Expert Opinion

TEMPE: Topical Eutectic-Like Mixture for Premature Ejaculation

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Background: Premature ejaculation (also known as rapid or early ejaculation) is the most common form of sexual dysfunction experienced by men, but there is presently an unmet need for a licensed pharmaceutical product that can be used on demand and that is effective from the first dose. *Objective*: TEMPE® (Topical Eutectic-Like Mixture for Premature Ejaculation; Plethora Solutions Plc.) is a proprietary metered-dose aerosol containing a combination of the well-known local anaesthetics lidocaine and prilocaine in a novel formulation. The authors evaluate here the progress that has been made towards the reformulation of these local anaesthetic agents into a unique eutectic-like formulation for use as a desensitising agent in the treatment of premature ejaculation, as well as examining other potential uses for the spray, such as pain relief at skin-graft donor sites. *Methods*: Both lidocaine and prilocaine are soluble in the hydrofluoroalkane (HFA-134a) propellant, providing a unique formulation in which the pressurised liquid propellant is used as the solvent. Deployment of the metered-dose chamber vaporises the propellant, spraying lidocaine and prilocaine, now forced into a eutectic-like combination that remains in liquid form at temperatures well below their individual melting points, onto the target surface. The site is thus easily covered in a controlled dose of pure local anaesthetic in base form, providing ideal circumstances for optimised absorption through non- or poorly-keratinised skin, mucus membranes and wound surfaces. *Results/conclusion*: TEMPE has been developed for use in premature ejaculation and preliminary results show promising improvements in intravaginal ejaculatory latency, as well as patient-reported outcomes.

Keywords: eutectic mixture, lidocaine, local anaesthesia, local anaesthetic, premature ejaculation, prilocaine, TEMPE

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1. Overview of the market

1.1 Premature ejaculation

Premature ejaculation (PE, also known as rapid or early ejaculation) is the most common form of sexual dysfunction experienced by men and, although reports of the actual incidence of PE vary depending on the definition used, it is generally estimated that PE symptoms are experienced by 21 – 30% of the male population at some time, in all countries surveyed [1-6]. A commonly used definition is '*a lifelong persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration and before the patient wishes it*' [7]. There are various theories on the aetiology of PE [8]. Historically PE was considered to be a learned behaviour and as a result behavioural therapy was the standard treatment. However, it is now generally accepted that both biological and psychological factors are important in the aetiology of PE. In practice, few men with PE consult a physician

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because of embarrassment and the belief that there is no effective treatment. However, PE has been found to have a similar qualitative impact on the individual as erectile dysfunction [9], with men reporting lower sexual satisfaction and decreased sexual confidence [5]. Stopwatch-measured change in intravaginal ejaculatory latency time (IELT) is a key variable used to characterise the study population in clinical trials and to evaluate potential therapies. Considerable variation exists as to where the threshold IELT should be set to define PE (or indeed, to define 'normal') in a clinical setting, although the consensus of opinion seems to be that men with PE tend to have an IELT of < 1 or 2 min [8,10,11], although some men consistently ejaculate before, during or within seconds of penetration. From the patients' perspective, prolongation of a previously unsatisfactory IELT, however short or long that might be, might be considered more relevant to patient satisfaction than achieving predefined IELT goals. Subjective measures such as ejaculatory control and improvements in the sexual quality of life (SQoL) of patients and their partners (as measured by validated questionnaires), are also important and might indeed be as relevant (if not more so) to men with this condition than simply prolonging IELT.

There are presently no approved medications for PE, and behavioural therapy has limited long-term success, is generally costly and is not widely available [12]. Ejaculatory delay is a side effect of many psychotropic or antidepressant drugs, and this is exploited in the off-label use of systemic treatments such as adrenergic antagonists, gamma-amino butyric acid (e.g., gabapentin) and selective serotonin reuptake inhibitors (SSRIs) for the treatment of PE [13-18]. Success with these agents has been variable and is associated with side effects, some of which are potentially serious and others such as anorgasmia and loss of libido can be particularly undesirable in a treatment for any sexual dysfunction. In addition, the frequency of sexual intercourse might be highly variable and many physicians might find it difficult to justify systemic treatment given on a continual or daily basis for a potentially infrequent event. Therefore, there is presently an unmet need for a licensed product that can be used on demand and that is effective from the first dose.

