Oral Agents for the Treatment of Premature Ejaculation: Review of Efficacy and Safety in the Context of the Recent International Society for Sexual Medicine Criteria for Lifelong Premature Ejaculation

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ABSTRACT

Introduction. New diagnostic criteria for lifelong premature ejaculation (PE) have been proposed by the International Society of Sexual Medicine (ISSM), including an intravaginal ejaculatory latency time (IELT) of less than about 1 minute, lack of control over ejaculation, and PE-related distress or bother.
Aim. The aim of this study was to review evidence supporting the efficacy and safety of oral agents for the treatment of PE in the context of the new ISSM criteria.
Methods. The PubMed database was searched for randomized, double-blind, placebo-controlled studies of oral agents in PE that included stopwatch measurements of IELT.
Main Outcome Measures. The main outcome measure used for this study was a review of the efficacy and safety data of oral agents for PE aligned with ISSM criteria.
Results. Since the latest meta-analyses using similar criteria (conducted in 2004 and 2005 for selective serotonin reuptake inhibitors [SSRIs] and phosphodiesterase type 5 [PDE-5] inhibitors, respectively), eight studies evaluated SSRIs vs. placebo, one compared SSRIs, two evaluated PDE-5 inhibitors, and one evaluated an SSRI/PDE-5 inhibitor combination. New agents included dapoxetine (five studies) and tramadol (one study). Six studies enrolled men who met an approximation of the ISSM criteria. Although evidence suggests that most SSRIs, tramadol, and dapoxetine increase IELT to varying degrees, few studies included control over ejaculation and PE-related distress or bother as enrollment criteria or used validated patient-reported outcome instruments to evaluate these parameters. Among studies that provided comprehensive adverse event data, safety and tolerability observations in men with PE were generally similar to those observed in other populations; however, with the exception of dapoxetine, known SSRI-class effects (e.g., withdrawal syndrome) were not evaluated in men with PE.
Conclusions. This systematic review of well-controlled clinical trials in PE has demonstrated that while many oral agents, particularly SSRIs, tramadol, and dapoxetine, have proven effective and safe for the treatment of men with PE, few have been evaluated for their effects on the specific elements of the ISSM criteria. **McMahon CG and Porst H. Oral agents for the treatment of premature ejaculation: Review of efficacy and safety in the context of the recent international society for sexual medicine criteria for lifelong premature ejaculation. J Sex Med 2011;8:2707–2725.**

Key Words. Premature Ejaculation; IELT; ISSM Criteria; Control over Ejaculation; Bother; Distress

Introduction

Common treatment interventions for premature ejaculation (PE) include off-label use of oral agents, such as selective serotonin reuptake inhibitor (SSRI) antidepressants [1–3], the tricyclic antidepressant clomipramine that blocks serotonin, dopamine, and norepinephrine transporters [4], phosphodiesterase (PDE)-5 inhibitors [1], or topical anesthetic creams or sprays [1–3,5]. Other

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agents, including α1-adrenoreceptor antagonists [6,7] and the analgesic opioid receptor agonist and noradrenaline reuptake inhibitor tramadol [8,9] have also been investigated for treating PE [2,10]. Psychotherapy and behavioral therapy also have a role, although well-designed, controlled trials that use such approaches are lacking [3,5,10]. To date, the largest trials of a treatment for PE have been conducted with dapoxetine [11–14], a short-acting SSRI that is the only oral agent approved for the treatment of PE in several European, Asia-Pacific, and South American countries.

Evidence-based criteria for the diagnosis of lifelong PE have recently been proposed by the International Society for Sexual Medicine (ISSM) [15], including an intravaginal ejaculatory latency time (IELT) of approximately 1 minute or less, lack of control over ejaculation, and negative psychological consequences such as distress, bother, frustration, and/or sexual avoidance. Consequently, recent proposals recommend that studies of PE should include stopwatch assessments of IELT and validated patient-reported outcome (PRO) measures for control over ejaculation and PE-related distress or bother [16,17].

This systematic review qualitatively examines the efficacy and safety of oral agents evaluated for the treatment of PE, including not only those agents for which data have accumulated over many years, but also on novel treatments for which data have recently become available. The majority of these data has been collected prior to the formal inclusion of IELT in the definition of PE; therefore, the purpose of this review was to reexamine how this evidence supports the use of these treatments in the context of the new ISSM criteria (Table 1).

Evidence Acquisition

All studies of oral treatments for PE published in peer-reviewed medical journals since 2004 were identified by searching for the keyword "premature ejaculation" in the PubMed database. This search was then manually cross-referenced for all papers, and well-designed studies of oral agents were manually extracted. Well-designed studies were defined as randomized, double-blind, placebo-controlled trials that included stopwatch-measured IELT as an outcome measure [17,18]. Studies of SSRIs and clomipramine published prior to 2004 were identified from a meta-analysis and systematic review by Waldinger [19], and studies evaluating PDE-5 inhibitors and SSRI/PDE-5 inhibitor combination therapies published prior to 2005 were identified from a systematic review by McMahon [20] and another recent study [21] (summarized in Table 2). Studies were selected for inclusion in this review after evaluation by the authors.

Evidence Synthesis

Outcome Measures Evaluated

The basis of ideal PE clinical trial design involves adequately defining the trial population, a cohort or case-study observational trial design, a double-blind placebo-controlled interventional randomized clinical trial design, or a double-blind, crossover randomized clinical intervention preference trial, and the use of sensitive, validated, and reproducible outcome measures.

PROs can be assessed using validated single-item questions, validated multi-item multi-domain PE inventories, or validated omnibus sexual inventories. PROs for use in clinical trials of investigational drugs be have robust reliability, reproducibility, and internal validity and should conform to the guidelines of the relevant regulatory agency [30]. Although each of the three PROs of PE (IELT, control, and distress) has been operationalized, they may not be equally weighted, may vary in importance between subjects, and may have

Table 1 Definition of approximations of the ISSM criteria for lifelong PE

	Enrollment criteria	Outcome measures
ISSM criteria [15]	ELT of about 1 minute Lack of control over ejaculation Negative psychological consequences	Stopwatch-measured IELT Validated PRO measures of control over ejaculation Validated PRO measures of distress or bother related to PE
Retrospective approximations of ISSM criteria for lifelong PE used in this analysis	Defined IELT threshold Applied consensus criteria for lack of control over ejaculation Applied consensus criteria for elements of PE-related distress or bother	Stopwatch measured IELT Validated PRO measures related to PE

ISSM = International Society for Sexual Medicine; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; PRO = patient-reported outcome.

