6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [715]. Several trials [582, 716, 717] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Meta-analyses have confirmed the efficacy and safety of these agents for the treatment of PE [718]. In a meta-analysis, the efficacy of local anaesthetics was best among the other treatment options including SSRIs, dapoxetine 30 and 60 mg, PDE5Is and tramadol for < 8 weeks of therapy [718].

6.2.6.2.3.1 Lidocaine/prilocaine cream

Lidocaine/prilocaine creams can significantly increase the stopwatch-measured IELT from 1-2 minutes to 6-9 minutes [719, 720]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. These anaesthetic creams/gels may be transferred to the partner, resulting in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream to their penis. Alternatively, the penis can be washed to clean off any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples seeking parenthood should not use topical lidocaine/prilocaine-containing substances [721].

6.2.6.2.3.2 Lidocaine/prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL), which has been officially approved by the EMA for the treatment of lifelong PE [722]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [723], without absorption through the penile shaft skin [724].

Several studies have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and PROs three sprays administered 5 min before sexual intercourse [725, 726]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over 3 months, with a month-by-month improvement through the course of the treatment in long-term studies [727]. A low incidence of local TEAEs in both patients and partners has been reported, including genital hypoaesthesia (4.5% and 1.0% in men and female partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [728, 729]. Lidocaine-only sprays are also available and found to be effective in the treatment of PE [730, 731].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and serotonin and noradrenaline re-uptake inhibition. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [732]. This mechanism of action distinguishes tramadol from other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours.

Several clinical trials evaluated the efficacy and safety of tramadol ODT (62 and 89 mg) and tramadol HCl in the treatment of PE [733]. Up to 2.5-fold increases in the median IELT have been reported among patients who received on demand tramadol treatment [734, 735].

Adverse effects were reported at doses used for analgesic purposes (≤ 400 mg daily) and included constipation, sedation and dry mouth. In May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [736]. The tolerability during the twelve-week study period in men with PE was acceptable [737]. Several other studies have also reported that tramadol exhibits a significant dose-related efficacy along with potential adverse effects during the treatment of PE [734, 735]. The Guidelines Panel considers tramadol as a potential alternative treatment to established first-line therapeutic options in men with PE; however, it should be clearly outlined that the use of tramadol has to be considered with caution since there is a lack of data on the long-term safety of the compound in this setting.

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and the refractory time to achieve a second erection after ejaculation [738, 739]. Several open-label studies have shown that a combination of PDE5Is and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [718, 740]: