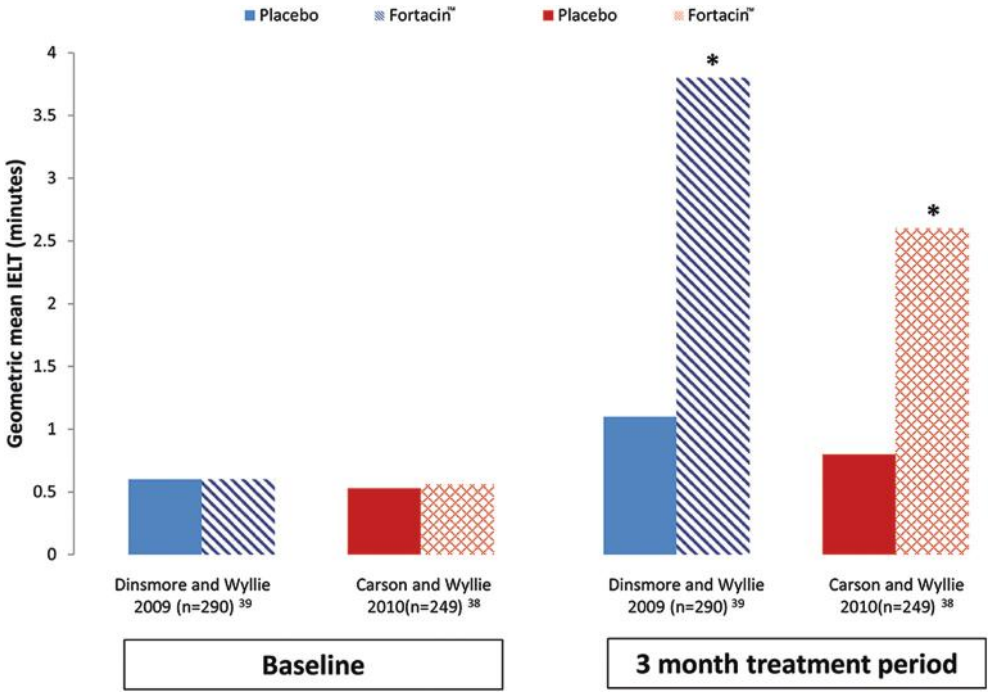

Fig. 3 - Geometric mean intravaginal ejaculation latency time (IELT) at baseline and at the end of the 3-month treatment period in patients treated with Fortacin™ or placebo. *p<0.001 versus baseline. Figure adapted from Dinsmore and Wyllie 2009 (39) and Carson and Wyllie 2010 (38).

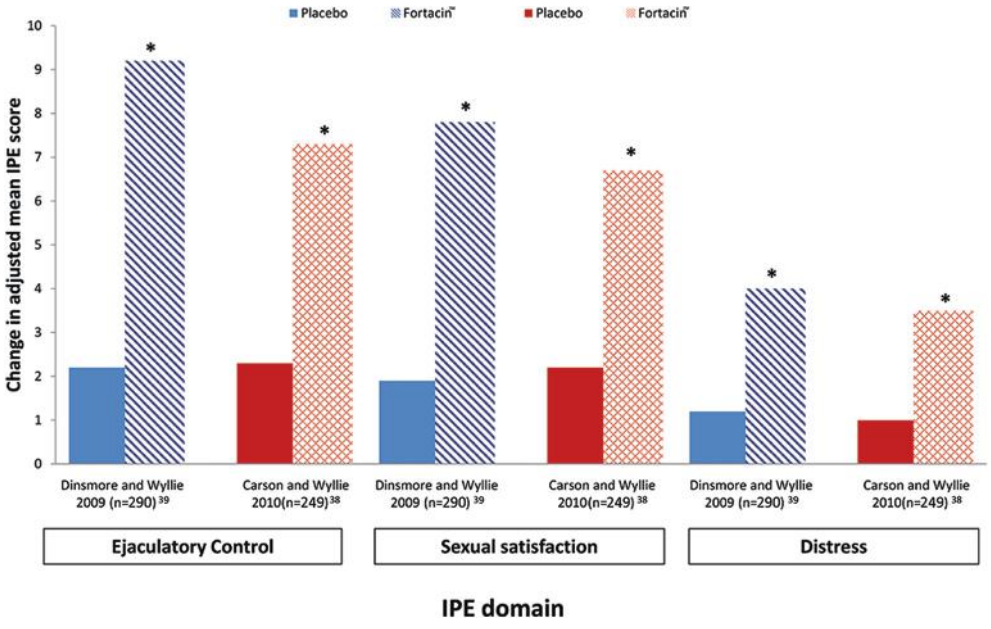

Fig. 4 - Change from baseline to month 3 in the adjusted mean Index of Premature Ejaculation (IPE) domain scores for ejaculatory control, sexual satisfaction, and distress in patients treated with Fortacin™ or placebo. *p<0.001 versus placebo. Figure adapted from Dinsmore and Wyllie 2009 (39) and Carson and Wyllie 2010 (38).

