uro

MDPI

Review

Topical Treatment of Premature Ejaculation: The Rise of Anesthetic Spray Formulations?

Edoardo Pozzi [1,2], Federico Belladelli [1,2], Carolina Bebi [3], Andrea Salonia [1,2] and Luca Boeri [1,3,*]

[1] Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, 20131 Milan, Italy; edoardopietro.pozzi@gmail.com (E.P.); belladelli.federico@gmail.com (F.B.); salonia.andrea@hsr.it (A.S.)
[2] University Vita-Salute San Raffaele, 20131 Milan, Italy
[3] Department of Urology, Foundation IRCCS Ca' Granda—Ospedale Maggiore Policlinico, University of Milan, Via della Commenda 15, 20122 Milan, Italy; carolina_bebi@hotmail.it
* Correspondence: dr.lucaboeri@gmail.com; Tel.: +39-02-55034501; Fax: +39-02-50320584

Received: 4 February 2021; Accepted: 8 March 2021; Published: 12 March 2021

Abstract: Topical anesthetics are one of the first line therapeutical options for men with premature ejaculation (PE). Real-life PE management often involves a range of interventions including systemic drug treatments (such as off-label and on-label selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, phosphodiesterase-5 inhibitors (PDE5Is)), topical anesthetic creams and sprays, and behavioral approaches. Among them, on-demand dapoxetine and lidocaine/prilocaine spray formulations are the only approved treatment options for lifelong PE. The earliest strategy to treat PE was based on the use of topical anesthetic agents. The rationale behind the use of anesthetics is that by reducing the glans penis sensitivity, the spinal and cerebral input of sexual arousal impulses may also be reduced. Oral SSRI proved to be effective to treat PE, but their high rate of side effects limit treatment adherence and both short and long term follow up data are lacking. Conversely, topical anesthetics have proved to increase ejaculatory latency, control, and sexual satisfaction in couple affected by PE with limited rates of adverse events. In this context, we aimed to perform a narrative review to summarize the most recent findings regarding the use of topical treatments for PE.

Keywords: premature ejaculation; local anesthetics; topical treatments; ejaculatory disorder

1. Introduction

Among sexual dysfunctions, premature ejaculation (PE) is one of the most commonly reported symptoms in everyday clinical practice. PE pathophysiology and treatment efficacy are characterized by an unfolding history of contrasting hypotheses and arguable debates [1–3]. In this context, the European Association of Urology (EAU) Guidelines endorses the first Evidence-Based definition of PE, developed by the International Society for Sexual Medicine (ISSM). According to such definition, PE is a sexual dysfunction characterized by; (i) ejaculation that always, or nearly always, occurs before, or within, about one minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE); (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (iii) this condition determines negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [1,4,5]. Over the last two decades, compelling evidence has accumulated regarding the pathophysiology of PE. As a matter of fact, positron emission tomography and functional magnetic resonance imaging studies have allowed a greater understanding of the involvement of neurotransmitters in sexual arousal and ejaculation, which contributed to improve the overall knowledge of ejaculatory disorders and orgasmic dysfunctions pathophysiology [6,7]. The increasing amount of novel evidence prompted urologists to stop considering PE as a mere psychogenic condition, and to acknowledge its possible different

interconnected etiologies, i.e., organic, iatrogenic and psychogenic [6,8]. In this regard, selective serotonin reuptake inhibitors (SSRI) have been extensively investigated over the past decades and proved to be efficacious in increasing overall intravaginal ejaculation latency time (IELT) and control over ejaculation in men suffering from both, life-long and acquired PE [8–10]. However, patients commonly report SSRI-related side effects, which limits compliance and predisposes to treatment discontinuation in the long term [11].