It has been suggested that abnormal autonomic reflex pathways for ejaculation, such a heightened sensory response to penile stimulation might be one of the initiating factors in PE. Men with PE were found in one study to have a vibration threshold significantly lower than that of normal men [19], and although this was not confirmed in two further studies [20,21], a significant correlation was seen between ejaculatory latency and threshold [20]. Shorter bulbocavernous latency time, and higher bulbocavernous evoked potentials have also been suggested for men with PE [22,23]. Topical anaesthetics have been used off-label in the symptomatic treatment of PE, with the rationale that reducing the sensory input from the glans penis with topical desensitising agents might be a way of improving IELT, without adversely affecting the sensation of ejaculation. Several products have been used, including lidocaine-prilocaine cream (EMLA®; AstraZeneca) [24-26] and one containing natural products (SS-cream, Cheil Jedan Corporation) [27-29]. Although both products have been shown to improve IELT, they have not become widely accepted, possibly due to the long time to onset of effect (20 to 30 min), the rather messy use of cream in a condom, and the possibility for the whole penis to be anaesthetised.

Despite the fact that few men with PE seek treatment for the condition, there is clearly a demand for products that claim to delay ejaculation. Lidocaine sprays that are specifically marketed to '*extend lovemaking*' and condoms containing benzocaine are now available over the counter, but there are no published data to support their efficacy. An ideal topical treatment for PE would desensitise the most sensitive areas of the glans rapidly after a simple application technique and allow sensation in the shaft of the penis to remain intact so that the sensation of vaginal penetration might still be enjoyed whilst latency is extended.

1.2 Topical anaesthetics

Local anaesthetics block neuronal sodium channels to interrupt neural conduction. Delivery to the target neurones is critical in both achieving the block and avoiding systemic toxicity. Clinically useful local anaesthetic agents are lipid-soluble weak base amphiphatic molecules that comprise an aromatic ring (conferring lipid solubility) and a terminal amine in tertiary (base) or quaternary (salt) form that determines its water or lipid-soluble state, respectively, based on its ionisation constant or pK_a. The intermediate amide or ester linkage between the two determines the method of biotransformation.

Aside from intrinsic lipid solubility, tissue penetration by a particular local anaesthetic is thus determined by the concentration of that drug and the proportion of that concentration in the base form (a good overview of local anaesthetic pharmacology can be found in [30]).

Topical anaesthetics are applied onto a body surface from which they will diffuse into the underlying tissue. Adequate delivery requires the drug to remain at the site long enough (residency) to be in its base form from the outset or be buffered somehow, and to be in sufficient concentration to cause an effective neuronal block at the depth of tissue required. Safety dictates controlling the dose of the drug to maintain safe systemic levels, and compliance dictates that the formulation be applied easily and painlessly for a timely onset of effect.

Various topical anaesthetics are available in creams, ointments, lotions and gels, and are targeted at intact skin and mucus membranes. The formulations of local anaesthetics required for effective and rapid penetration of keratinised versus non-keratinised skin and mucosa are quite different. Keratinocytes of the stratum corneum (the outermost layer of the epidermis) produce keratin – a protein that gives skin

Figure 1. TEMPE spray canister.

its strength and flexibility and waterproofs the skin surface. To penetrate intact fully keratinised skin a topical formulation requires a high water content in order to hydrate the stratum corneum and facilitate penetration [31].

Lidocaine and prilocaine are crystalline solids at room temperature, which, when mixed together, form a eutectic mixture resulting an oily liquid that can be advantageously formulated into preparations without the use of a non-aqueous solvent. EMLA (Eutectic Mixture of Local Anaesthetics) is formulated as an emulsion of this eutectic mixture in water, forming a cream that hydrates the stratum corneum, thereby enabling drug penetration [31].

1.3 Topical anaesthesia of non-keratinised skin

The skin in some areas of the body, including the glans penis and external female genitals, is non-keratinised or poorly keratinised and exhibits drug absorption properties similar to mucous membranes such as the buccal cavity, the lining of the urethra and the rectum. Local anaesthetics are readily absorbed when applied topically to mucous membranes or genital mucosa [32,33]. As water is not required for hydration, a formulation that contains no aqueous solvent can contain purely base forms of local anaesthetics, allowing higher concentrations of anaesthetic to be formulated into the preparation and maintained during application, enabling faster onset of action.