A higher proportion of patients treated with Fortacin™ had a mean IELT of >1 minute, >2 minutes, >3 minutes or >4 minutes compared with placebo based on combined data of the intent-to-treat population during the 3-month double-blind treatment period from both pivotal studies (Fig. 6) (40). Most patients (85.2%) in the active treatment group achieved a mean IELT of >1 minute versus only 46.4% in the placebo group.

Participants in both pivotal studies had the option to enter the open-label treatment phase in which all patients received Fortacin™. In total, 497 patients (98.4% of those completing the double-blind phase) entered the open-label extension; of these, 326 subjects had received active treatment and 171 had received placebo in the double-blind phase (40).

Fortacin™ was shown to be as effective for the treatment of PE at the end of the open-label phase as it was at the end of the double-blind treatment phase, with no evidence of tachyphylaxis despite repeated use. The positive changes in the geometric mean IELT observed during the double-blind phase were maintained and augmented during the open-label phase, with a marked improvement in geometric mean IELT in patients who converted from placebo to active treatment (Fig. 7) (2). The effectiveness of the topical spray increased with repeated use over time (Fig. 8), and improvements could be observed for all IPE domain scores (mean change from baseline for ejaculatory control, sexual satisfaction, and distress scores were 12.3, 10.9, and 5.3 points, respectively, at the end of the open-label phase) (40).

