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Topical anaesthetics for premature ejaculation: a systematic review and meta-analysis

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Eutectic Mixture of Local Anaesthetics (EMLA) is recommended for use off-label as a treatment for premature ejaculation (PE). Other topical anaesthetics are available, some of which have been evaluated against oral treatments. The purpose of this systematic review was to evaluate the evidence from randomised controlled trials (RCTs) for topical anaesthetics in the management of PE. Bibliographic databases including MEDLINE were searched to August 2014. The primary outcome was intra-vaginal ejaculatory latency time (IELT).

Methodological quality of RCTs was assessed. IELT and other outcomes were pooled across RCTs in a meta-analysis. Between-trial heterogeneity was assessed. Nine RCTs were included. Seven were of unclear methodological quality. Pooled evidence (two RCTs, 43 participants) suggests that EMLA is significantly more effective than placebo at increasing IELT ($P < 0.00001$). Individual RCT evidence also suggests that Topical Eutectic-like Mixture for Premature Ejaculation (TEMPE) spray and lidocaine gel are both significantly more effective than placebo ($P = 0.003$; $P < 0.00001$); and lidocaine gel is significantly more effective than sildenafil or paroxetine ($P = 0.01$; $P = 0.0001$). TEMPE spray is associated with significantly more adverse events than placebo ($P = 0.003$). More systemic adverse events are reported with tramadol, sildenafil and paroxetine than with lidocaine gel. Diverse methods of assessing sexual satisfaction and ejaculatory control with topical anaesthetics are reported and evidence is conflicting. Topical anaesthetics appear more effective than placebo, paroxetine and sildenafil at increasing IELT in men with PE. However, the methodological quality of the existing RCT evidence base is uncertain.

Topical anaesthetics were compared with placebo and oral agents for the treatment of premature ejaculation in a systematic review and meta-analysis. Topical anaesthetics are significantly more effective than placebo, sildenafil or paroxetine at increasing intra-vaginal ejaculatory latency time. Topical Eutectic-like Mixture for Premature Ejaculation spray is associated with erectile dysfunction, numbness and burning. More systemic adverse events are reported with tramadol, sildenafil and paroxetine than with lidocaine gel.

Introduction

Premature ejaculation (PE) is commonly defined by a short ejaculatory latency, a perceived lack of ejaculatory control; both related to self-efficacy; and distress and interpersonal difficulty.¹ PE can be either

lifelong (primary), present since first sexual experiences, or acquired (secondary), beginning later.² A range of definitions for PE exist, having been drafted by various professional organisations.^{3,4} The recently updated International Society of Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation (PE) propose that PE is a male sexual dysfunction characterised by ejaculation within approximately 1 min of vaginal penetration (lifelong PE) or a reduction in latency time to ≤ 3 min (secondary PE), the inability to delay ejaculation, and negative personal consequences.⁵

The treatment of PE should attempt to alleviate concern about the condition as well as increase sexual satisfaction for the patient and the partner.⁶ Available treatment pathways for the condition are varied and treatments may include both behavioural and/or pharmacological interventions. The use of local anaesthetics to delay ejaculation reduces the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.⁷ Based on randomised controlled trial (RCT) evidence, the European Association of Urology guidelines for the management of PE recommend on-demand topical lidocaine-prilocaine cream.⁸ Systematic reviews that have presented a meta-analysis have either not been able to pool data across all RCTs due to missing data,⁹ or have pooled outcome measures reported as arithmetic or geometric means together using a standardised mean difference.¹⁰

The aim of this study was to systematically review the evidence for topical anaesthetics in the management of PE, by summarising evidence from randomised controlled trials (RCTs) and to undertake a meta-analysis across the current evidence base.

Methods

The review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹¹

Searches

The following databases were searched from inception to 5 August 2014 for published and unpublished research evidence: MEDLINE; Embase; Cumulative Index to Nursing and Allied Health Literature (CINAHL); The Cochrane Library including the Cochrane Systematic Reviews Database (CDSR), Cochrane Controlled Trials Register (CCRT), Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database; ISI Web of Science (WoS), including Science Citation Index; and the Conference Proceedings Citation Index-Science. Full search terms are reported elsewhere.¹² The USA Food and Drug Administration (FDA) website and the European Medicines Agency (EMA) website were also searched. Existing systematic reviews were also checked for eligible studies. All citations were imported into Reference Manager Software (version 12, Thomson ResearchSoft, Carlsbad, California) and any duplicates deleted.

Eligible studies

Randomised control trials recruiting adult men with PE were included. RCTs that evaluated Severance Secret cream (SS-cream – a topical plant-based preparation comprising extracts of nine plants) were excluded as this agent is available for use only in one country (Korea).¹³ RCTs that evaluated other topical anaesthetic agents were eligible for inclusion. Randomised cross-over design studies were excluded to avoid double counting of

participants in the meta-analysis. Theses and dissertations were not included. Non-English publications were included where sufficient data could be extracted from an English-language abstract or tables.

Outcomes

The primary outcome was intra-vaginal ejaculatory latency time (IELT). Other outcomes included sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem, quality of life, treatment acceptability and adverse events.

Data extraction

One reviewer performed data extraction of each included study. All numerical data were then checked by a second reviewer.