Table 2 Well-designed studies for the treatment of PE*

Agent(s)	Source	Study	Dosing regimen	Study design	Approximates ISSM criteria	Stopwatch-measured IELT	Validated PROs
Single agent vs. placebo							
Fluoxetine	Waldinger 2004 meta-analysis and systematic review [19]	Novaretti et al. 2002 [22]	Fluoxetine 20 mg or placebo once daily	Double-blind, randomized, crossover	Not clear: "complaint of PE" followed by interview (assume DSM-IV)	Yes	Yes: Hamilton Anxiety and Depression Scale; Beck Depression Inventory
	Waldinger 2004 meta-analysis and systematic review [19,23]	Kara H et al. 1996 [24]	Fluoxetine 40 mg or placebo daily (after 1-week titration on fluoxetine 20 mg or placebo daily)	Double-blind, randomized, parallel group	Partially: DSM-III	Yes	Yes: Hamilton Depression Scale
Duloxetine	Database search	Athanasios 2007 [25]	Duloxetine 40 mg or placebo twice daily (following 1 week titration with duloxetine 20 mg or placebo twice daily)	Double-blind, randomized, parallel group	Partially: DSM-III-R	Yes	Yes: CGI-I
Citalopram	Waldinger 2004 meta-analysis and systematic review [19]	Atmaca M et al. 2002 [26]	Citalopram 20–60 mg or placebo 1–3 pills once daily (individual titration based on response and tolerability)	Double-blind, randomized, parallel group	Partially: DSM-III-R	Yes	Yes: CGI-I; YSFI-II
Clomipramine	Waldinger 2004 meta-analysis and systematic review [19]	Althof SE et al. 1995 [4]	Clomipramine 25 or 50 mg or placebo once daily	Double-blind, crossover, randomized	Partially: IELT ≤4 minutes	Yes	Yes: Symptom Checklist-90-R, Dyadic Adjustment Scale, State-Trait Anxiety Inventory, Harder Self-Esteem Inventory
Sildenafil	McMahon 2006 systematic review [20]	McMahon et al. 2005 [27]	Sildenafil 50–100 mg or placebo prn	Double-blind, randomized, parallel group	Yes: DSM-IV criteria + IELT ≤2 minutes	Yes	Yes: IPE
Vardenafil	Database search	Aversa et al. 2009 [21]	Vardenafil 10 mg or placebo prn	Double-blind, randomized, crossover	Yes: ISSM criteria with IELT ≤1 minute on 90% of attempts, PEDT score ≥11	Yes	Yes: IPE
Dapoxetine	Database search	Pryor et al. 2006 [11]	Dapoxetine 30 or 60 mg or placebo prn (1–3 hours prior to intercourse)	Double-blind, randomized, parallel group	Yes: DSM-IV criteria + IELT ≤2 minutes	Yes	Yes: single-items for control over ejaculation and satisfaction with sexual intercourse; CGI

Table 2 Continued

Agent(s)	Source	Study	Dosing regimen	Study design	Approximates ISSM criteria	Stopwatch-measured IELT	Validated PROs
	Database search	Buvat et al. 2009 [12]	Dapoxetine 30 or 60 mg or placebo prn (1–3 hours prior to intercourse)	Double-blind, randomized, parallel group	Yes: DSM-IV criteria + IELT ≤2 minutes (including sub-analyses of IELT ≤1 minute and ≤0.5 minute)	Yes	Yes: PEP; CGI
	Database search	McMahon et al. 2010 [14]	Dapoxetine 30 or 50 mg or placebo prn (1–3 hours prior to intercourse	Double-blind, randomized, parallel group	Yes: DSM-IV criteria + IELT ≤2 minutes (including sub-analyses of IELT ≤1 minute and ≤0.5 minute)	Yes	Yes: PEP; CGI
Combination therapy trials							
Tadalafil, Fluoxetine, Fluoxetine + tadalafil, and placebo	Database search; publication resulting from abstract cited in McMahon 2006 systematic review	Mattos 2008 [23]	Tadalafil 20 mg or placebo prn (1–36 hours prior to intercourse); Fluoxetine 90 mg or placebo once/ week	Double-blind, randomized, double-dummy, parallel group	Yes: DSM-IV criteria + IELT ≤90 seconds	Yes	No
Comparative trials							
Fluoxetine, fluvoxamine, paroxetine, sertraline, and placebo	Waldinger 2004 meta-analysis and systematic review [19]	Waldinger et al. 1998 [28]	Fluoxetine 20 mg, fluvoxamine 100 mg, paroxetine 20 mg, sertraline 50 mg, or placebo once daily	Double-blind, randomized, parallel group	Partially: IELT ≤1 minute	Yes	No
Paroxetine, sertraline, nefazodone and placebo	Waldinger 2004 meta-analysis and systematic review [19]	Waldinger et al. 2001 [29]	Paroxetine 20 mg, sertraline 50 mg, nefazodone 400 mg or placebo daily	Double-blind, randomized, parallel group	Partially: IELT ≤1 minute	Yes	No

*Criteria for inclusion in the table were appropriate placebo control, randomized, double-blind, and stopwatch measurement of IELT.
ISSM = International Society for Sexual Medicine; IELT = intravaginal ejaculatory latency time; PRO = patient-reported outcome; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; IPE = Index of Premature Ejaculation; IIEF = International Index of Erectile Function; CGI-I = clinical global impression-improvement; PEP = Premature Ejaculation Profile; AIPE = Arabic Index of Premature Ejaculation.

differing meanings in different cultures where the attitude of the partner and culturally determined extent of emancipation may have an impact upon the subject's subjective diagnosis of PE. Inventories must be psychometrically validated to demonstrate reliability, convergent and divergent validity, and sensitivity between individual items and items within domains in order to provide a reliable tool to detect changes in subjects with PE. Many of the inventories used in contemporary PE observational and interventional trials have been incompletely validated.