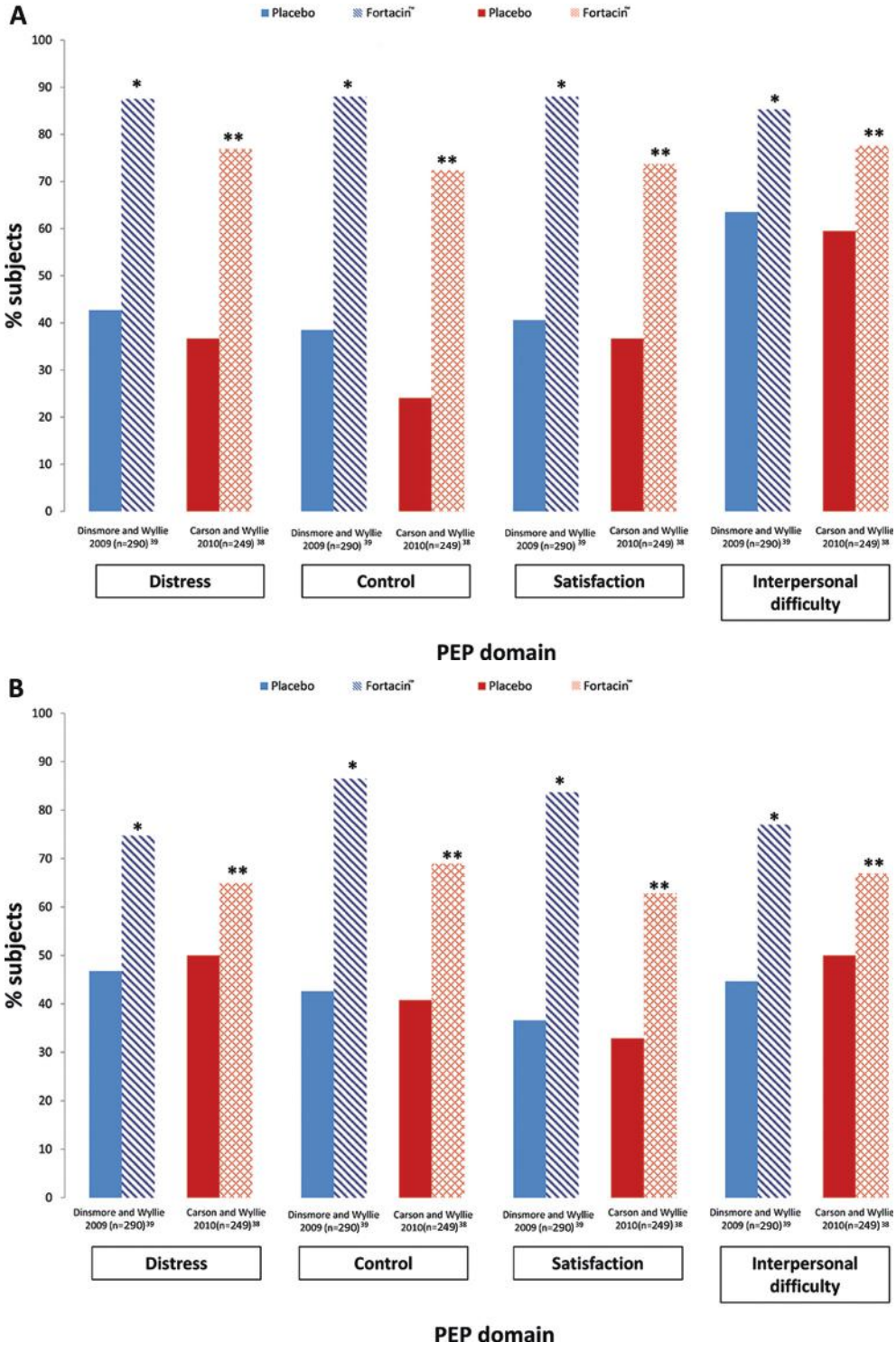

Fig. 5 - Percentage of patients (**A**) and female sexual partners (**B**) reporting an improvement of at least one point in Premature Ejaculation Profile (PEP) domains after 3 months' treatment with Fortacin™ or placebo. *p<0.001 for all between-treatment comparisons. **p<0.0001 for all between-treatment comparisons. Figure adapted from Dinsmore and Wyllie 2009 (39) and Carson and Wyllie 2010 (38).

Tolerability of Fortacin™

In all studies, Fortacin™ has shown a good safety profile with only a low incidence of mild-to-moderate local AEs according to a combined evaluation of 596 male patients and 584 female partners who participated in the clinical trials (40). In general, most treatment-related AEs occurred immediately or within 24 hours and most were mild or moderate in intensity (40). The incidence of treatment-related AEs was low in both patients (9.6%) and their female partners (6.0%) (40). The most frequent adverse reactions reported in male patients were local effects of genital hypoesthesia (4.5%) and erectile dysfunction (4.4%), with discontinuation of treatment in 0.2% and 0.5% of patients, respectively. The most frequent adverse reactions reported in female partners were vulvovaginal burning sensation (3.9%), and genital hypoesthesia

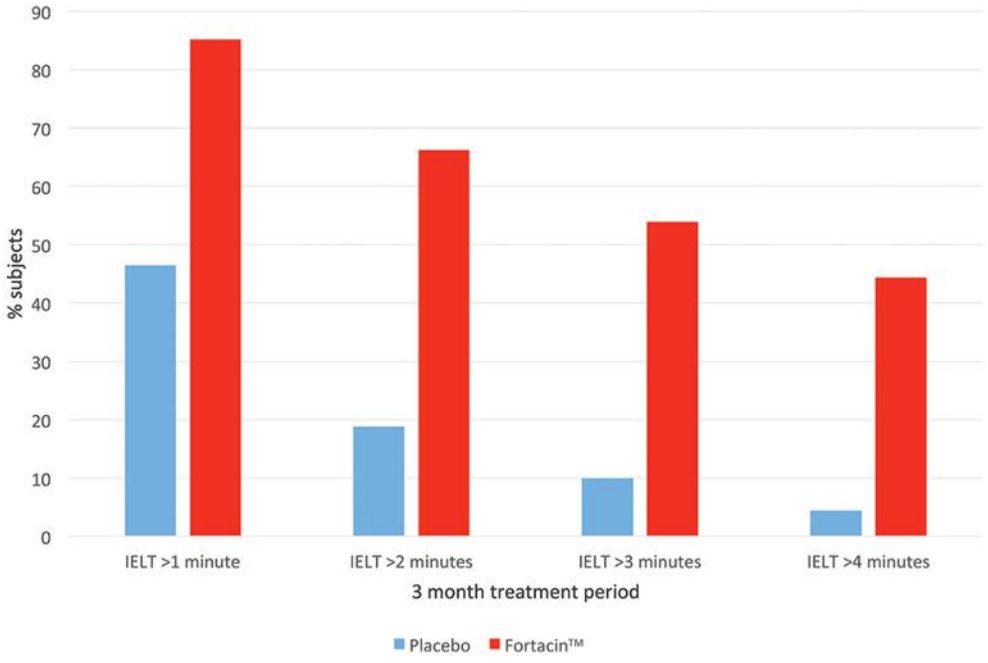

Fig. 6 - Proportion of patients with mean intravaginal ejaculation latency time (IELT) >1 minute, >2 minutes, >3 minutes, or >4 minutes during the 3 month double-blind treatment with Fortacin™ or placebo [combined data of the intent-to-treat population from both pivotal phase III studies (38, 39)]. Figure adapted from the 2013 Committee for Medicinal Products for Human Use assessment report on Lidocaine/Prilocaine (40).