2. How the TEMPE technology works

2.1 TEMPE formulation provides optimum residency and speed of onset of action

TEMPE is a metered-dose spray (see **Figure 1**) that delivers a eutectic-like mixture of lidocaine and prilocaine for topical anaesthesia. Each actuation dispenses 7.5 mg lidocaine and 2.5 mg prilocaine in their base forms. The hydroflouroalkane (HFA-134a; 1,1,1,2-tetrafluoroethane) serves as both propellant and solvent, creating a simple stable solution without the need for organic solvents such as ethanol, which is the present standard practice in HFA aerosol formulations. The metered-dose spray delivery system allows the desensitising agents to be deposited in a dose-controlled, concentrated film onto the glans penis. The instant vaporisation of the propellant forces the lidocaine and prilocaine out of solution into a eutectic-like mixture, forming a slightly oily substance ideal for topical application by ensuring good residency at the site of application. Uniquely, there are no gels or creams to impede the movement of local anaesthetic down the concentration gradient. The eutectic mixture has a pH of 8.0, which is favourable for absorption through mucous membranes. Importantly, lidocaine and prilocaine are delivered in their base form, optimising penetration of the drugs, maximising the depth of neural blockade and minimising time to onset of numbness (see **Figure 2**).

The local anaesthetics in TEMPE are incapable of penetrating intact fully keratinised skin. This is a distinct advantage in the treatment of PE, as full sensation can be maintained in the shaft of the penis [34]. Circumcision has been shown to result in increased keratinisation of the glans, but the sensitive areas of the frenulum and ureathral meatus remain unkeratinised [35,36]. The applied drug can (and should be) easily wiped off with a damp cloth in order to minimise transference to the sexual partner [37]. Unlike with aqueous creams, condoms are not required for occlusion, but can be used if required.

As well as their topical anaesthetic properties, lidocaine and prilocaine also possess inherent anti-inflammatory and anti-bacterial actions [38-40], and although these properties have not yet been examined in the TEMPE formulation, might offer additional advantages and provides an interesting area for future research.

The aerosol used in clinical trials for PE could provide a supply for up to 6 months at an average usage of 4- to 5-times per month, with the actuation system providing the ability to apply a precise dose.

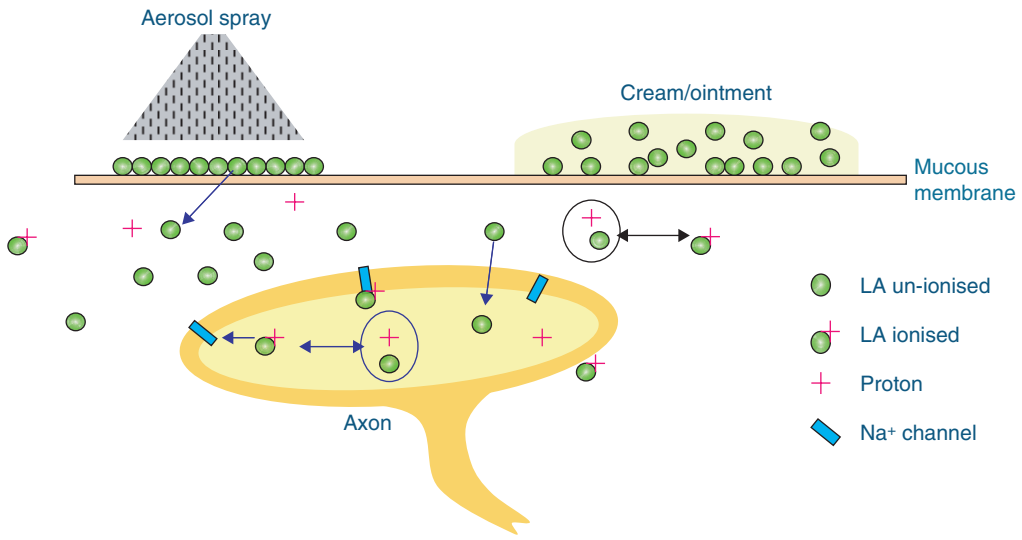

Figure 2. Mode of action of TEMPE. TEMPE aerosol spray contains purely base (uncharged) forms of local anaesthetics, but local anaesthetics creams contain a mixture of base and ionised forms. Only the uncharged base forms are able to penetrate skin or mucous membranes. Local anaesthetics produce localised reversible inhibition of nerve conduction by reducing the permeability of the neuronal membranes to sodium ions, the movement of which is necessary for the transmission of nerve impulses.
LA: Local anaesthetic.