Since 2004, the most widely used outcome measure in PE studies is IELT, reported as an average (arithmetic mean) [11,12,14,31], geometric mean [12,14,31], or fold-increase (proportional increase from baseline) [31]. Some studies do not describe how IELT data were collected and/or analyzed [4,23–27], and those studies were not included in the analysis.

Control over ejaculation and PE-related distress or bother have not been as commonly evaluated, and their assessment has been hampered by the array of instruments available. These PROs are assessed using single-item questions or as part of validated instruments, such as the Index of Premature Ejaculation (IPE) [32], the Premature Ejaculation Questionnaire (PEQUEST) [33], the Chinese Index of Premature Ejaculation (CIPE) [34], the Arabic Index of Premature Ejaculation (AIPE) [35], and the Premature Ejaculation Profile (PEP) [11,13,36,37]; other instruments, such as the International Index of Erectile Function (IIEF) [38,39] and Yonsei Sexual Function Inventory (YSFI) [40], have also been utilized. Studies that did not include PROs were not excluded from the analysis.

Efficacy of Oral Agents in the Treatment of PE

Table 3 summarizes the efficacy results from well-designed studies (randomized, double-blind, placebo-controlled trials that included stopwatch-measured IELT) of oral agents in the treatment of PE.

SSRI Antidepressants and Clomipramine

This review identified five well-designed studies of SSRIs and clomipramine for the treatment of PE. Compared with placebo, daily fluoxetine [22,24], citalopram [26], duloxetine [25], and clomipramine [4] significantly increased IELT. Few validated PROs were reported, although duloxetine [25] and citalopram [26] were associated with improvements in PE based on the Clinical Global Impression-Improvement (CGI-I) scale. None of these studies enrolled men who met an approximation of the ISSM criteria. A meta-analysis of published data suggests that daily dosing of paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline [41].

PDE-5 Inhibitors

A 2005 systematic review [20] identified a single study of PDE-5 inhibitors that fulfilled the criteria for a well-designed PE trial. This study [27] showed that men (N = 144) who met an approximation of the ISSM criteria for PE had a nonsignificant ($P = 0.3$) increase in IELT (minutes) after 8 weeks of treatment with sildenafil (baseline, 1.04; endpoint, 2.60) compared with placebo (baseline, 0.96; endpoint, 1.63). Subjects randomized to sildenafil demonstrated significantly higher scores for the IPE items of ejaculatory control (1.8 vs. 1.5, respectively), ejaculatory confidence (2.2 vs. 1.9, respectively), and overall sexual satisfaction (3.1 vs. 2.8, respectively) at the end of treatment ($P < 0.05$ vs. placebo for all); PE-related distress or bother were not evaluated. One additional well-designed study [21] was identified, in which 42 potent men with lifelong PE (based on the ISSM definition) were randomized to receive on-demand vardenafil or placebo. In this study, vardenafil was associated with a 7.5-fold increase in geometric mean IELT (0.6 ± 0.3 vs. 4.5 ± 1.1 minute with placebo; $P < 0.01$), and significant improvements in the IPE domains of ejaculatory control, confidence, overall sexual satisfaction, and distress. This study suggests that the role of PDE-5 inhibitors should be further evaluated in additional well-designed studies. A 2007 review of PDE-5 inhibitors for PE considered preclinical and clinical data to understand potential central and peripheral mechanisms of action of these agents and their overall effectiveness in PE [42]. The authors concluded that data were limited but encouraging, and emphasized the need for large, randomized, double-blind, placebo-controlled studies of these agents in men with PE.

The Third International Consultation on Sexual Dysfunction (ICSD) and International Society for Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation have assigned level 4d evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE-5 inhibitors in the treatment of lifelong PE in men with normal erectile function. Treatment of lifelong PE with PDE-5 inhibitors in

Table 3 Summary of efficacy data for well-designed, randomized, placebo-controlled trials of oral agents to treat PE

Agent(s)	Study	N	Treatment period	Method of IELT calculation	IELT results	Other validated efficacy measures
Single agent vs. placebo						
Fluoxetine	Novaretti et al. 2002 [22]	Both groups: 50	8 weeks	Arithmetic mean	Mean (SD) IELT, baseline Fluoxetine: 60.6 seconds(51.83) Placebo: 62.7 seconds (64.12) Mean (SD) IELT, endpoint Fluoxetine: 199.3 seconds (178.98) Placebo: 68.1 seconds (64.30)	N/A
	Kara H et al. 1996 [24]	Fluoxetine: 9 Placebo: 8	4 weeks	Mean—not specified	Mean (SD) IELT, baseline Fluoxetine: 25 seconds (12.6) Placebo: 30 seconds(8.6) Mean (SD) IELT, endpoint Fluoxetine: 180 seconds (99.5) Placebo: 60 seconds (46.9)	N/A
Duloxetine	Athanasios 2007 [25]	Duloxetine: 10 Placebo: 10	12 weeks	Mean—not specified	Mean (SD) IELT, baseline Duloxetine: 38.21 seconds (16.45) Placebo: 34.79 seconds (18.35) Mean (SD) IELT, endpoint Duloxetine: 129.34 seconds (67.58) Placebo: 38.61 seconds (16.99)	For CGI-I, 80% of subjects were considered "very much improved" (40%) or "much improved" (40%) with duloxetine; 10% were considered "much improved" with placebo
Citalopram	Atmaca M et al. 2002 [26]	Citalopram: 13 Placebo: 13	8 weeks	Mean—not specified	Mean (SD) IELT, baseline Citalopram: 33.46 seconds (17.96) Placebo: 30.38 seconds (14.64) Mean (SD) IELT, endpoint Citalopram: 283.85 seconds (80.50) Placebo: 35.77 seconds (13.52)	YSFI-II scores for sexual desire, quality of erection, anxiety for rapid ejaculation, satisfaction with ejaculation, partner's satisfaction with ejaculation, overall sexual satisfaction, and partner's overall satisfaction improved significantly with citalopram, compared with placebo For CGI-I, 38.5% of patients were considered "very much improved" with citalopram, and 30.8% were considered "much improved"; 7.7% were considered "much improved" with placebo
Clomipramine	Althof SE et al. 1995 [4]	All groups: 15 couples	2–7 weeks	Mean—not specified	Mean IELT, baseline 81 seconds Mean IELT, following treatment with clomipramine 25 mg 202 seconds Mean IELT, following treatment with clomipramine 50 mg 419 seconds	N/A
Sildenafil	McMahon et al. 2005 [27]	Sildenafil: 73 Placebo: 71	8 weeks	Mean—not specified	Mean (SD) IELT, baseline Sildenafil: 0.96 minute (0.48) Placebo: 1.04 minutes (0.48) Mean (SD) IELT, endpoint Sildenafil: 2.60 minutes (6.16) Placebo: 1.63 minutes (2.16)	IPE scores were not significantly different between placebo and sildenafil; however, subjects treated with sildenafil reported significantly higher IPE scores for ejaculatory control, ejaculatory confidence, and overall sexual satisfaction
Vardenafil	Aversa et al. 2009 [21]	Vardenifil: 31 Placebo: 11	8 weeks + 4 weeks after crossover	Geometric mean	Mean (SD) IELT, baseline Vardenafil: 0.6 minute (0.3) Placebo: 0.7 minute (0.3) Mean (SD) IELT, endpoint (8 weeks) Vardenafil: 4.5 minutes (1.1) Placebo: 0.9 minute (1.0)	IPE scores for control, satisfaction, and distress were significantly ($P < 0.01$) greater with vardenafil vs. placebo at 8 weeks.