In the light of these findings, topical anesthetic agents have regained popularity as a viable alternative to oral treatments [1,12]. For many years, the rationale behind the off-label prescription of topical anesthetic agents for PE was to raise the local sensitivity threshold in men who were presumed to be hypersensitive [13]. In fact, penile hypersensitivity has been considered one of the main pathologic mechanism of PE. However, the link between penile hypersensitivity and PE lacks a definitive conclusion. Xin et al. in a case-control study suggested that PE patients had hypersensitivity in the glans penis and penile shaft [13]. However, other investigations did not show a correlation between penile sensitivity and PE [14–16]. More recently, Guo et al. showed that patients with lifelong PE had a hypersensitivity profile in terms of peripheral sensory thresholds [17]. Penile hypersensitivity appeared to be a factor contributing to short intravaginal ejaculation latencies in lifelong PE men. Although evidence regarding penile hypersensitivity is mixed, few reports have proposed selective dorsal neurectomy as a potential treatment option for PE, due to the reduction in sensory input that are likely to attenuate central sexual arousal in men with PE [18]. Liu et al. in a group of Chinese men, showed that the dorsal penile nerve branches of patients with lifelong PE were more and thicker than those without lifelong PE, and that selective dorsal neurectomy was effective in improving IELT and ejaculatory control, with few postoperative complications [18].

In this specific context, the role of topical anesthetic agents in reducing penile sensitivity in men with PE has emerged. In addition to this, more recent findings demonstrated how topical anesthetics could lead to significant benefits for both male patients and their partners in terms of increased ejaculatory latency, control, and sexual satisfaction [12,19]. This narrative review aims to discuss topical therapies for PE with a specific focus on newly released compounds.

2. Materials and Methods

We performed a literature search for English-language original and review articles either published or e-published up until January 2021 using Google and the National Library of Medicine's PubMed database. The mesh terms used for the search were: Premature ejaculation; topical treatment; anesthetic, cream, spray. The retrieved articles were gathered and examined. Reference lists of retrieved articles as well as relevant review articles were also studied.

The exclusion criteria were as follows: (1) Editor letters and single case report; (2) non-English language publications; (3) studies with insufficient or unconfirmed information; and, (4) studies not involving PE patients. The evidence acquisition is presented according to PRISMA diagram (Figure 1).

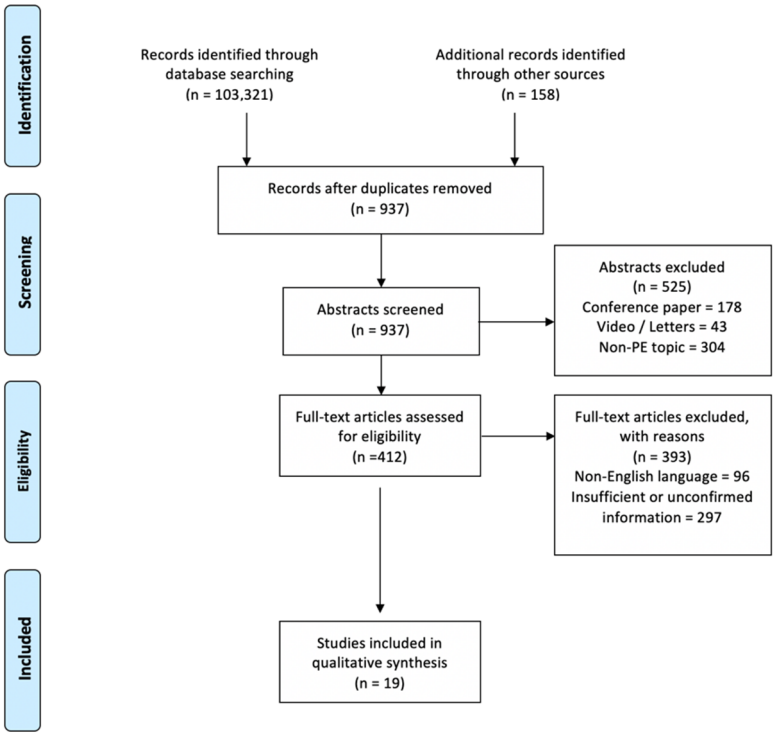

Figure 1. Evidence acquisition according to PRISMA diagram.