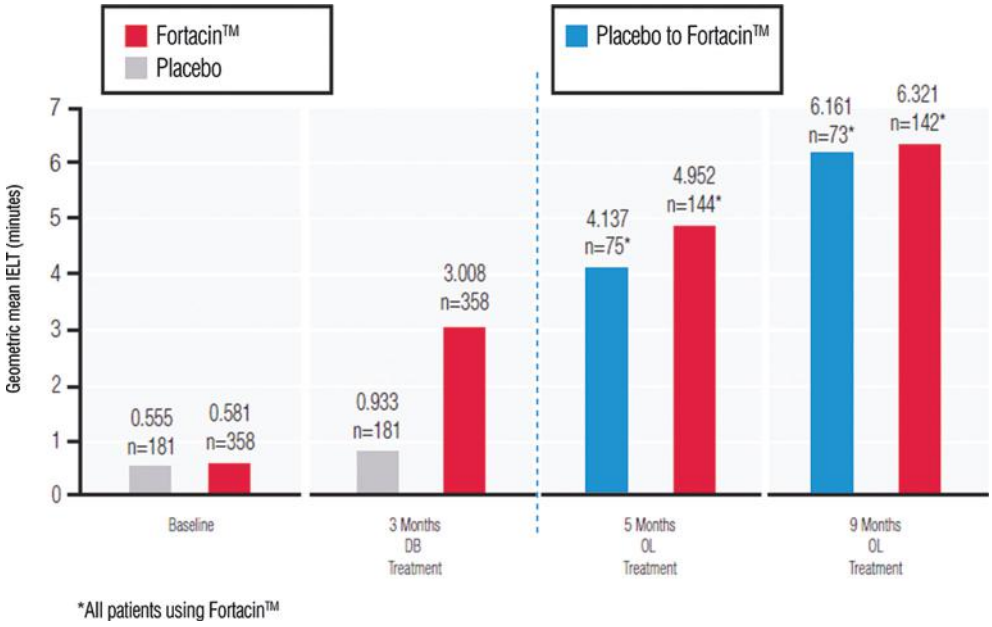

Fig. 7 - Change in the geometric mean intravaginal ejaculation latency time (IELT) over 12 months in patients treated with Fortacin™ or placebo [combined data from the double-blind and open-label phases of both pivotal phase III studies (38, 39)]. Figure adapted from Wyllie and Powell 2012 (2).

(1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects. In addition to moderate-to-low AEs, there was little or no desensitization of the genitalia neither in the patient nor in their partner with the topical spray, which did not detract from sexual satisfaction as evidenced by the increase in IPE and PEP scores after 3-months' treatment compared with baseline. It is also noteworthy that the topical spray was unlikely to be associated with systemic AEs (46).

Positioning Fortacin™ in the treatment of PE

Due to the easy application of Fortacin™ and short time to efficacy (i.e. within 5 minutes) this new treatment is unlikely to interfere with spontaneity of sexual activities. After retraction of the foreskin, the topical spray is applied to the glans penis 5 minutes before intercourse using three successive actuations of the aerosol to deliver the approved dose and ensure complete coverage, with any excess spray easily removed prior to sexual intercourse minimizing transmission to the sexual partner (27, 28). A maximum of 3 doses can be used within 24 hours, with a minimum interval of 4 hours between doses.