Dapoxetine	Pryor et al. 2006 [11]	Dapoxetine 30 mg prn: 874 Dapoxetine 60 mg prn: 870 Placebo: 870	12 weeks	Mean—not specified	Mean (SD) IELT, baseline Dapoxetine 30 mg prn: 0.92 minute (0.50) Dapoxetine 60 mg prn: 0.91 minute (0.48) Placebo: 0.9 minute (0.47) Mean (SD) IELT, endpoint Dapoxetine 30 mg prn: 2.78 minutes (3.48) Dapoxetine 60 mg prn: 3.32 minutes (3.68) Placebo: 1.75 minutes (2.21)	Scores for perceived control over ejaculation increased from approximately 0.45 in all groups at baseline to 1.65 and 1.82 after 12 weeks with dapoxetine 30 and 60 mg prn, respectively (vs. 1.05 with placebo) Scores for satisfaction with sexual intercourse increased from approximately 1.70 in all groups at baseline to 2.21 and 2.31 after 12 weeks with dapoxetine 30 and 60 mg prn, respectively (vs. 1.70 with placebo) For CGI, 58% and 67% of subjects reported that their PE was at least "slightly better" with dapoxetine 30 and 60 mg prn, respectively (vs. 26% with placebo)
	Buvat et al. 2009 [12]	Dapoxetine 30 mg prn: 388 Dapoxetine 60 mg prn: 389 Placebo: 385	24 weeks	Arithmetic and geometric	Mean (SD) IELT, baseline, arithmetic Dapoxetine 30 mg prn: 0.9 minute (0.50) Dapoxetine 60 mg prn: 0.9 minute (0.49) Placebo: 0.9 minute (0.51) Mean (SE) IELT, baseline, geometric Dapoxetine 30 mg prn: 0.7 minute (1.04) Dapoxetine 60 mg prn: 0.7 minute (1.04) Placebo: 0.7 minute (1.04) Mean (SD) IELT, endpoint, arithmetic Dapoxetine 30 mg prn: 3.1 minutes (4.88) Dapoxetine 60 mg prn: 3.5 minutes (3.80) Placebo: 1.9 minutes (2.89) Mean (SE) IELT, endpoint, geometric Dapoxetine 30 mg prn: 1.8 minutes (1.06) Dapoxetine 60 mg prn: 2.3 minutes (1.06) Placebo: 1.1 minutes (1.06) The above data are for the overall population. This study also included sub-analyses of men with baseline IELT ≤ 1 minute and ≤0.5 minute.	All PEP measures improved significantly with dapoxetine 30 and 60 mg prn, compared to placebo, with a significantly greater proportion of subjects reporting "good" or "very good" perceived control over ejaculation and satisfaction with sexual intercourse, and significantly fewer subjects reporting "moderate," "quite a bit," or "extreme" ejaculation-related personal distress and interpersonal difficulty, at study endpoint ($P < 0.0001$ for all) For CGI, 57.7% and 72.4% of subjects reported that their PE was at least "slightly better" at study endpoint with dapoxetine 30 and 60 mg prn, respectively (vs. 32.0% with placebo ($P < 0.001$ for both)
	McMahon et al. 2010 [14]	Dapoxetine 30 mg prn: 284* Dapoxetine 60 mg prn: 279* Placebo: 295*	12 weeks	Arithmetic and geometric	Mean (SD) IELT, baseline, arithmetic Dapoxetine 30 mg prn: 1.1 minutes (0.45) Dapoxetine 60 mg prn: 1.1 minutes (0.48) Placebo: 1.0 minute (0.47) Mean (SE) IELT, baseline, geometric Dapoxetine 30 mg prn: 1.0 minute (1.03) Dapoxetine 60 mg prn: 0.9 minute (1.04) Placebo: 0.9 minute (1.04) Mean (SD) IELT, endpoint, arithmetic Dapoxetine 30 mg prn: 3.9 minutes (3.94) Dapoxetine 60 mg prn: 4.2 minutes (3.97) Placebo: 2.4 minutes (2.05) Mean (SE) IELT, endpoint, geometric Dapoxetine 30 mg prn: 2.7 minutes (1.05) Dapoxetine 60 mg prn: 3.1 minutes (1.05) Placebo: 1.8 minutes (1.05) The above data are for the overall population. This study also included sub-analyses of men with baseline IELT ≤ 1 minute and ≤0.5 minute.	For all PEP items, there was a statistically significant increase in mean scores from baseline to endpoint for both dapoxetine 30 and 60 mg prn, compared with placebo ($P \leq 0.007$ for all) For CGI, 71.4% and 79.2% of subjects reported that their PE was at least "slightly better" at study endpoint with dapoxetine 30 and 60 mg prn, respectively (vs. 52.8% with placebo; $P < 0.001$ for both)