3. Results

3.1. Topical Anesthetics for PE

A limited number of pharmacological therapies are currently approved for PE [12]. This has led to the use of 'off-label' products such as local anesthetics in the everyday clinical practice [19]. When compared to PE treatments, topical agents are appealing since they are easy to use and can be applied on-demand. Moreover, local anesthetic agents do not cause systemic side effects [12,19,20]. Conversely, a downside of the application of a desensitizing substance to the glans is the potential for some degree of penile hypoesthesia. Furthermore, theoretically, the hypoesthesia might pass on to the partner, making sexual intercourse more difficult and leading to even more serious consequences such as erectile dysfunction [21].

3.2. Cream Formulations

The choice between oral therapy with SSRIs and topical anesthetics, either in cream or in spray formulation, is a decision that should be made in conjunction with the patient. Most physicians consider the use of topical therapy as a prudent first step for the treatment of PE, thanks to the favorable risk/benefit ratio of these products. Patients with PE often complain of augmented sensory responses to penile stimulation [16]. In support of this claim, the discovery of abnormal reflex pathways during ejaculation has led to the conclusion that penile hypersensitivity and PE are truly interconnected [16]. In this framework, EMLA (eutectic mixture of lidocaine-prilocaine) is an off-label anesthetic cream used for the treatment of both primary and acquired PE. In 1995, the first study on EMLA on 11 healthy men with PE showed encouraging results in delaying ejaculation [22]. Subsequently, Atikeler et al. investigated the efficacy of this preparation in a larger cohort of patients, observing a statistically significant increase in ejaculation time, which increased from around 1 min. to 6–8 min [23]. Additionally, they demonstrated that the optimal timing for EMLA application is 20 min before sexual intercourse [23]. Busato et al. demonstrated a significant increase of mean IELT among men using a lidocaine-prilocaine cream in comparison to placebo administration [24]. Similarly, Atan et al.

compared the use of Sildenafil alone, Sildenafil plus EMLA and placebo confirming the superiority of topical anesthetics in delaying ejaculation as compared to placebo [25]. A recent study conducted by Gameel et al. compared the efficacy of Tramadol, Sildenafil, SSRI and a Lidocaine 2.5% anesthetic gel for the treatment of PE. Lidocaine 2.5% gel confirmed its superiority in respect to the other treatment regimens in increasing IELT (OR 5.23, $p < 0.001$) [26].

In conclusion, anesthetic creams have shown moderate efficacy for the treatment of primary and acquired PE. However, these preparations carry the risks of sensibility reduction for both patients and their partners, which may potentially lead to erectile dysfunction and skin irritation [27]. Additionally, cream preparations for PE are used on-demand, which could result in loss of spontaneity and subsequent loss of sexual arousal [28] causing treatment discontinuation and poor patient's compliance.

3.3. Spray Formulations

3.3.1. Lidocaine-Only Spray

Lidocaine 9.6 % spray, marketed as 'Studd 100' or 'Premjact', has been available over-the-counter for over 25 years in some countries and it has been employed as an off-label drug to delay ejaculation.

A recent study by Alghibary et al., analysed data from men with lifelong PE randomized to oral dapoxetine 60 mg or topical lidocaine 10% spray for 12 weeks and then asked to switch to the other treatment for another 12 weeks. Participants were evaluated using the Arabic Index for PE (AIPE) and the Sexual Health Inventory for Men (SHIM) questionnaire. Authors showed that both medications significantly increased both IELT and AIPE scores when compared with baseline evaluation, but the results were shown to be significantly better with topical lidocaine with respect to oral dapoxetine [28].