Table 1. Mean dose accuracy (n = 2) for the amount of each active ingredient and for the total amount of formulation expelled per actuation over time for a batch of TEMPE for a batch of TEMPE manufactured by a European contract manufacturing organisation.

Test parameter	Initial	Months in storage (at room temperature)			
		3	6	12	18
Lidocaine (mg/actuation)	7.38	7.68	7.70	7.49	7.77
Prilocaine (mg/actuation)	2.48	2.54	2.58	2.47	2.60
Total amount expelled per actuation	50.1 – 63.5 mg	59.5 – 63.0 mg	54.8 – 62.8 mg	58.2 – 62.0 mg	58.0 – 62.2 mg

2.2 Stability, shelf life, dosing accuracy and reliability

In the EU, an 18-month shelf life has been established with the Medicines and Healthcare Products Regulatory Agency, based on a completed stability study. Presently, two stability studies, planned to run for 24 months, are ongoing for batches made at both European and US contract manufacturing organisations. Preliminary results are available for the European batch, supporting a 12-month shelf life for the product when stored at the recommended temperature (below 25°C).

The data shown in **Table 1** for a batch of TEMPE manufactured by a European contract manufacturing organisation shows that the dose accuracy, both for the amount of each active pharmaceutical ingredient and for the total amount of formulation expelled per actuation, is both accurate and reliable over time. Different spray heads can be used for different indications – the canister used for PE being fitted with a spray head, which gives a small spray area.

3. Clinical profile

Although no pre-clinical data are available for the TEMPE spray *per se*, its constituents of lidocaine and prilocaine have been used extensively, in both topical and systemic formulations, for many years without resulting in toxicological concerns. In addition, the safe and effective use of EMLA cream is well established for various topical applications to the skin and genital mucosa in clinical practice [41].

3.1 Pharmacokinetics

TEMPE is presently in the pre-registration phase of development and at the time of writing specific pharmacokinetics data on systemic exposure following the application of TEMPE to the glans penis is the subject

Table 2. Preliminary lidocaine pharmacokinetic parameters: TEMPE applied to skin donor sites in burns patients undergoing skin grafts (from an ongoing study, Plethora Solutions Plc.).

Subject/dose	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-4} (ng h/ml)
n	3	3	3
Mean	572.8	–	1790.9
SD	278.9	–	828.0
Min	359.0	1.5	1189.0
Median	470.6	1.5	1449.1
Max	888.0	2.0	2735.0
CV%	48.7	–	46.2

AUC: Area under the curve; C_{max}: Maximum plasma concentration; CV%: Coefficient of variation expressed as a percentage; T_{max}: Time to maximum plasma concentration.

Table 3. Preliminary prilocaine pharmacokinetic parameters: TEMPE applied to skin donor sites in burns patients undergoing skin grafts (from an ongoing study, Plethora Solutions Plc.).

Subject/dose	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-4} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	$t_{½}$ (h)
N	3	3	3	3	3
Mean	55.3	–	152.8	294.4	3.34
SD	18.5	–	64.6	159.7	0.88
Min	35.7	0.5	83.9	137.5	2.73
Median	57.8	1.0	162.6	288.8	2.93
Max	72.4	1.0	211.9	456.7	4.35
CV%	33.4	–	42.3	54.2	26.4

AUC: Area under the curve; C_{max}: Maximum plasma concentration; CV%: Coefficient of variation expressed as a percentage; T_{max}: Time to maximum plasma concentration.

of ongoing studies. However, there are preliminary pharmacokinetic data for TEMPE from the first three patients completing an ongoing, uncontrolled open-label Phase II study in the management of pain from skin graft donor sites in burns subjects (unpublished data, Plethora Solutions Plc.). Subjects received a single application of TEMPE spray to their donor site(s); one actuation of spray per 10 cm^2 up to a maximum of 0.35 sprays/kg before the application of a Hypafix™ dressing (BSN Medical Ltd). The three subects received 11, 28 or 29 sprays for total doses of 82.5 mg – 217.5 mg lidocaine and 27.5 – 72.5 mg prilocaine. Samples were analysed by HPLC and summaries of the pharmacokinetic profiles of lidocaine and prilocaine are presented in **Tables 2** and **3**, respectively. These data indicate that both lidocaine and prilocaine are absorbed following a single dose applied directly to the donor site. Lidocaine showed prolonged absorption that did not decline sufficiently to enable a half-life ($t_{1/2}$) calculation by 4 h after application. Prilocaine appeared to be absorbed slightly faster, and plasma concentrations started to decline in all three subjects beyond 1 h following dosing, with a mean $t_{1/2}$ of 2.4 h (± 0.9). The mean maximum plasma concentrations for lidocaine and prilocaine were 572.8 ng/ml (± 278.9) and 55.3 ng/ml, respectively, which are well below the toxic plasma levels for both drugs (toxic levels > 5000 ng/ml for lidocaine and > 6000 ng/ml for prilocaine) [41].