Table 3 Continued

Agent(s)	Study	N	Treatment period	Method of IELT calculation	IELT results	Other validated efficacy measures
Combination therapy trials						
Tadalafil, fluoxetine, fluoxetine + tadalafil, and placebo	Mattos 2008 [23]	Tadalafil: 15 Fluoxetine: 15 Fluoxetine + tadalafil: 15 Placebo: 15	12 weeks	Mean—not specified	Mean (SD) IELT, baseline Tadalafil: 49.26 seconds (19.43) Fluoxetine: 56.55 seconds (18.55) Fluoxetine + tadalafil: 49.57 seconds (25.87) Placebo: 49.86 seconds (19.43) Mean (SD) IELT, endpoint Tadalafil: 186.53 seconds (159.05) Fluoxetine: 233.62 seconds (105.08) Fluoxetine + tadalafil: 336.13 seconds (224.77) Placebo: 67.82 seconds (46.18)	N/A
Comparative trials						
Fluoxetine, fluvoxamine, paroxetine, sertraline, and placebo	Waldinger et al. 1998 [28]	Fluoxetine: 12 Fluvoxamine: 12 Paroxetine: 12 Sertraline: 12 Placebo: 12	6 weeks	Geometric mean	Fold-increase (95% CI), based on geometric mean Fluoxetine: 6.6 (0.73–59) Fluvoxamine: 1.9 (0.12–31) Paroxetine: 7.8 (0.71–86) Sertraline: 4.4 (0.49–40) Placebo: 1.5 (0.37–6.1)	N/A
Paroxetine, sertraline, nefazodone and placebo	Waldinger et al. 2001 [29]	Paroxetine: 12 Sertraline: 12 Nefazodone: 12 Placebo: 12	6 weeks	Geometric mean	Fold-increase, based on geometric mean Paroxetine: 9.1 Sertraline: 3.5 Nefazodone: 1.4 Placebo: 1.43	N/A

*Number of completers.
IELT = intravaginal ejaculatory latency time; SD = standard deviation; N/A = not applicable; prn = as needed; CI = confidence interval.

men with normal erectile function is not recommended and further evidence-based research is encouraged to understand conflicting data [43,44].

α_1-Receptor Antagonists

No well-designed studies of α_1-receptor antagonists in treating PE were identified, although two studies were found that evaluated measures of satisfaction and subjective feelings of improvement [6,7]. In the first study [6], subjects received terazosin, alfuzosin, and placebo for 2 months each, and approximately 50% of the subjects reported that their ejaculation time had been sufficiently prolonged to satisfy both partners following active treatment (vs. 24% with placebo, $P < 0.05$ for both). In the second study [7], 35% of men with PE and lower urinary tract symptoms (without chronic prostatitis or benign prostatic hyperplasia [BPH]) treated with terazosin for 1 month were able to delay their ejaculation until their partner reached orgasm, and 33.3% were able to increase their time to ejaculation; however, it is unclear how time to ejaculation was measured. Both studies were limited by the use of nonvalidated endpoints of patient impression of change and sexual satisfaction, and they did not evaluate actual ejaculatory latency.

Tramadol

While no studies met the criteria for a well-designed study, tramadol has been evaluated in a single-blind, placebo-controlled study, and in an open-label study. On-demand tramadol (25 mg) significantly increased IELT vs. placebo in 60 men with lifelong PE ($P < 0.0001$) [8,9]. In the open-label crossover comparator study of daily paroxetine (20 mg) and on-demand tramadol (50 mg) in 35 subjects with lifelong PE, superior IELT fold-increases and PRO responses were demonstrated with paroxetine (22-fold vs. fivefold for tramadol) after 12 weeks of treatment [9]. Although this study was limited by the use of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) definition to diagnose PE, 66% of men had an IELT of ≤1 minute at baseline, suggesting that the overall population is reasonably representative of the ISSM definition. A large, international, prospective, randomized, placebo-controlled, double-blind trial of tramadol for the treatment of PE (NCT00983151) was recently stopped prematurely, although no reason has been provided; another similar study (NCT00983736) was stopped because of recruitment difficulties.

The Third International Consultation on Sexual Dysfunction (ICSD) and International Society for Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation have assigned level 2d evidence to support the efficacy and safety of daily dosing of α1-adrenoceptor antagonists and tramadol in the treatment of PE and their use as a treatment for PE cannot be recommended [43,44].

Combination Therapies

One well-designed study [23] compared the efficacy of fluoxetine and tadalafil alone and in combination in men who met an approximation of the ISSM criteria for lifelong PE. Mean IELT increased from 51.3 seconds across groups at baseline to 233.6 seconds with fluoxetine, 186.5 seconds with tadalafil, and 336.1 seconds with fluoxetine plus tadalafil (vs. 67.8 seconds with placebo; $P \leq 0.001$ for all). Assessments of control over ejaculation or ejaculation-related distress or bother were not included.