3.3.2. Prilocaine–Lidocaine Spray

TEMPE (topical eutectic mixture for premature ejaculation) is a proprietary formulation of lidocaine and prilocaine in a metered-dose aerosol delivery system specifically designed for use in PE. The system delivers 7.5 mg lidocaine base plus 2.5 mg prilocaine base per actuation. The mixture is alcohol-free, which limits the chance of stinging on application. Despite being oil-free, the mixture forms a clear, slightly oily, odorless solution that remains adherent to the application site and may be wiped off with a damp cloth if necessary, without the stringent need to apply a condom [29]. The metered-dose spray delivery system allows the desensitizing agents to be deposited in the form of a dose-controlled, concentrated film on the glans penis, which can then penetrate the glans within 5–10 min of its application [29]. The eutectic mixture penetrates intact keratinized skin more slowly and is therefore not likely to anesthetize the penis shaft or the hands [29]. In the first open-label pilot study, 11 patients recorded their IELT at baseline and on five subsequent encounters after the application of TEMPE 15 min before sexual intercourse [29]. The average IELT increased from 1 min 24 s to 11 min 21 s ($p = 0.008$), which represents an average eight-fold increase. In addition, 8 out of 11 patients and 7 out of 11 partners rated their sexual satisfaction as either 'better' or 'much better'. In a more recently published phase 2, placebo-controlled trial, 54 patients using the prilocaine–lidocaine spray were able to prolong their IELT from a baseline of 1.0 min to 4.9 min [30]. The treatment was also well tolerated, with only 3 (12%) patients experiencing hypoesthesia and one patient experiencing loss of erection. None of the adverse events resulted in treatment discontinuation. The spray was also well tolerated by female partners, with only few experiencing a mild genital burning sensation during intercourse. Two double-blind placebo-controlled multi-centre phase 3 clinical trials have been completed thereafter [31,32], including over 550 PE patients assessed with the IELT and two questionnaires [index of premature ejaculation (IPE) and the premature ejaculation profile (PEP). IELT changes were mirrored in all domains of the IPE and PEP questionnaire as well as in the PEP domain scores from partners [31,33]. There was little or no evidence of systemic side effects, but only minimal desensitization of the genitalia in either patient or partner [31,33].

3.4. Fortacin™

For decades topical anesthetic agents have been used as off-label treatments for PE, with the specific aim of raising the threshold of local sensitivity in people who were thought to be hypersensitive [16]. More recently, Fortacin™ was officially approved for use in the European Union in 2013 and finally launched in the United Kingdom in November 2016 for the treatment of men with primary PE [34]. Fortacin is a metered-dose aerosol spray and 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]. An original prescription information leaflet suggests using the compound as follows: One dose, namely three sprays, to be applied on the glans penis at least five minutes before sexual attempts [34]. Prost et al. found that Fortacin™ increased ejaculatory latency, control, and sexual satisfaction in men with primary PE, demonstrating the significant benefits for both patients and their partners when using the drug [20]. Likewise, other groups confirmed the above mentioned findings making local anesthetics a viable alternative for lifelong and acquired PE [13,15,29]. Recently, the results from an expert panel discussion on the management of PE reported that most patients perceive PE as a bother rather than a disease, and that on-demand treatment options and the topical route of administration are mostly preferred [35].

This formulation has been reported to optimize the penetration through the glans surface leading to a rapid reduction in penile sensitivity (within 5 min)—namely termed desensitization—without adversely affecting the actual sensation of ejaculation. Moreover, Fortacin™ administration might be "personalized" in clinical practice in order to obtain a further patient-oriented treatment.

3.5. Combination of Oral and Local Treatment for PE

Only few reports have investigated the efficacy and tolerability of a combination therapy of SSRI and topical anesthetics. Metin et al. [36] investigated the effect of on-demand fluoxetine 20 mg taken about 4 h before sexual intercourse, followed by 3 months of combination therapy of fluoxetine plus lidocaine ointment (applied 30 min prior to sexual activity) in 46 men with PE. Authors reported that PE grade and IELT improved with combination treatment and that 86.9% of patients reported a total significant and moderate improvement in PE rate. In another small trial fluoxetine 20 mg/day followed by fluoxetine 40 mg/day was compared to the outcome of a combination therapy of fluoxetine 20 mg/day plus local lidocaine for 2 months [25]. Patients under combination therapy showed higher rates of PE improvement compared to those in monotherapy.