Based on results from clinical trials, which have shown significant benefits for both patients and their female partners in ejaculatory latency, control, and sexual satisfaction, Fortacin™ should be recommended as a first-line topical treatment of PE. It is also noteworthy that the pivotal phase III studies demonstrated increased effectiveness of the topical spray over time,

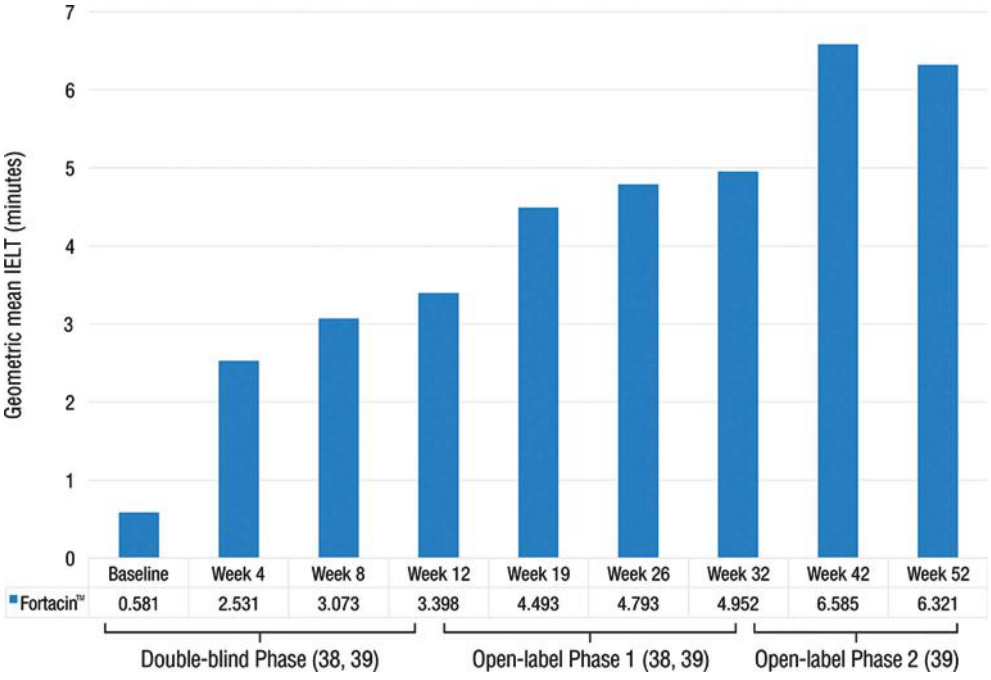

Fig. 8 - Geometric mean intravaginal ejaculation latency time (IELT) over time in patients treated with Fortacin™ in both the double-blind and open-label phases of the pivotal phase III studies (38, 39). Figure adapted from the 2013 Committee for Medicinal Products for Human Use assessment report on Lidocaine/Prilocaine (40).

which was most likely due to improved sexual confidence (2). By prolonging IELT with repeated use of the topical spray, presumably via activity on neuro-biogenic factors, a patient's psychological mindset may be positively influenced, which may improve his confidence and ability to control ejaculation with further improvement in the signs and symptoms of PE (2).

PE involves a complex sensory pathway controlled by the SEG, which can be targeted for the treatment of PE at two main sites: in the CNS, where SSRIs increase serotonin levels, leading to a delay in the transmission of ejaculation processing neural stimuli, and at the level of penile sensory receptors, where topical anesthetics can reduce penile sensitivity and afferent sensory neural stimuli. Hence, Fortacin™ could be considered not only as an alternative therapy to SSRIs but also, because of their different site of action, as an adjunctive therapy to oral SSRIs in severe PE patients. It is also apparent that patients with PE are sometimes not satisfied when treated regularly with SSRIs and therefore the addition of Fortacin™ to a patients' regular SSRI regimen may be advantageous.

Conclusions

PE can have detrimental effects on the quality of life of the patient and his partner with a negative impact on emotions, habits, and behavior, ultimately affecting the relationship and even leading to relationship break-ups. It is obvious that adequate and efficient medical help is needed to address this debilitating condition. Fortacin™ is the first officially approved topical prescription therapy for the treatment of primary PE in adult men. Its formulation optimizes fast penetration through the glans surface while the metered-dose spray delivery system allows the desensitizing agents, lidocaine and prilocaine, to be deposited in a dose-controlled, concentrated film onto the glans penis. This leads to a reduction in penile sensitivity, thus delaying the ejaculatory latency time without adversely affecting the sensation of ejaculation. The efficacy and safety of Fortacin™ have been proven in numerous large scale studies with improvements demonstrated in ejaculatory latency, control, and sexual satisfaction. The topical spray has a good safety profile with only a low incidence of mild-to-moderate local AEs seen in patients and partners, and is unlikely to be associated with systemic side effects. Overall, Fortacin™ significantly improves the quality of the sexual performance, has a durable effect over time, and may help break the vicious cycle of PE.

Disclosures

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