Methodological quality of studies

Methodological quality of RCTs was assessed using the Cochrane Collaboration risk of bias assessment criteria.¹⁴ We classified RCTs as being at overall ‘low’ risk of bias if they were rated as such for all three of the following key domains – (i) allocation concealment; (ii) blinding of outcome assessment; and (iii) completeness of outcome data (attrition <30%). We classified RCTs as being at overall ‘high’ risk of bias if they were rated as such for any of these domains.

Data synthesis

Where possible, between-group differences for direct comparisons (e.g. selective serotonin re-uptake inhibitors (SSRI) vs placebo) were pooled across trials in a pairwise meta-analysis using Cochrane RevMan software (version 5.2) (RevMan 2012).¹⁵ Continuous outcomes reported as arithmetic and geometric means were analysed separately as the mean difference (MD). Where standard deviations or standard errors were not presented in the trial report, these were estimated from the range (where reported) using the method described by Hozo et al.¹⁶ For pooled comparisons where there was little apparent clinical heterogeneity and the I^2 value (I^2 statistic¹⁷) was 40% or less, a fixed-effect model was applied. Random-effects models were applied where the I^2 value was >40%. Between-group effect estimates were considered significant at $P < 0.05$. Where more than five RCT comparisons were available, publication bias was assessed by visual inspection of funnel plots.

Results

Search results

The searches identified 2331 citations (as part of a wider project assessing a variety of treatments for PE).¹² Of these, 2319 citations were excluded as titles/abstracts. Twelve full-text articles were obtained as potentially relevant. The study selection process is fully detailed in the PRISMA flow diagram in Fig. 1. A total of nine RCTs that evaluated a topical anaesthetic agent against a comparator (placebo or another agent) were identified.

Details of the included RCTs, the comparator(s), outcomes assessed and the risk of bias assessment are detailed in Table 1.

Risk of bias assessment of RCTs

The majority of RCTs were considered to be at an overall unclear risk of bias mainly due to lack of reporting of information to inform the risk of bias assessment. Only one RCT reported that a random sequence generation method,¹⁸ and only one reported that treatment allocation was concealed.¹⁹ One RCT prescribed either an oral or a topical treatment to treatment groups and as such, participants and caregivers would not have been blinded.²⁰ One RCT was described as being single-blind.¹⁸ Both these RCTs were considered to be at high risk of performance bias. In one RCT, numbers withdrawing were imbalanced across groups [placebo 44%, Eutectic Mixture of Local Anaesthetics (EMLA), 28%] and data were analysed per-protocol (withdrawals exclude).¹⁹ One reported that 30% of participants withdrew overall but did not report how many withdrew by treatment group.²¹ Both RCTs were considered to be at an overall high risk due to attrition bias. A summary of the risk of bias assessment for each included RCT is presented in Fig. 2.

Characteristics of RCTs

Randomised control trial details of the treatments, efficacy and safety outcomes, and the risk of bias assessment are presented in Table 1. Where reported, the definition of PE was varied and was defined according to: DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria,^{19,20,22,23} ISSM (International Society for Sexual Medicine) criteria,²⁴ an IELT of 2 min or less,¹⁸ 1 min or less,²⁵ or was not reported.²⁶ The majority of RCTs recruited samples comprising men with lifelong PE and without erectile dysfunction.

A Eutectic Mixture of Local Anaesthetics cream containing lidocaine and prilocaine was prescribed by four RCTs,^{19,20,25,26} whereas three RCTs prescribed topical eutectic-like mixture for premature ejaculation (TEMPE) spray containing lidocaine and prilocaine.^{22–24} One RCT prescribed a lidocaine gel¹⁸ and one a lidocaine spray.²¹ Application of topical anaesthetic agents ranged from 5 min²² to 45 min before sexual intercourse.²⁵ One RCT compared applications of EMLA 20, 30 and 45 min before sexual intercourse.²⁵

With the exception of one RCT,²¹ all RCTs included a placebo group comparison. Other comparators included SSRI,^{18,21} phosphodiesterase-5 (PDE5) inhibitors,^{18,20} electric stimulation²⁶ and tramadol.¹⁸ Treatment duration ranged from five applications to 12 weeks. The majority of included RCTs were of 4 weeks' duration. Four RCTs were undertaken in North America or EU countries.^{21–24} The remainder were undertaken in Brazil,¹⁹ Egypt,¹⁸ Tunisia²⁶ and Turkey.^{20,25}

Outcome data reported by RCTs

With the exception of the RCT by Atan et al.,²⁰ IELT was assessed by all of the included RCTs (Table 1, Figs 3,4). Where reported, the assessment method was by stopwatch. The reporting of other efficacy outcomes was much more varied, both in the assessment method and the outcome data available (Table 1). Across the majority of RCTs, outcome data for adverse event reporting was disparate in terms of limited reporting of types of adverse events and patient numbers.

Data synthesis

Intra-vaginal ejaculatory latency time as a mean outcome with a variance estimate was available for all but two RCTs that reported IELT outcomes, but without any variance estimates. Mallat et al.²⁶ reported a P-value for IELT of $P < 0.001$, but it was unclear if this was across or between groups, or whether this was for end of

study values or change from baseline. Steggall et al.²¹ reported a P-value for median IELT change from baseline of $P = 0.038$ for lidocaine spray and $P < 0.0005$ for paroxetine.