Dapoxetine

Dapoxetine was evaluated in five large randomized, double-blind, placebo-controlled phase III trials including >6,000 men in >25 countries; four of these trials met the criteria for a well-designed study [11,12,14], while one study was conducted primarily to evaluate safety [13]. Dapoxetine is the only SSRI for which well-designed studies in PE populations have included on-demand dosing. Results summarized in Table 3 report each manuscript individually; data below are from an integrated analysis [31] and is the only study where results are reported separately for men with IELTs of ≤1 minute and ≤0.5 minute, as well as for the overall study population. In the four studies that evaluated IELT, increases in IELT were significantly ($P < 0.001$) greater with dapoxetine vs. placebo beginning with the first dose, which was maintained at all subsequent time points [31]. Dapoxetine 30 and 60 mg on-demand significantly increased arithmetic and geometric mean IELT compared with placebo (1.9 and 1.2 minutes for placebo, 3.1 and 2.0 minutes for dapoxetine 30 mg, and 3.6 and 2.3 minutes for dapoxetine 60 mg, respectively). This represents a 1.6-, 2.5-, and 3.0-fold increase over baseline geometric mean IELT for placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively. IELT increases with dapoxetine were significantly ($P < 0.001$) greater than placebo beginning with the first dose, which was maintained at all subsequent time points. Similar results were observed in men with IELTs ≤1

minute and ≤0.5 minute at baseline. Progressively greater fold-increases were observed with decreasing baseline average IELTs. Subjects with baseline average IELTs of 1.5–2 minutes, 1–1.5 minutes, 0.5–1 minute, and less than 0.5 minute showed geometric mean fold-increases of 1.5, 1.6, 1.6, and 1.7, respectively, with placebo treatment; 2.2, 2.3, 2.4, and 3.4, respectively, with dapoxetine 30 mg; and 2.6, 2.5, 3.0, and 4.3 with dapoxetine 60 mg.

The PEP [45] or individual PEP items were used to evaluate control over ejaculation (five trials), satisfaction with sexual intercourse (five trials), and ejaculation-related personal distress and interpersonal difficulty (three trials). Clinical global impression of change (CGI) in PE was also measured on a 7-point scale (five trials). Two studies [12,14] included stopwatch-measured IELT and all four PEP items and enrolled men based on an IELT of ≤2 minutes on 75% of occasions, low control over ejaculation, and ejaculation-related personal distress. Despite varied populations in each study, and the use of the DSM-IV-TR definition to diagnose PE, the overall population was reasonably representative of the ISSM definition of lifelong PE (64.9% had lifelong PE; 58% had an IELT <1 minute).

Overall, subjects reported significant improvements in all PEP items with dapoxetine ($P \leq 0.001$ vs. placebo for all), and results were similar for men with IELT values of <1 minute at baseline [31]. "Good" or "very good" control over ejaculation was reported by <1% across groups at baseline and increased among the overall population (26.2% with dapoxetine 30 mg and 30.2% with dapoxetine 60 mg vs. 11.2% with placebo; $P < 0.001$ for both) and among men with IELT values of <1 minute at baseline (19.7% with dapoxetine 30 mg and 26.0% with dapoxetine 60 mg vs. 7.2% with placebo; $P < 0.001$ for both) at 12 weeks. Similarly, "good" or "very good" satisfaction with sexual intercourse was reported by approximately 15.0% of men across groups at baseline and increased among the overall population (37.9% with dapoxetine 30 mg and 42.8% with dapoxetine 60 mg vs. 24.4% with placebo; $P < 0.001$ for both) and among men with IELT values of <1 minute at baseline (32.9% with dapoxetine 30 mg and 40.0% with dapoxetine 60 mg vs. 32.9% with placebo; $P < 0.001$ for both) at 12 weeks. At baseline, ~70% of subjects across groups reported their level of ejaculation-related personal distress as "quite a bit" or "extremely," which decreased to 28.2% and 22.2% with dapoxetine 30 and 60 mg, respectively, among the overall population at Week 12 (vs. 41.9% with placebo, $P < 0.001$) and to 34.9% and 28.8% with dapoxetine 30 and 60 mg, respectively, among men with IELT values of <1 minute at baseline (vs. 50.7% with placebo, $P < 0.001$). Approximately, one-third of the subjects reported "quite a bit" or "extremely" for their level of ejaculation-related interpersonal difficulty at baseline; by Week 12, this decreased among the overall population to 16.0% and 12.3% with dapoxetine 30 and 60 mg, respectively (vs. 23.8% with placebo, $P < 0.001$) and to 17.7% and 13.9% with dapoxetine 30 and 60 mg, respectively, among men with IELT values of <1 minute at baseline (vs. 28.2% with placebo, $P < 0.001$). Significantly more men receiving dapoxetine 30 or 60 mg reported that their PE was at least "better" at Week 12 (30.7% and 38.3%, respectively, among the overall population and 25.2% and 34.9% for men with IELT values of <1 minute at baseline, respectively) compared with placebo (13.9% and 9.4% among the overall population and for men with IELT values of <1 minute at baseline, respectively; $P \leq 0.05$ for all).

The dapoxetine phase III study populations of >6,000 men represented a heterogeneous population with both lifelong and acquired PE and included some men with mild erectile dysfunction (ED). In a post-hoc analysis of data from three phase 3 clinical trials [46], study-end dapoxetine mean IELT and PRO responses were superior to placebo and dose-dependent, with a similar pattern for men with lifelong and acquired PE. However, the presence of mild ED diminished PRO responsiveness in both subtypes, particularly in men with lifelong PE.

Female partners also reported improvements in sexual functioning [31], including their perception of the male subject's control over ejaculation and CGIC and their own satisfaction with sexual intercourse in three studies [11,12], and their own ejaculation-related interpersonal difficulty and personal distress in one study [12]. Significant improvements in partner perception of the man's control over ejaculation and CGIC were observed at Week 12; 26.7% and 34.3% reported the man's control over ejaculation as "good" or "very good" with dapoxetine 30 and 60 mg, respectively, vs. 11.9% with placebo ($P < 0.0001$ for both) [31]. Female partners of men treated with dapoxetine also reported significant improvements in their own satisfaction with sexual intercourse, with 37.5% and 44.7% reporting "good" or "very good" satisfaction with sexual intercourse with dapoxetine 30 and 60 mg, respectively, vs. 24.0%

with placebo at Week 12 ($P < 0.001$ for both). Significant improvements in female partner-rated ejaculation-related personal distress and interpersonal difficulty related to ejaculation were also observed with dapoxetine vs. placebo.

Safety and Tolerability

The safety and tolerability findings from well-designed studies of oral agents for PE are summarized in Table 4.