Only a limited number of studies investigated the efficacy of combination therapy of local anesthetics and phosphodiesterase type 5 inhibitors (PDE5i) for PE. Atan et al. assessed the effect of combination therapy with sildenafil and EMLA-cream vs. monotherapy and placebo in 84 men with PE. They found that combination treatment had a higher efficacy (86.4%) compared to placebo (40%) and to either monotherapy (sildenafil 50 mg: 55%; EMLA: 77.3%) [20]. In another study, including 78 men with primary PE, the efficacy of lidocaine spray 10 g/100 mL, tadalafil 5 mg daily and tadalafil 5 mg daily plus lidocaine spray was investigated over 3 months [37]. Mean IELT and satisfaction scores were significantly higher in patients with combination therapy than those of patients on monotherapy at 3 months.

4. Discussion

Despite being one of the most commonly reported sexual dysfunctions, which treatment is adequate and efficacious for PE remains controversial [38,39]. SSRI represented the cornerstone for PE treatment over the last few decades and dapoxetin, a short-acting SSRI, has been the only officially approved oral drug for PE in Europe and many countries worldwide. Nevertheless, SSRI treatment is associated with high rates of treatment discontinuation at both short and long-term follow up [9,12,40]. Commonly reported reasons for discontinuation are efficacy below expectations, costs, side effects and

loss of interest in sexual activity [40]. In light of this issues, topical anesthetic agents have regained importance as possible alternatives to oral treatments.

When compared to systemic therapy, topical anesthetic compounds offer various advantages such as lack of systemic side effects and limited number of local reactions. However, depending on the formulation, they may require a latency time between application and maximum effect. Furthermore, they should either to be used with a condom, washed-off or wiped-off before intercourse, which could have an effect on spontaneity during sex (Table 1). Local anesthetic cream formulations (lidocaine-prilocaine and dyclonine-alprostadil) require application 5–20 min beforehand and the potential use of a condom, whereas spray formulations (lidocaine–prilocaine, TEMPE) have to be applied 5–15 min in advance [21]. The new dose-metered lidocaine-prilocaine spray (Fortacin) has gained increasing popularity among PE-affected couples, especially because of its unique galenic preparation, which renders its handling effortless and customer friendly. In addition to this, several studies have proved the clinical efficacy of lidocaine-prilocaine spray in terms of IELT improvement, ejaculatory control, sexual satisfaction, and distress [19]. Physicians should always bear in mind that the pathophysiology of PE is multifactorial, with an interlink between psychogenic, organic and neurobiological factors. Consequently, it is likely that the most efficacious treatment of PE is multifactorial as well.

Table 1. Summary of advantages/disadvantages of topical treatment for PE.

Type of Treatment	Advantages	Disadvantages
Cream formulations EMLA	• Significant increase in ejaculation time compared to placebo • Additive effect when used in combination therapy	• Risk for sensibility reduction for both partners and skin irritation with subsequent loss of sexual desire and erectile dysfunction • Condom use is advised with cream formulations
Spray formulations		
Prilocaine–Lidocaine Spray Fortacin™	• Increase ejaculatory latency, control, and sexual satisfaction in men with primary PE • Metered-dose aerosol delivery system allows for dose-controlled action • Not likely to anesthetize the penis shaft or the hands • Condom use is not necessary	• Mild hypoesthesia and genital burning • Rare cases of erectile dysfunction

5. Conclusions

Topical anesthetics proved to be safe and effective as a treatment option for men with PE of various types. Patients treatment compliance is higher than that for oral medications. The new dose-metered lidocaine-prilocaine spray has shown promising results for the treatment of lifelong PE in terms of efficacy, and because of its unique galenic preparation, its handling is easy and patient friendly. Combination therapy of local anesthetics and oral medications seems to be superior than monotherapy alone, but data is still scarce to support its systematic use.