IELT: topical anaesthetics vs placebo

Meta-analysis of mean IELT (min) following an application of EMLA cream ≤ 20 min pre-intercourse, based on two RCTs ($n = 49$), displayed low heterogeneity ($I^2 = 0\%$). The pooled mean difference (MD) in IELT was 6.44, significantly favouring EMLA [MD (fixed effect) 95% confidence interval (CI), 6.01 to 6.87; $P < 0.00001$]. The between-group difference in mean IELT (min) based on one RCT ($n = 54$), was 3.10, significantly favouring TEMPE spray [MD (fixed effect) 95% CI, 1.33 to 5.27; $P = 0.001$]. Meta-analysis of geometric mean IELT (min) based on two RCT study group comparisons ($n = 49$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 2.10 significantly favouring TEMPE spray [MD (fixed effect) 95% CI, 1.27 to 2.93; $P < 0.00001$]. The between-group difference in end of study values based on one RCT ($n = 57$) was 3.29 min (95% CI 2.60 to 3.98; $P < 0.00001$), in favour of lidocaine gel. The forest plot for these analyses is presented in Fig. 3.

Other outcomes: topical anaesthetics vs placebo

Three RCTs did not report any effectiveness outcomes other than IELT (Atikeler et al. 2002;²⁵ Atan et al. 2006;²⁰ Steggall et al. 2008²¹). A statistically significant between-group difference in sexual satisfaction in favour of EMLA cream after 2 months was reported by Busato and Galindo (2004).¹⁹ There appeared to be no difference between EMLA cream and placebo on the International Index of Erectile Dysfunction (IIEF) number of coitus per week and sexual satisfaction values reported by one RCT (Mallat et al. 2012).²⁶ The between-group differences on the Index of Ejaculatory Control and Sexual Quality of Life (SQoL) for both men and women were reported as being not statistically significant at 4 weeks in one RCT comparing TEMPE with placebo (Dinsmore et al. 2007²³). However, two RCTs reported that the TEMPE spray was significantly more effective than placebo at 12 weeks on the Index of Premature Ejaculation (IPE) measures including ejaculatory control, sexual satisfaction and distress, and on the Premature Ejaculation Profile (PEP) (Dinsmore and Wyllie 2009;²⁷ Carson and Wyllie 2010;²²). One RCT¹⁸ reported that end of study mean improvement in sexual satisfaction was significantly higher with lidocaine gel than that of the placebo group ($P < 0.05$).

IELT: topical anaesthetics vs oral agent

One RCT¹⁸ compared a lidocaine gel with tramadol, sildenafil and paroxetine, in addition to comparison with a placebo. The between-group difference in end of study values were 0.83 min (95% CI 0.05–1.16; $P = 0.04$) in favour of lidocaine gel compared with sildenafil and 1.53 min (95% CI 0.76–2.30; $P = 0.0001$) in favour of lidocaine gel compared with paroxetine. Tramadol was significantly more effective than lidocaine gel (1.21 min, 35 95% CI 0.23–2.19; $P = 0.02$). The forest plot for these analyses is presented in Fig. 4. The same RCT reported that end of study mean improvement in sexual satisfaction was significantly higher with both tramadol and sildenafil when compared with lidocaine gel ($P < 0.05$).

Adverse events: topical anaesthetics vs placebo

Meta-analysis of patient numbers experiencing adverse events following treatment with topical anaesthetics displayed low heterogeneity ($I^2 = 0\%$). The between-group difference in EMLA cream applied for ≥ 20 min

compared with placebo was not statistically significant [RR 9.06 (fixed effect) 95% CI 0.55–150.06; $P = 0.12$]. However, Atikeler et al. (2002)²⁵ reported that EMLA cream caused 6/10 men in the 30 min application group and 10/10 men in the 45 min application group to report erection loss or numbness.

The pooled relative risk (RR) across three trials comparing TEMPE spray with placebo (593 participants) was 3.25 [RR (fixed effect) 95% CI 1.50–7.02; $P = 0.003$] in favour of placebo (lower risk). The forest plot for this analysis is presented in Fig. 5.

Adverse events were not reported for one RCT (Steggall et al. 2008²¹). Where reported, adverse events associated with topical anaesthetics included: erectile dysfunction/loss of erection, loss of sensitivity/numbness (men and women) and irritation/burning (men and women). One RCT reported 22/30 (73%) participants receiving lidocaine gel reported penile anaesthesia in the lidocaine gel group, compared with none receiving sildenafil, paroxetine, tramadol or placebo. Greater sleep disturbance, dry mouth, nausea, dizziness, fatigue, vomiting, sweating and headache were reported with tramadol, sildenafil and paroxetine. All side-effects were reported as being tolerable.¹⁸

Discussion

The aim of this study was to systematically review the evidence for topical anaesthetics in the treatment of PE and to pool evidence from RCTs for the effects of topical anaesthetics on IELT in a mean difference meta-analysis. The present systematic review is an extension to our HTA (Health Technology Assessment) short report on treatments for premature ejaculation.¹² In the HTA short report, searches were run to August 2013 and rapid review methods were employed by extracting RCT outcome data reported in existing reviews without obtaining the RCT publication in full. Only RCTs not already captured by existing reviews were obtained in full for data extraction and assessment of methodological quality. The present review has run searches to August 2014, has applied full systematic review methods, obtaining in full all RTCs evaluating topical anaesthetics identified for inclusion for data extraction and assessment of methodological quality. Two further RCTs published subsequent to the HTA short report searches have been identified,^{18,26} one of which compares topical anaesthetics with oral agents.¹⁸