3.2 Clinical information: dosage selection of TEMPE

As TEMPE is topically applied there is no risk of inadvertent intravascular administration. The rationale for the dosage selection of TEMPE is presently based on consideration of existing data for both the topical application of lidocaine hydrochloride, prilocaine hydrochloride and particularly for lidocaine and EMLA cream used in studies of extent of exposure following application to the oral mucosa.

The maximum effective dose is expected to be achieved when a thin-layer filament of drug is deposited over the whole surface of the glans penis. Due to the shape of the glans, this can be best achieved by applying three sprays of drug, each spray covering a third of the glans. Any less might leave an area of the glans untreated. Systemic absorption would be expected to be lower than the absorption from an open wound. However, even assuming similar absorption, three actuations of TEMPE

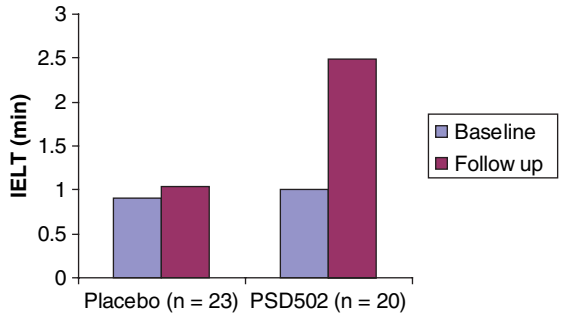

Figure 3. Geometric mean change in intravaginal ejaculatory latency time from baseline in patients with premature ejaculation after treatment with TEMPE or placebo (three actuations of spray per treatment on four occasions over a period of 1 month).

$p < 0.01$ for between-treatment comparison of change from baseline.
Adapted from [35].
IELT: Intravaginal ejaculatory latency time.

would be expected to achieve plasma concentrations 50-fold and 600-fold below the toxic ranges of lidocaine and prilocaine, respectively.

3.3 TEMPE in the treatment of premature ejaculation

The first open-label pilot study of TEMPE was undertaken to establish the safety and efficacy of the spray after application to the glans penis, aimed at prolonging the IELT in 14 men with PE [37]. Subjects timed their IELT using a stopwatch, and both partners rated their level of satisfaction during six sexual encounters. The first sexual encounter (baseline) was without treatment, and for the next five consecutive encounters patients used the spray at a dosage of three sprays applied to the glans penis, and left for 15 min before being wiped off before intercourse.

The results for the 11 patients completing this study showed an increase in IELT from a mean baseline of 1 min 24 s to 11 min 21 s ($p = 0.008$). This represents an average eightfold increase over baseline. In addition, 8/11 patients and 7/11 partners rated their sexual satisfaction as 'better' or 'much better'.

In a recently published Phase II, placebo-controlled trial in the UK and the Netherlands [34], 54 patients with a history of primary PE of ≥ 6 months duration and a baseline IELT of ~ 1 min, used a standard dose of three actuations of TEMPE onto the glans penis 15 min before sexual intercourse. Log transformed data were used to calculate geometric means, as IELT data were not normally distributed. Men with PE were able to prolong their IELT to a geometric mean of 2.50 min (95% CI 1.60, 3.89) with TEMPE, compared with 1.04 min (95% CI 0.69, 1.55) for placebo, indicating that TEMPE was 2.4-times more effective at prolonging IELT than placebo and bringing IELT into what would be generally accepted as being within the normal range (**Figure 3**) [8,10,11].

Patients in this study used TEMPE on only four occasions each over the course of a month, which is insufficient usage to expect a significant change in SQoL or index of ejaculatory control. However, even after such limited use there was an encouraging trend to improvements in ejaculatory control and SQoL in men and their partners [34]. Patient-reported outcomes are being evaluated further in longer-term studies.