Author Contributions: Conceptualization, L.B., F.B., A.S. and E.P.; methodology, E.P.; writing—original draft preparation, E.P., F.B., L.B.; writing—review and editing, L.B., C.B. and A.S.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Salonia, A.; Bettocchi, C.; Carvalho, J.; Corona, G.; Jones, T.H.; Kadioglu, A.; Martinez-Salamanca, I.; Minhas, S.; Serefoğlu, E.C.; Verze, P.; et al. EAU Guidelines on Sexual and Reproductive Health. Available online: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2020.pdf (accessed on 5 April 2020).
2. McCabe, M.P.; Sharlip, I.D.; Lewis, R.; Atalla, E.; Balon, R.; Fisher, A.D.; Laumann, E.; Lee, S.W.; Segraves, R.T. Incidence and Prevalence of Sexual Dysfunction in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. *J. Sex. Med.* **2016**, *13*, 144–152. [CrossRef]
3. Irfan, M.; Hussain, N.H.N.; Noor, N.M.; Mohamed, M.; Sidi, H.; Ismail, S.B. Epidemiology of Male Sexual Dysfunction in Asian and European Regions: A Systematic Review. *Am. J. Men's Health* **2020**, *14*, 1557988320937200. [CrossRef]
4. Serefoglu, E.C.; McMahon, C.G.; Waldinger, M.D.; Althof, S.E.; Shindel, A.; Adaikan, G.; Becher, E.F.; Dean, J.; Giuliano, F.; Hellstrom, W.J.G.; et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: Report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *J. Sex. Med.* **2014**, *11*, 1423–1441. [CrossRef]
5. Waldinger, M.D.; Schweitzer, D.H. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II—Proposals for DSM-V and ICD-11. *J. Sex. Med.* **2006**, *3*, 693–705. [CrossRef]
6. Georgiadis, J.R.; Simone Reinders, A.A.T.; Van der Graaf, F.H.C.E.; Paans, A.M.J.; Kortekaas, R. Brain activation during human male ejaculation revisited. *NeuroReport* **2007**, *18*, 553–557. [CrossRef]
7. Waldinger, M.D.; Berendsen, H.H.; Blok, B.F.; Olivier, B.; Holstege, G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: The involvement of the serotonergic system. *Behav. Brain Res.* **1998**, *92*, 111–118. [CrossRef]
8. Park, H.J.; Park, N.C.; Kim, T.N.; Baek, S.R.; Lee, K.M.; Choe, S. Discontinuation of Dapoxetine Treatment in Patients with Premature Ejaculation: A 2-Year Prospective Observational Study. *Sex. Med.* **2017**, *5*, E99–E105. [CrossRef]