The pooled evidence across two RCTs^{19,25} including 49 participants suggests that EMLA cream is effective in significantly increasing IELT in men with PE when compared with placebo [mean difference 6.44 (95% CI 6.01–6.87) min, $P < 0.00001$]. Evidence from one RCT²³ (54 participants) suggests that TEMPE spray is effective in significantly increasing IELT in men with PE when compared with placebo [mean difference 3.10 (95% CI 1.05–5.15) min, $P = 0.003$]. Evidence from one RCT¹⁸ suggests that lidocaine gel is significantly more effective than placebo [57 participants, mean difference 3.29 (95% CI 2.60–3.98) min, $P < 0.00001$], that lidocaine gel significantly more effective than sildenafil (60 participants, 0.83 min, $P = 0.04$), and that lidocaine gel is also significantly more effective than paroxetine (58 participants, 1.53 min, $P = 0.0001$). However, evidence from the same trial also suggests that tramadol is significantly more effective than lidocaine gel (59 participants, 1.21 min, $P = 0.02$).

Evidence from one RCT¹⁹ comparing EMLA cream with placebo suggests significant improvements in sexual satisfaction with EMLA, while another RCT suggests no significant difference.²⁶ Conflicting evidence also exists for TEMPE spray. Evidence from two RCTs^{22,27} comparing TEMPE with placebo suggest significant

improvements in both sexual satisfaction and ejaculatory control with TEMPE, while another RCT suggests no significant difference in sexual quality of life or ejaculatory control.²³ One RCT comparing lidocaine gel with placebo suggests significant improvements in sexual satisfaction with lidocaine gel.¹⁸ However, diverse assessment methods are evident across the RCTs reporting these outcomes.

Pooled evidence across three RCTs^{22–24} (49 participants) suggests there are significantly more adverse events associated with TEMPE compared with placebo or EMLA. These include loss of sensitivity/numbness and irritation/burning for both men and women. Erectile dysfunction and loss of erection are also reported with EMLA, but appear to be related to treatment applications ≥ 20 min pre-intercourse. Greater sleep disturbance, dry mouth, nausea, dizziness, fatigue, vomiting, sweating and headache are reported with tramadol, sildenafil and paroxetine use.

Two of the RCTs^{19,21} reported high rates of attrition and two^{18,20} were considered at high risk of performance bias as they were not of a double-blind. The majority of RCTs were considered at overall unclear risk of bias mainly due to lack of reporting of information to inform the risk of bias assessment. The findings should therefore be interpreted with caution given the methodological quality of the available evidence. Key aspects of best practice in RCT design to minimise bias include a robust randomisation method, concealment of treatment group allocation, and, where possible, blinding of participants and trial personnel, and blinded outcome assessment; all of which should be clearly stated in the RCT report.²⁸ In addition, patient acceptability of this treatment modality (topical application) for PE has not been evaluated in the current evidence base.

Although our database search strategy was comprehensive, the possibility of a publication bias cannot be discounted. Insufficient numbers of RCT comparisons were available for a formal assessment of publication bias using funnel plots to be undertaken. Nonetheless, although the majority of RCTs identified for inclusion were of unclear methodological quality, it could be considered unlikely that any additional, unpublished data for the effects of topical anaesthetics would contribute significantly to the overall findings of this review.

The results observed by this review for the effectiveness of topical anaesthetics in the treatment of PE are comparable with other reviews.^{9,10} However, where meta-analyses have previously been undertaken, IELT data reported as arithmetic means have been pooled with geometric means using a standardised mean difference.¹⁰ This review has pooled data across RCTs, where appropriate, in a meta-analysis using a mean difference to summarise IELT outcomes, analysing separately RCTs reporting geometric means (log-transformed). Log-transformed and untransformed data are not recommended to be pooled together in a meta-analysis.²⁹ Furthermore, this review has been able to include evidence for topical anaesthetics compared with oral agents prescribed off-label for the treatment of PE.

The RCTs evaluating topical anaesthetics identified for inclusion in this review evaluated treatments over 4–12 weeks. None reported a long-term follow up on efficacy and safety outcomes or treatment persistence. Systemic adverse events were more prevalent with oral treatments, which may make topical anaesthetics more acceptable. Likewise, the rapid action of topical anaesthetics compared with planning to take oral medication in advance might also be more acceptable. Conversely, the inconvenience of washing and transfer of the agent to the partner might be limiting factors to acceptability. Participant preference was not an outcome assessed by any RCT. However, more important is a requirement for clearer evaluations of the relationship between treatment-

related increases in IELT, ejaculatory control and sexual satisfaction associated with topical anaesthetics. One RCT suggests that tramadol is more effective than topical anaesthetics at increasing IELT in men with PE; however, the long-term use of tramadol for the treatment of PE, in terms of a safety profile including addiction potential, is unclear from the current evidence base.

The European Association of Urology 2014 Guidelines on male sexual dysfunction recommend that pharmacological treatment options include ‘on demand’ dapoxetine, daily use of a longer-acting SSRI (off-label use), daily use of clomipramine (off-label use), ‘on demand’ topical lidocaine–prilocaine cream (off-label use) and ‘on demand’ tramadol (off-label use).⁸ Given that topical anaesthetics have been extensively evaluated against placebo for the treatment of PE in the current evidence base, with limited head-to-head comparisons between topical anaesthetics and other treatments (paroxetine, sildenafil and tramadol), further direct comparisons between topical anaesthetics and other SSRIs, including dapoxetine and other PDE5 inhibitors, should now be investigated. While the observed increases in IELT were statistically significant in favour of topical anaesthetics for most comparators, it is difficult to quantify how acceptable and meaningful these changes are for men with PE, without being able to evaluate the relationship between IELT, ejaculation control and sexual satisfaction from the current RCT evidence-base for topical anaesthetics. The trade-off between IELT and other effectiveness outcomes versus adverse effects should also be further evaluated as should treatment acceptability and persistence.