SSRI Antidepressants and Clomipramine

In well-designed studies of SSRI antidepressants in PE subjects, adverse events (AEs) were reported by 3 of 13 men receiving citalopram [25,26] and 3 of 10 men receiving duloxetine, but AE incidence was not reported in every study (Table 4). The most common AEs included nausea, dry mouth, headache, and insomnia. Two of nine men receiving fluoxetine discontinued because of AEs (nausea and insomnia) [24]. None of these studies reported the incidence of serious AEs. It is important to note that these studies used chronic daily dosing, based on the dosing schedule used in the approved indications. However, these agents may be taken as needed or continuously [47], which may alter the incidence of AEs and may influence patient preference for a particular dosing schedule [48].

The majority of safety and AE information for SSRIs is derived from studies in subjects with depression and other psychiatric/behavioral disorders. In a meta-analysis [49] of studies in patients with major depressive disorder, the incidence of AEs with SSRIs ranged from 8.5% to 16.3% and included dry mouth, nausea, dizziness, headache, fatigue, constipation, diarrhea, somnolence, insomnia, nervousness, sweating, and anorexia.

SSRIs have several class-related effects, including agitation, irritability, unusual changes in behavior, anxiety, impulsivity, akathisia, hypomania, mania, and the potential for suicidality in children, adolescents, and young adults. Abrupt discontinuation of SSRIs may result in SSRI withdrawal syndrome (typically characterized by headache, diarrhea, nausea, vomiting, chills, dizziness, or fatigue). One retrospective study [50] of patients (N = 352) who were treated with SSRIs reported that 30.8%, 20.0%, and 2.2% of subjects who discontinued treatment with clomipramine, paroxetine, and sertraline, respectively, experienced withdrawal symptoms; no subjects reported symptoms following discontinuation of fluoxetine. Data on SSRI withdrawal symptoms with citalopram are limited; however, it has been reported that withdrawal-like symptoms following abrupt discontinuation of citalopram are mild and transient, and are likely associated with the re-emergence of depression [51]. None of the well-designed studies of SSRIs in men with PE specifically evaluated class-related effects, although improvements in psychometric assessments, including Symptom Checklist 90-R scores, Dyadic Adjustment Scale scores, and measures of anxiety were reported with clomipramine [4].

PDE-5 Inhibitors

In the two well-designed studies of PDE-5 inhibitors (sildenafil and vardenafil) identified in this review, the overall incidence of AEs was not reported; however, the most common AEs included headache (10–15%), flushing (12–15%), dyspepsia (5–10%), abnormal vision (5%), and rhinitis (5%), which tended to attenuate and disappear with continued use [21,27]. These data are similar to those reported in a recent systematic review [52] of the use of PDE-5 inhibitors in men with ED. In that analysis, overall AE rates were 50% with sildenafil and 47% with tadalafil; the overall AE rate for vardenafil was not reported. Common AEs included headache (13–17%), dyspepsia (3.8–10%), flushing (4.8–13%), and rhinitis (3.1–7.9%). The rate of serious AEs was low (1.2–2.5%).

α_1-Receptor Antagonists

In the study [6] by Cavallini comparing alfuzosin and terazosin with placebo, hypotension was the most common AE leading to discontinuation (four patients [4.4%]; two each with terazosin and alfuzosin). Other AEs included headache (one patient with alfuzosin) and headache with epigastralgia (one patient with terazosin), neither of which resulted in discontinuation. In the study by Başar and coworkers of terazosin vs. placebo daily for 1 month [6], published safety data were limited to the finding that none of the patients discontinued treatment because of AEs. These data in men with PE are comparable to what has been observed in men with hypertension or BPH. The most common AEs with terazosin include postural hypotension (3.9%), dizziness (9.1%), somnolence (3.6%), nasal congestion/rhinitis (1.9%), and impotence (1.6%) [53]. With alfuzosin, common AEs in men with BPH include dizziness (5.7%), upper respiratory infections (3.0%), headache (3.0%), and fatigue (2.7%) [46].

Tramadol

In the single-blind, placebo-controlled study, eight (13.3%) men experienced mild dyspepsia (n = 5)

Table 4 Summary of safety results from well-designed, randomized, placebo-controlled trials of oral agents to treat PE

Agent(s)	Study	N	Overall incidence of AEs	Most common AEs with active treatment	Incidence of serious AEs	Subject withdrawal due to AEs	Other safety measures
Single agent vs. placebo							
Fluoxetine	Novaretti et al. 2002 [22]	Both groups: 50	NR	Drowsiness (30%), headache (14%), insomnia (6%), decreased libido (4%), dry mouth (2%), dizziness (2%); significant differences from placebo were noted for drowsiness ($P = 0.002$) and headache ($P = 0.03$)	NR	None in either group	No change from baseline with either treatment for the Beck Depression Inventory or the Hamilton Anxiety Scale
	Kara H et al. 1996 [24]	Fluoxetine: 9 Placebo: 8	NR	Nausea (2 subjects), headache (1 subject), insomnia (1 subject)	NR	2 subjects with fluoxetine because of insomnia and nausea	In 3 patients (fluoxetine, 2; placebo, 1), mean Hamilton score decreased from 32.3 at baseline to 26.2 after 4 weeks
Duloxetine	Athanasios 2007 [25]	Duloxetine: 10 Placebo: 10	Duloxetine: 3 subjects Placebo: 1 subject	Nausea and dry mouth were reported in 3 subjects	NR	None in either group	N/A
Citalopram	Atmaca M et al. 2002 [26]	Citalopram: 13 Placebo: 13	Citalopram: 3 subjects Placebo: 1 subject	Nausea and headache were reported in 3 subjects	NR	None in either group	In 1 subject with major depressive disorder, HDRS score decreased from 30 at baseline to 18 at endpoint; in another subject with obsessive compulsive disorder, Y-BOCS score decreased from 29 at baseline to 12 at study endpoint
Clomipramine	Althof SE et al. 1995 [4]	All groups: 15 couples	NR	Clomipramine 25 mg/day*: dry mouth (7%), feeling "different" (8%), constipation (1%) Clomipramine 50 mg/day*: dry mouth (33%), feeling "different" (21%), constipation (18%)	NR	NR	Symptom Checklist 90-R scores decreased significantly from baseline to endpoint, with greater decreases associated with both clomipramine doses Dyadic Adjustment Scale scores improved significantly for the men, but not for the women, with all 3 treatments There were no changes in overall state anxiety for the men or the women; there was a significant change in trait anxiety for the men There were no significant effects on self-esteem among men or women