9. Jenkins, L.C.; Gonzalez, J.; Tal, R.; Guhring, P.; Parker, M.; Mulhall, J.P. Compliance with Fluoxetine Use in Men with Primary Premature Ejaculation. *J. Sex. Med.* **2019**, *16*, 1895–1899. [CrossRef]
10. Salonia, A.; Rocchini, L.; Saccà, A.; Pellucchi, F.; Ferrari, M.; Carro, U.D.; Ribotto, P.; Gallina, A.; Zanni, G.; Dehò, F.; et al. Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. *J. Sex. Med.* **2009**, *6*, 2868–2877. [CrossRef]
11. Mondaini, N.; Fusco, F.; Cai, T.; Benemei, S.; Mirone, V.; Bartoletti, R. Dapoxetine treatment in patients with lifelong premature ejaculation: The reasons of a "Waterloo". *Urology* **2013**, *82*, 620–624. [CrossRef]
12. Castiglione, F.; Albersen, M.; Hedlund, P.; Gratzke, C.; Salonia, A.; Giuliano, F. Current Pharmacological Management of Premature Ejaculation: A Systematic Review and Meta-analysis. *Eur. Urol.* **2016**, *69*, 904–916. [CrossRef]
13. Xin, Z.C.; Chung, W.S.; Choi, Y.D.; Seong, D.H.; Choi, Y.J.; Choi, H.K. Penile sensitivity in patients with primary premature ejaculation. *J. Urol.* **1996**, *156*, 979–981. [CrossRef]
14. Rowland, D.L.; Haensel, S.M.; Blom, J.H.; Slob, A.K. Penile sensitivity in men with premature ejaculation and erectile dysfunction. *J. Sex Marital Ther.* **1993**, *19*, 189–197. [CrossRef]
15. Perretti, A.; Catalano, A.; Mirone, V.; Imbimbo, C.; Balbi, P.; Palmieri, A.; Longo, N.; Fusco, F.; Verze, P.; Santoro, L. Neurophysiologic evaluation of central-peripheral sensory and motor pudendal pathways in primary premature ejaculation. *Urology* **2003**, *61*, 623–628. [CrossRef]
16. Salonia, A.; Saccà, A.; Briganti, A.; Del Carro, U.; Dehò, F.; Zanni, G.; Rocchini, L.; Raber, M.; Guazzoni, G.; Rigatti, P.; et al. Quantitative sensory testing of peripheral thresholds in patients with lifelong premature ejaculation: A case-controlled study. *J. Sex. Med.* **2009**, *6*, 1755–1762. [CrossRef]
17. Guo, L.; Liu, Y.; Wang, X.; Yuan, M.; Yu, Y.; Zhang, X.; Zhao, S. Significance of penile hypersensitivity in premature ejaculation. *Sci. Rep.* **2017**, *7*, 10441. [CrossRef]
18. Liu, Q.; Li, S.; Zhang, Y.; Cheng, Y.; Fan, J.; Jiang, L.; Li, S.; Tang, Y.; Zeng, H.; Wang, J.; et al. Anatomic Basis and Clinical Effect of Selective Dorsal Neurectomy for Patients with Lifelong Premature Ejaculation: A Randomized Controlled Trial. *J. Sex. Med.* **2019**, *16*, 522–530. [CrossRef]