Conclusion

Topical anaesthetics appear more effective than placebo, paroxetine and sildenafil at increasing IELT in men with PE. However, these findings should be interpreted with caution given the limited methodological quality of the available evidence.

Conflicts of interest

All authors have no conflicts of interest.

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Fig. 1. Study selection process. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Fig. 2. Risk of bias assessment summary by randomised controlled trial (RCT).

Fig. 3. Eutectic mixture of local anaesthetics (EMLA) cream, topical eutectic-like mixture for premature ejaculation (TEMPE) spray or lidocaine gel vs placebo: forest plot of intra-vaginal ejaculatory latency time (IELT) outcomes.

Fig. 4. Lidocaine gel vs sildenafil, paroxetine or tramadol: forest plot of intra-vaginal ejaculatory latency time (IELT) outcomes.

Fig. 5. Topical anaesthetics vs placebo: forest plot of adverse events.

Table 1. Randomised control trial (RCT) characteristics, efficacy and safety outcomes and risk of bias assessment

AE, adverse events; DSM, Diagnostic and Statistical Manual of Mental Disorders; ED, erectile dysfunction; IELT, intra-vaginal ejaculatory latency time; IIEF, International Index of Erectile Function; EMLA, eutectic mixture of local anaesthetics; IPE, Index of Premature Ejaculation; ISSM, International Society for Sexual Medicine; NR, not reported; PC, pre-coitus; PE, premature ejaculation; PEP, Premature Ejaculation Profile; sQoL, sexual quality of life; TEMPE, topical eutectic-like mixture for premature ejaculation

RCT (country)	PE definition, Duration	Treatment, comparator, numbers analysed/ PE, erectile dysfunction	Efficacy outcomes and results	Adverse events	Risk of bias assessment
Atan et al. 2006 ²⁰ (Turkey) 8 weeks	DSM-IV Lifelong and acquired ED, IIEF ED <21 excluded	– Topical EMLA applied 15 min PC, n=22 – Sildenafil 50 mg 45 min PC, n=20 – Sildenafil 50 mg 45 min PC + topical EMLA applied 15 min PC, n=15 – Oral placebo, n=20 n analysed NR assume 100%	IELT not assessed ‘Improvement’ or ‘cure’: EMLA, 77%; Sildenafil, 55% ($P > 0.05$); Sildenafil + EMLA, 86%; Placebo, 40%. (Not reported if P-value across or between groups)	Only patients receiving sildenafil experienced side effects: headache, 26%; flushing, 26%	Unclear risk – no statement on allocation concealment, blinded outcome assessment or withdrawals
Atikeler et al. 2002 ²⁵ (Turkey) ≥ 5 applications	IELT <1 min Lifelong ED, NR	– EMLA 2.5 g applied with condom: – 20 min PC, n=10 – 30 min PC, n=10 – 45 min PC, n=10 – Placebo cream applied with condom 20 min PC, n=10 n analysed NR assume 100%	IELT (stopwatch): see Fig. 3. No other outcomes reported	n/N (%) experiencing AEs: EMLA 20 min, 0/10 (0%); placebo, 0/10 (0%) Erection loss or numbness: 30 min group, 6/10; 45 min group, 10/10	Unclear risk - no statement on allocation concealment or blinded outcome assessment
Busato and Galindon 2004 ¹⁹ (Brazil) 4–8 weeks	DSM-IV Lifelong and acquired ED excluded	– EMLA 2.5 g with condom 10–20 min PC, 16/24 (67%) – Placebo cream with condom 20 min PC, 13/18 (72%)	IELT (stopwatch): see Fig. 3. Sexual satisfaction: EMLA, 5/16 (31.3%); placebo, 0/13 (0%) n/N reporting ‘great’ or ‘excellent’ satisfaction: EMLA, 6/16; 5/16; Placebo, 3/13; 0/13	n/N (%) experiencing AEs: EMLA, 5/16 (31.3%); placebo, 0/13 (0%) EMLA-associated AEs: Men, 2/29 retarded ejaculation, 2/29 loss of sensitivity, 2/29 penile irritation; Women 1/29 decreased	High risk – numbers withdrawing imbalanced across groups – placebo 44%, EMLA 28%; analysed per-protocol