The treatment was also well tolerated, with only 3/26 patients experiencing mild hypoaesthesia (numbness of penis) and a fourth patient experiencing erectile failure (on a single occasion), none resulting in treatment discontinuation. TEMPE was also well tolerated by the female partners, with no reports of numbness of the vagina, and only one partner experiencing a mild burning sensation during intercourse each time her partner used the spray, which did not result in discontinuation of treatment.

In ongoing studies, the pre-application time of TEMPE has been reduced to 5 min, as this is considered to be sufficient time for optimal desensitising of the glans penis.

3.4 Potential additional applications for TEMPE

As the TEMPE spray supplies a non-aqueous formulation of lidocaine and prilocaine in their base forms, it is able to provide fast-acting topical anaesthesia. This spray could theoretically be used in any situation where desensitisation or pain relief of non-keratinised or poorly-keratinised skin or mucous membranes would be beneficial. **Box 1** provides examples of potential future uses of TEMPE, most of which are yet to be investigated in clinical trials.

The first study of TEMPE for pain relief is presently ongoing. The first four subjects enrolled have completed the first (open, uncontrolled) part of the study and received a single dose of TEMPE applied directly to the donor site. Preliminary efficacy results are available in three of the four subjects treated. The three patients experienced mild, minimal or no pain at donor sites within the first 24 h after a single dose of TEMPE as assessed by a visual analogue pain scale. The spray was also generally well tolerated, although one subject experienced a slight, transient, burning sensation on application.

4. Alternative technologies

4.1 Alternative topical therapies for pain management

EMLA cream is a popular and effective desensitising agent for use on intact skin, genial mucosa and leg ulcers. However, it is not suitable for application to open wounds such as burns and skin graft donor sites. EMLA is most effective when used with an occlusive dressing in order to prevent water evaporation. A number of single-agent anaesthetic sprays and gels are available for topical application in Europe

Box 1. Examples of potential applications for TEMPE.

Sexual dysfunction

Treatment of premature ejaculation*

Treatment of burns, plastic surgery and dermatology

Treatment of acute burns

Burn debridement and application of burns dressing

Management of donor sites for skin grafts*

Treatment/debridement of leg ulcers

Eczema and psoriasis – relief of pain and itching

Facial chemical peels

Obstetrics and gynaecological conditions

Dyspareunia

Other genital pain (e.g., associated with herpes)

Minor gynaecological operations, such as intracavitary brachitherapy

Biopsy of vulval or cervical mucosa

Removal of genital warts (both sexes)

Urological procedures

Urethral dilation

Urethrocytoscopy

Topical anaesthesia before infiltration anaesthesia in highly sensitive areas (e.g., before frenuloplasty to release a tight frenulum)

Post-circumcision

Paediatric indications

Severe grazes

Separation of preputial adhesions in boys with unretractable foreskins

Procedures related to

Gastrostomies

Illiostomies

Colostomies

Dental anaesthesia and nasopharangeal anaesthesia

Minor surgical procedures in the

Mouth

Nasal cavity

Pharnx

Epipharynx

*Applications presently under investigation. All other potential applications are yet to be investigated in a clinical trial setting.

and the US. However, these agents are generally dissolved in ethanol to produce an ionised solution, which is not optimal for absorption. See **Box 2** for examples of products available (availability varies between countries).

4.2 Alternative therapies for the treatment of premature ejaculation

There are presently no licensed therapies for the treatment of PE, although off-label topical treatments are now relatively widely used, despite limited supportive efficacy data (reviewed in [42]). EMLA cream has been clinically tested in PE and is effective at increasing IELT. However, it requires the use a condom (for occlusion and to minimise mess), and as the cream has a water-based formula, the local anaesthetics can be absorbed by the keratinised skin of the shaft of the penis as well as the glans, with a resultant high risk of unwelcome loss of sensitivity in this area [24-26]. In the largest placebo-controlled trial of EMLA cream, 17% of men reported hypoaesthesia, retarded ejaculation (> 30 min) or penile irritation [26]. Other topical treatments designed specifically for use in PE are in various stages of development. SS-cream is a product in development in Korea and contains extracts from nine natural products, some of which have local anaesthetic as well as vasoactive properties. The cream is applied to the glans penis 1 h before intercourse and either washed off before intercourse or covered with a condom. Double-blind studies have shown a dose-dependent prolongation of IELT [27,28]. Despite these promising results, SS-cream has an unpleasant smell and colour which makes it unacceptable to some patients, and there is likely to be considerable resistance to approval of a 'herbal' product in Europe and the US. In addition, no trials have been conducted outside Korea.