19. Porst, H.; Burri, A. Novel Treatment for Premature Ejaculation in the Light of Currently Used Therapies: A Review. *Sex. Med. Rev.* **2019**, *7*, 129–140. [CrossRef]
20. Porst, H.; Burri, A. Fortacin™ Spray for the Treatment of Premature Ejaculation. *Urologia* **2017**, *84*, 1–10. [CrossRef] [PubMed]
21. Wyllie, M.G.; Powell, J.A. The role of local anaesthetics in premature ejaculation. *BJU Int.* **2012**, *110*, E943–E948. [CrossRef] [PubMed]
22. Berkovitch, M.; Keresteci, A.G.; Koren, G. Efficacy of prilocaine–lidocaine cream in the treatment of premature ejaculation. *J. Urol.* **1995**, *154*, 1360–1361. [CrossRef]
23. Atikeler, M.K.; Gecit, I.; Senol, F.A. Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* **2002**, *34*, 356–359. [CrossRef] [PubMed]
24. Busato, W.; Galindo, C.C. Topical anaesthetic use for treating premature ejaculation: A double-blind, randomized, placebo-controlled study. *BJU Int.* **2004**, *93*, 1018–1021. [CrossRef] [PubMed]
25. Atan, A.; Basar, M.M.; Tuncel, A.; Ferhat, M.; Agras, K.; Tekdogan, U. Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. *Urology* **2006**, *67*, 388–391. [CrossRef]
26. Gameel, T.A.; Tawfik, A.M.; Abou-Farha, M.O.; Bastawisy, M.G.; El-Bendary, M.A.; El-Gamasy, A.E.-N. On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial. *Arab. J. Urol.* **2013**, *11*, 392–397. [CrossRef]
27. Martyn-St James, M.; Cooper, K.; Kaltenthaler, E.; Dickinson, K.; Cantrell, A.; Wylie, K.; Frodsham, L.; Hood, C. Tramadol for premature ejaculation: A systematic review and meta-analysis. *BMC Urol.* **2015**, *15*, 6. [CrossRef]
28. Alghobary, M.; Gaballah, M.; El-Kamel, M.F.; State, A.F.; Ismail, S.R.; Selim, M.K.; Mostafa, T. Oral dapoxetine versus topical lidocaine as on-demand treatment for lifelong premature ejaculation: A randomised controlled trial. *Andrologia* **2020**, *52*, e13558. [CrossRef]
29. Henry, R.; Morales, A. Topical lidocaine–prilocaine spray for the treatment of premature ejaculation: A proof of concept study. *Int. J. Impot. Res.* **2003**, *15*, 277–281. [CrossRef]
30. Dinsmore, W.W.; Hackett, G.; Goldmeier, D.; Waldinger, M.; Dean, J.; Wright, P.; Callander, M.; Wylie, K.; Novak, C.; Keywood, C.; et al. Topical eutectic mixture for premature ejaculation (TEMPE): A novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. *BJU Int.* **2007**, *99*, 369–375. [CrossRef]
31. Dinsmore, W.W.; Wyllie, M.G. PSD502 improves ejaculatory latency, control and sexual satisfaction when applied topically 5 min before intercourse in men with premature ejaculation: Results of a phase III, multicentre, double-blind, placebo-controlled study. *BJU Int.* **2009**, *103*, 940–949. [CrossRef]
32. Carson, C.C.; Levine, L.A. Outcomes of surgical treatment of Peyronie's disease. *BJU Int.* **2014**, *113*, 704–713. [CrossRef]
33. *FORTACIN™: Summary of Product Characteristics*; European Medicine Angency (EMC): Amsterdam, The Netherlands, 2014.
34. Lidocaine/prilocaine spray for premature ejaculation. *Drug Ther. Bull.* **2017**, *55*, 45–48. [CrossRef] [PubMed]
35. Fusco, F.; Creta, M.; Mangiapia, F.; Cirigliano, L.; Trama, F.; Pandolfo, S.D.; Imbimbo, C.; Longo, N.; Mirone, V. Perceptions, Expectations, Preferences, and Attitudes Toward Premature Ejaculation, Its Diagnosis and Topical Treatment with Fortacin™ Spray: Results from an Expert Panel Discussion. *Res. Rep. Urol.* **2020**, *12*, 211–216. [CrossRef]
36. Metin, A.; Kayigil, O.; Ahmed, S.I. Does lidocaine ointment addition increase fluoxetine efficacy in the same group of patients with premature ejaculation? *Urol. Int.* **2005**, *75*, 231–234. [CrossRef]
37. Dell'Atti, L.; Galosi, A.B.; Ippolito, C. A randomized single-center study to compare the efficacy and tolerability of tadalafil once daily plus lidocaine anesthetic spray on premature ejaculation. *Eur. Rev. Med. Pharmacol. Sci.* **2017**, *21*, 1036–1040.
38. Pozzi, E.; Capogrosso, P.; Boeri, L.; Cazzaniga, W.; Matloob, R.; Ventimiglia, E.; Oreggia, D.; Schifano, N.; Candela, L.; Abbate, C.; et al. Trends in reported male sexual dysfunction over the past decade: An evolving landscape. *Int. J. Impot. Res.* **2020**. [CrossRef] [PubMed]
39. Porst, H.; Montorsi, F.; Rosen, R.C.; Gaynor, L.; Grupe, S.; Alexander, J. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: Prevalence, comorbidities, and professional help-seeking. *Eur. Urol.* **2007**, *51*, 816–824. [CrossRef]

40. Liu, H.; Zhang, M.; Huang, M.; Cai, H.; Zhang, Y.; Liu, G.; Deng, C. Comparative efficacy and safety of drug treatment for premature ejaculation: A systemic review and Bayesian network meta-analysis. *Andrologia* **2020**, *52*, e13806. [CrossRef] [PubMed]