RCT (country) Duration	PE definition, lifelong/acquired PE, erectile dysfunction	Treatment, comparator, numbers analysed/ randomised (%), when taken	Efficacy outcomes and results	Adverse events	Risk of bias assessment
Carson and Wyllie 2010 ²² (USA, Canada and Poland) 12 weeks	DSM-IV and ISSM Lifelong and acquired ED excluded	<ul style="list-style-type: none"> - TEMPE spray 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 5 min PC, 167/167 (100%) - Placebo spray 3 actuations, 82/82 (100%) 	<p>IELT (stopwatch): see Fig. 3.</p> <p>Ejaculatory control (IPE): TEMPE, 11.6; (10%); placebo, 6.5</p> <p>Sexual satisfaction (IPE): TEMPE, 13.4; placebo, 8.6</p> <p>Distress (IPE): TEMPE, 6.1; placebo, 3.7</p> <p>PEP \geq 1 point improvement: P < 0.0001 (unclear if between groups or baseline)</p>	<p>n/N (%) experiencing AEs: TEMPE, 17/167 (10%); placebo, 1/82 (<1%)</p>	Unclear risk – no statement on allocation concealment or blinded outcome assessment
Dinsmore and Wyllie 2007 ²³ (UK and The Netherlands) 4 weeks	DSM-IV Lifelong ED excluded	<ul style="list-style-type: none"> - TEMPE 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 15 min PC, 20/27 (74%) - Placebo spray 3 actuations, 23/28 (82%) 	<p>IELT (stopwatch): see Fig. 3.</p> <p>Ejaculatory control (IEC) change: TEMPE, 6.7; placebo, 3.0; P = 0.12</p> <p>SQoL change: TEMPE, men 7.0, women 3.3. Placebo, men 5.5, women 1.8. P-value men, 0.48; women, 0.56</p>	<p>n/N (%) experiencing AEs: TEMPE, 6/26 (23%); placebo, 4/28 (14%)</p> <p>TEMPE: hypoesthesia, 3/26; erectile dysfunction, 1/26. Women: mild burning 1/26</p>	Unclear risk – no statement on allocation concealment or blinded outcome assessment
Dinsmore and Wyllie 2009 ²⁴ (31 sites across Europe) 12 weeks	ISSM Lifelong and acquired ED excluded	<ul style="list-style-type: none"> - TEMPE 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 5 min PC, 191/200 (96%) - Placebo spray 3 actuations, 99/100 (99%) 	<p>IELT (stopwatch): see Fig. 3.</p> <p>Ejaculatory control (IPE): TEMPE, 14.3; placebo, 7.4</p> <p>Sexual satisfaction (IPE): TEMPE, 14.8; placebo, 9.1</p> <p>Distress (IPE): TEMPE, 7.1; placebo, 4.5</p> <p>PEP \geq 1 point improvement: P < 0.001 (unclear if</p>	<p>n/N (%) experiencing AEs: TEMPE, 18/191 (9%); placebo 3/99 (3%)</p> <p>Genital burning, erythema and hypoesthesia (male) and vulvovaginal burning discomfort (female) reported with TEMPE, but not placebo</p>	Unclear risk – no statement on allocation concealment or blinded outcome assessment

RCT (country)	PE definition, duration	Treatment, comparator, numbers analysed/randomised (%), when taken	Efficacy outcomes and results	Adverse events	Risk of bias assessment
Gameel et al. 2013 ¹⁸ (Egypt) 4 weeks	IELT of <2 min in >75% of episodes. All had PE for >1 year ED, excluded	– Lidocaine gel 15 min PC + oral multivitamin 1–4 h PC, 30/30 (100%) – Tramadol 50 mg 2 h PC + inert lubricating gel 15 min PC, 29/30 (97%) – Sildenafil 50 mg 1 h PC + inert lubricating gel 15 min PC, 30/30 (100%) – Paroxetine 20 mg 4 h PC + inert lubricating gel 15 min PC, 28/30 (93%) – Placebo (oral multivitamin 1–4 h PC + inert lubricating gel 15 min PC), 27/30 (90%)	IELT (stopwatch): see Fig. 3 and Fig. 4. Sexual satisfaction (0 to 5 point scale: end of study mean improvement in all active-treatment groups was significantly higher than in the placebo group ($P < 0.05$). Tramadol and sildenafil significantly greater than lidocaine gel ($P < 0.05$)	22/30 (73%) reported penile anaesthesia in lidocaine gel group (none in other groups). Greater sleep disturbance, dry mouth, nausea, dizziness, fatigue, vomiting, sweating and headache were reported with tramadol, sildenafil and paroxetine. All side-effects were reported as being tolerable.	Unclear risk – allocation method and blinded outcome assessment not reported
Mallat et al. 2012 ²⁶ (Tunisia) 12 weeks	PE definition, NR Lifelong/acquired, NR ED, NR	– EMLA applied 1 h PC, n=30 – Electric stimulation – not described, n=30 – Placebo – not described, n=30 n analysed NR, assume 100%	IELT (method NR): EMLA increased to 3.35 min; ES increased to 4.05; placebo to 0.57, $P < 0.001$ but unclear if change from baseline or across groups. No variance estimates reported. Mean weekly intercourse and IIEF intercourse satisfaction $P < 0.05$ but unclear if change from baseline or across groups	More adverse events associated with EMLA (not described), but no withdrawals due to AEs	Unclear risk – no statement on allocation concealment, blinded outcome assessment or withdrawals
Steggall et al. 2008 ²¹ (UK) 4 weeks	DSM IV diagnosis plus IELT ≤ 3 min. Lifelong and acquired ED, NR	– Lidocaine 3–8 sprays applied 10 min PC, n=17 – Paroxetine 20 mg per day, n=27 Total analysed, 44/60 (73.3%) n randomised by group NR	IELT (stopwatch) week 4: Lidocaine – mean, 3.03 min; median, 2.75 ($P = 0.038$, assume for change); geometric mean, 3.68 Paroxetine – mean, 4.71 min; median, 3.00 ($P < 0.0005$, assume for change); geometric	Adverse events NR	High risk – 30% withdrew overall and not reported how many withdrew by group.

RCT (country)	PE definition, lifelong/acquired	Treatment, comparator, numbers analysed/ randomised (%), when taken	Efficacy outcomes and results	Adverse events	Risk of bias assessment
Duration	PE, erectile dysfunction		mean, 3.68		
			No variance estimates reported		

Figure 1. Study Selection Process - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

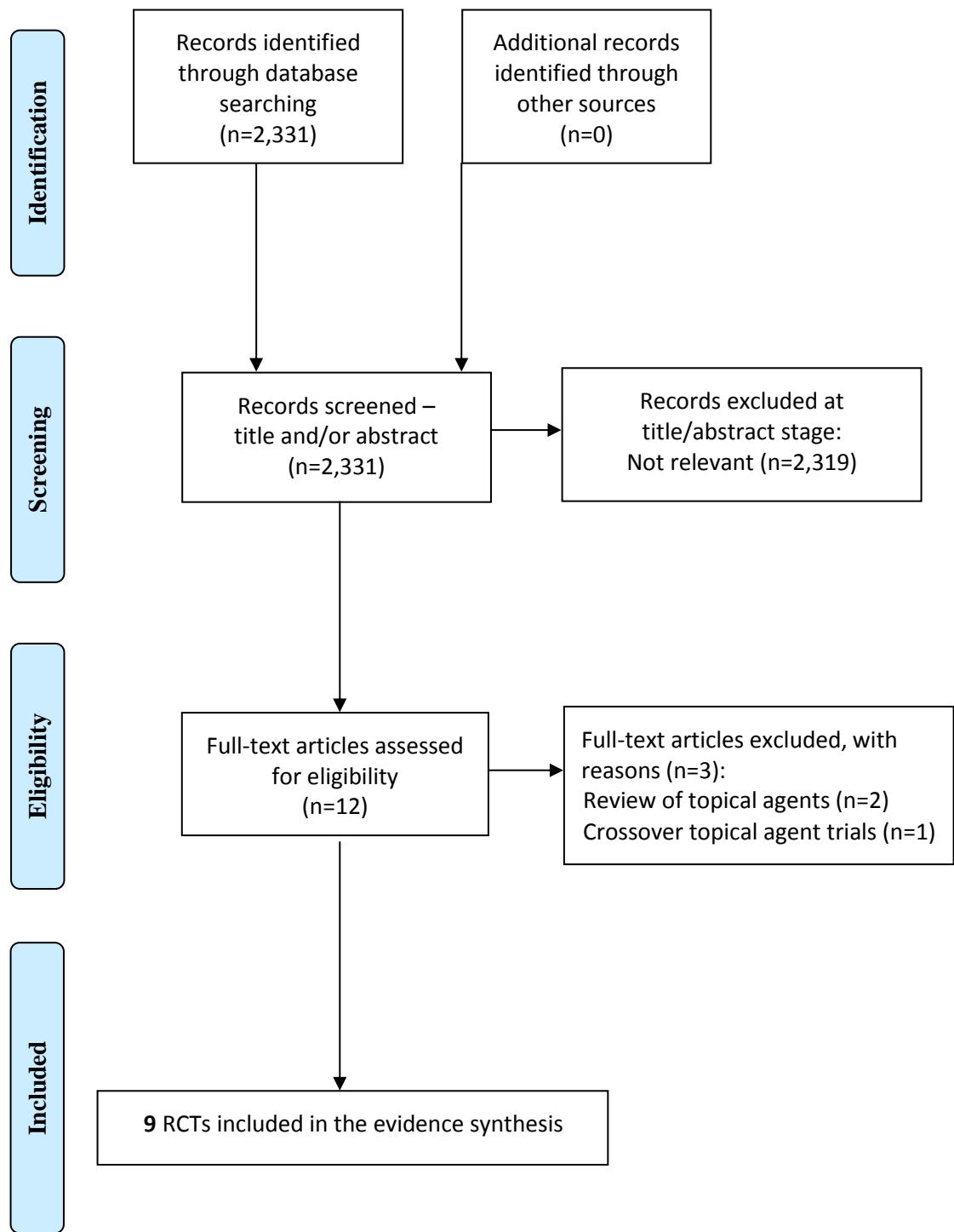


Figure 2. Risk of bias assessment summary by RCT

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall
Atan 2006	?	?	-	?	+	?	?
Atikeler 2002 20min	?	?	?	?	+	+	?
Busato 2004	?	+	+	?	-	+	-
Carson 2010	?	?	+	?	+	+	?
Dinsmore 2007	?	?	+	?	+	+	?
Dinsmore 2009	?	?	+	?	+	+	?
Gameel 2014	+	?	-	?	+	+	?
Mallatt 2012	?	?	?	?	?	+	?
Steggall 2008	?	?	?	?	-	+	-

?, unclear risk of bias; +, low risk of bias, -, high risk of bias

Figure 3. EMLA cream, TEMPE spray or lidocaine gel vs. placebo - forest plot of IELT outcomes