A topical cream containing the local anaesthetic dyclonine, combined with alprostadil (prostaglandin E1) is also in the early stage of development (NexMed, Inc.) as a topical treatment for PE. Only limited published data are presently available [43], but the rationale for this combination is that alprostadil is thought to inhibit the ejaculatory process by its potential effects on sympathetic nerves and perineal muscles in emission and ejaculatory processes, and they might presumably work in synergy with the local anaesthetic.

In the absence of an effective alternative that is acceptable to patients, off-label systemic pharmacotherapy has become a popular treatment for PE, and several antidepressants that are known to delay ejaculation are used. These include the SSRIs fluoxetine, paroxetine, sertraline, duloxetine and the tricyclic antidepressant clomipramine [44-46]. However, such treatments carry the risk of unpleasant as well as potentially serious side effects, which limits their acceptability by both patients and physicians. Dapoxetine, a novel rapid-onset SSRI, providing pharmacokinetic differentiation from conventional SSRIs, is the first oral agent specifically developed by Johnson & Johnson for the management of PE. It has been shown to be effective in extending IELTs, it is well tolerated and it is claimed to be suitable for on-demand use [47]. The FDA recently issued a non-approval letter

Box 2. Alternative technologies.

Examples of products sold specifically as desensitisers or to 'extend lovemaking'	
SS-cream (not available outside Korea)	*Angelicae gigantis radix, Cistanchis herba, Torilis semen, Ginseng radix alba, Zanthoxyli fructose, Bufonis venenum, Asiasari radix, Caryophylli flos, Cinnamomi cortex*
Stud 100® (Pound International) spray	9.6% Lidocaine in a stearate base. Contains fragrance, isopropyl myristate, solvent, stearic acid
Mandelay® (Majestic Drug Co.) spray	Benzocaine 7.5%, PEG-8, polyglycerylmethacryalte, propylene glycol
Play Longer lubricant (Durex®) gel	Benzocaine 7.5% benzocaine, carbomer, polyethylene gycol
Products for topical pain management before medical or cosmetic procedures. Some are available over the counter in some countries and may be used as desensitisers to treat premature ejaculation 'off label'	
EMLA® cream (AstraZeneca)	Each gram of cream contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters, carboxypolymethylene, sodium hydroxide and purified water
Topicaine® 4% gel (ESBA)	Each gram of Topicaine contains lidocaine 40 mg in a gel composed of water, ethanol (35% w/w), glycerin, jojoba oil, aloe vera oil, glyceryl monolaurate, benzyl alcohol, carbomer 940, EDTA
Xylocaine spray® (AstraZeneca)	Each dose (spray) contains lidocaine Ph. Eur 10 mg, ethanol, Macrogol 400, essence of banana, menthol natural, saccharin and purified water
LMX 4® (formerly ELA-Max) liposomal lidocaine cream (Ferndale Labs)	4% Lidocaine encapsulated in a liposomal vehicle. Also contains benzyl alcohol, carbomer 940, cholesterol, hydrogenated soy lecithin, polysorbate 80, propylene glycol, vitamin E acetate, water
Ametop gel® (Smith & Nephew)	Amethocaine (tetracaine) 4% gel containing 40 mg of amethocaine base per gram, sodium hydroxide, sodium methyl-p-hydroxybenzoate, sodium propyl-p-hydroxybenzoate, monobasic potassium phosphate, xanthan gum, sodium chloride, purified water

for the use of dapoxetine in the treatment of PE, although plans for regulatory submissions in Europe are apparently ongoing [48].

Men with PE are highly motivated to seek a solution or treatment for their problem, but for reasons of embarrassment, shame or the belief that no medical treatment exists, are also highly likely to try (off-label) treatment with products bought over the counter from pharmacies, sex shops and over the internet. Such products include creams, herbal remedies and 'delay' condoms or the use of double condoms. In one study, 89% of men with PE were reported to have tried some form of self-mediation [9]. With the exception of topical anaesthetics, there is no published evidence that any of these treatments work. A number of topical anaesthetic products are available over the counter in US and Europe for use in a variety of medical conditions, and these are increasingly used to numb the skin before cosmetic procedures. In February 2007, the FDA released a public health advisory warning about the non-medically supervised use of topical anaesthetic creams after a small number of fatalities followed the use of large amounts of unusually high-strength non-FDA approved 'compounded' (i.e., specially prepared in pharmacies) topical anaesthetic creams before cosmetic procedures. This highlights the importance of developing effective and safe products with regulatory approval for use in areas of unmet clinical need, such as PE, where patients are also likely to self-medicate.

5. Conclusion

TEMPE was originally developed as a topical treatment for PE, but its unique formulation means that it is also expected to provide fast-onset anaesthesia to non-keratinised and poorly keratinised skin and mucous membranes where other topical local anaesthetics are unsuitable either due to their consistency or slow onset or short duration of action. At present, TEMPE is in clinical development for two indications where there is presently an unmet need for treatment. Results from clinical trials of the use of TEMPE as a topical treatment for PE so far suggest that it has a number of advantages over other potential treatments for this common sexual problem. It is easy to use, has a fast onset of action, does not require the use of a condom for occlusion and is effective in delaying ejaculation, with minimal adverse events reported by patients or their partners.

Studies have shown that TEMPE produces a clinically and statistically significant improvement in patients' IELT when compared with placebo, and the results are comparable to those reported in the recent literature for effective PE products, including a topical anaesthetic cream [24-26] and oral treatments for PE [45-47].

Clinical trials for the use of TEMPE in pain management are at an earlier stage than for PE, with preliminary, but promising, data in terms of safety and efficacy. The non-aqueous formulation of TEMPE means that it has the potential to be a suitable and convenient method of pain management for use on non-keratinised skin, wounds and mucous membranes.

6. Expert opinion

The development of TEMPE illustrates the advantage of developing products comprising constituents that have been marketed for other indications. Re-formulation in this way gives both a fast track back into clinical development and theoretically back to the market place; the latter is ensured by the availability of a large established clinical safety data base – in the case of TEMPE, that for EMLA). The re-formulation provides an inventive step and in part forms the basis for the creation and protection of *de novo* intellectual property.

Regulatory authorities (particularly the FDA) have become increasingly focussed on benefit–risk ratios for non-life-threatening conditions (e.g., sexual dysfunction). We have already seen evidence that the benefit–risk ratio deemed acceptable in one disease might not be acceptable in another: duloxetine has been approved in the US as Cymbalta® (Eli Lilly) for depression, but was not approved for stress incontinence.

A particular issue in the treatment of sexual dysfunction (erectile dysfunction and PE) is that most of us don't have sex daily: the statistical average is apparently 57-times per annum [49]. Both for the regulatory and cost perspectives, an 'on-demand' treatment would, therefore, seem preferable. Based on present clinical practice, it would seem unlikely that this is achievable with SSRIs. On this basis, not only might topical therapy with TEMPE be the first to reach the market, given that it in many ways will fulfil patient expectations (on demand, fast onset, good duration, no condom required), but it might well take and maintain considerable market share.

The benefit–risk ratio issue relates not only to the development of drugs for sexual dysfunction, but to the management of all non-life-threatening conditions [50]. In many diseases it looks like we have exhausted the pharmacologists' ability to achieve target organ selectivity and thereby an acceptable clinical benefit risk profile. On this basis, irrespective of whether it is for novel chemical entities or products such as TEMPE, other options for drug targeting of specific organs will be increasingly attempted. The various orifices of the urogenital sinus make this a viable option for the treatment of not only PE and erectile dysfunction, but instillation of drugs for benign prostatic hyperplasia, stress and urinary urge incontinence, interstitial cystitis and various uro-gynaecological indications.

In terms of localising drug action, many superficial painful conditions are readily accessible. Potentially TEMPE could have even wider use as a locally applied analgesic therapy in situations where the epidermal integrity is compromised. Given the extensive existing long-term clinical data base on EMLA, there is a good possibility in the short-term that TEMPE could be made available over the counter. In disease-specific terms, the potential of TEMPE, given not only its analgesic properties but also its anti-inflammatory and bactericidal actions, might be worth further clinical evaluation.

Declaration of interest

MG Wyllie is a director and shareholder in Plethora Solutions.

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