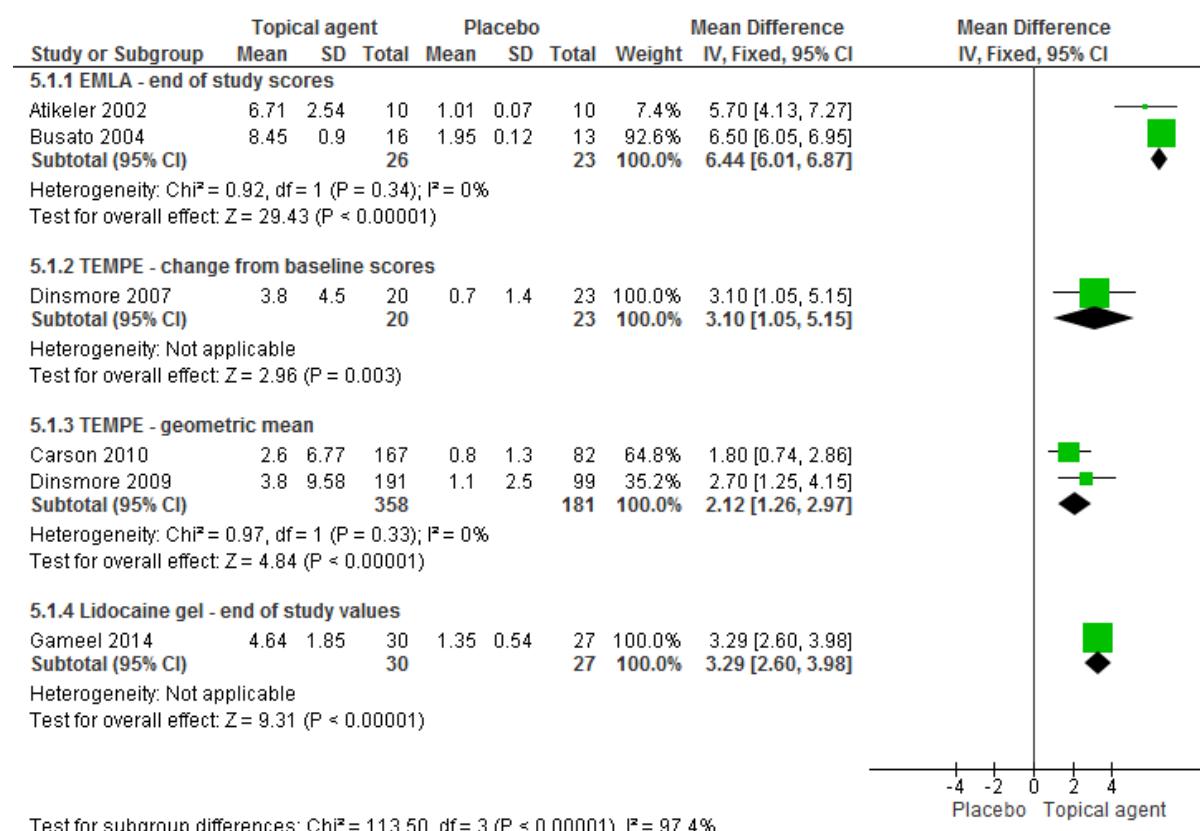


Figure 4. Lidocaine gel vs. sildenafil, paroxetine or tramadol - forest plot of IELT outcomes

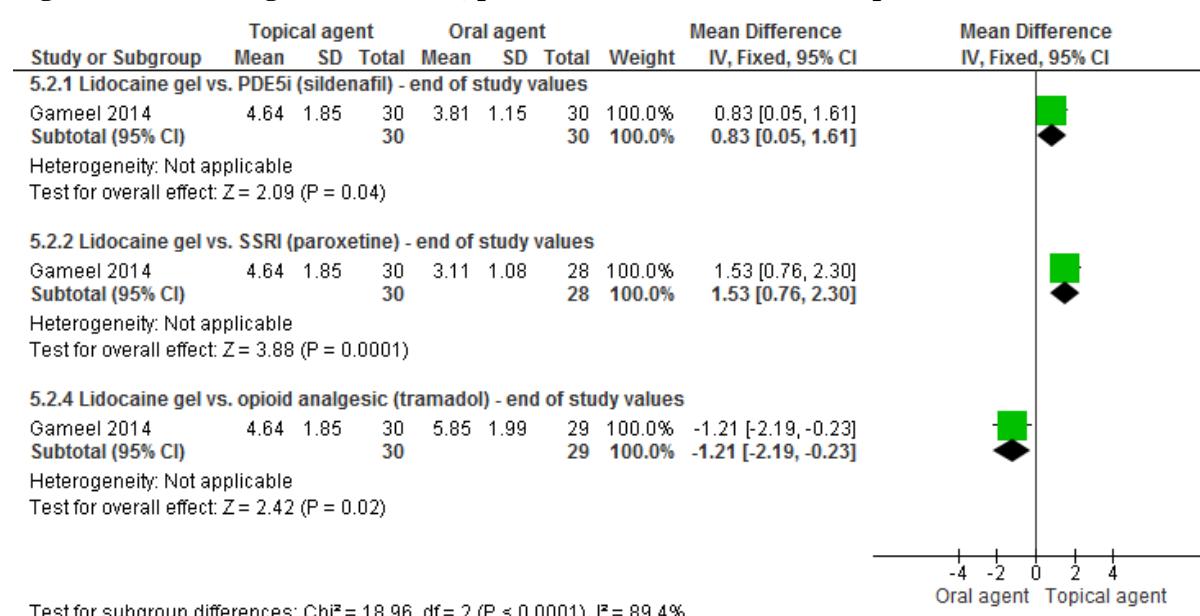


Figure 5. Topical anaesthetics vs. placebo - forest plot of adverse events