Sildenafil	McMahon et al. 2005 [27]	Sildenafil: 73 Placebo: 71	NR	Headache (15%), flushing (15%), dyspepsia (5%), abnormal vision (5%), rhinitis (5%)	None in either group	None in either group	N/A
Vardenafil	Aversa et al. 2009 [21]	Vardenifil: 31 Placebo: 11	NR	At 4 weeks: Flushing (12 pts), headache (10 pts), dyspepsia (10 pts), all $P < 0.01$ vs. placebo	NR	NR	NR
Dapoxetine	Pryor et al. 2006 [11]	Dapoxetine 30 mg prn: 874 Dapoxetine 60 mg prn: 870 Placebo: 870	NR	Dapoxetine 30 mg prn: nausea (8.7%), diarrhea (3.9%), headache (5.9%), dizziness (3.0%) Dapoxetine 60 mg prn: nausea (20.1%), diarrhea (6.8%), headache (6.8%), dizziness (6.2%)	Dapoxetine 30 mg prn: 0.3% Dapoxetine 60 mg prn: 0.6% Placebo: 0.9%	35, 87, and 8 subjects with dapoxetine 30 mg prn, dapoxetine 60 mg prn, and placebo, respectively; most common events leading to withdrawal included nausea, dizziness, and diarrhea	Syncope was reported in 3 (0.3%), 2 (0.2%), and 2 (0.2%) subjects with dapoxetine 30 mg prn, dapoxetine 60 mg prn, and placebo, respectively Sexual side effects were noted in 4.3% and 5.3% of subjects with dapoxetine 30 and 60 mg prn, respectively (vs. 1.9% with placebo)
	Buvat et al. 2009 [12]	Dapoxetine 30 mg prn: 388 Dapoxetine 60 mg prn: 389 Placebo: 385	Dapoxetine 30 mg prn: 56.2% Dapoxetine 60 mg prn: 68.1% Placebo: 38.4%	Dapoxetine 30 mg prn: nausea (5.4%), dizziness (3.1%), orthostatic hypotension (1.5%), somnolence (1.3%) Dapoxetine 60 mg prn: nausea (10.8%), dizziness (6.4%), diarrhea (3.6%), headache (3.3%)	Dapoxetine 30 mg prn: 1.0% Dapoxetine 60 mg prn: 0.8% Placebo: 1.0%	15 (4%), 32 (8%), and 5 (1%) subjects with dapoxetine 30 mg prn, dapoxetine 60 mg prn, and placebo, respectively; most common event leading to withdrawal was nausea	Syncope occurred in 2 subjects with dapoxetine 60 mg prn; the events spontaneously resolved without sequelae No effects on clinical laboratory tests or vital signs were observed Abrupt discontinuation of dapoxetine was not associated with SSRI withdrawal syndrome or any effects on mood, affect, or suicidal ideation [31]
	McMahon et al. 2010 [14]	Dapoxetine 30 mg prn: 284† Dapoxetine 60 mg prn: 279† Placebo: 295†	Dapoxetine 30 mg prn: 33.3% Dapoxetine 60 mg prn: 49.7% Placebo: 17.9%	For both doses of dapoxetine: nausea, dizziness, somnolence, headache, vomiting, diarrhea, and nasopharyngitis	Dapoxetine 30 mg prn: 3 subjects Placebo: 3 subjects	1.7%, 5.1%, and 0.3% of subjects with dapoxetine 30 mg prn, dapoxetine 60 mg prn, and placebo, respectively; most common events leading to withdrawal included nausea and dizziness	No effects on clinical laboratory tests were observed

Table 4 Continued

Agent(s)	Study	N	Overall incidence of AEs	Most common AEs with active treatment	Incidence of serious AEs	Subject withdrawal due to AEs	Other safety measures
	Kaufman et al. 2009 [13]	Dapoxetine 60 mg prn: 491 Placebo: 245 Dapoxetine 60 mg qd‡: 502	Dapoxetine 60 mg: 61.3% Placebo: 44.1% Dapoxetine 60 mg qd‡: 62.5%	Nausea (15.3%), dizziness (10.2%), headache (8.1%), insomnia (6.5%), diarrhea (6.1%)§	Dapoxetine 60 mg prn: 2 (0.5%) subjects Placebo: 1 (0.5%) subject	10% and 2% of subjects with dapoxetine 60 mg prn and placebo, respectively; most common events leading to withdrawal included dizziness, diarrhea, and insomnia	Discontinuation-Emergent Signs and Symptoms checklist assessments indicated that the incidence of withdrawal syndrome was 1.3% and 0.7% with dapoxetine 60 mg qd and prn, respectively; these results were not significantly different from what was observed with placebo (1.3%) [31]
Combination therapy trials							
Tadalafil, Fluoxetine, Fluoxetine + tadalafil, and placebo	Mattos 2008 [23]	Tadalafil: 15 Fluoxetine: 15 Fluoxetine + tadalafil: 15 Placebo: 15	Tadalafil: 26% Fluoxetine: 33% Fluoxetine + tadalafil: 40% Placebo: 12%	Tadalafil: headache (3 subjects), facial redness (2 subjects), palpitation (2 subjects) Fluoxetine: yawning and somnolence (3 subjects), asthenia (3 subjects), nausea (1 subject) Fluoxetine + tadalafil: yawning and somnolence (3 subjects), nausea (2 subjects) palpitation (1 subject), muscle soreness (1 subject)	NR	NR	N/A
Comparative trials							
Fluoxetine, fluvoxamine, paroxetine, sertraline, and placebo	Waldinger et al. 1998 [28]	Fluoxetine: 12 Fluvoxamine: 12 Paroxetine: 12 Sertraline: 12 Placebo: 12	NR	"There were no statistically significant differences between the active treatment groups and the placebo group with respect to nonsexual side effects, including nausea and headache."	NR	2, 2, 1, and 1 subjects with fluoxetine, fluvoxamine, paroxetine, and sertraline, respectively	N/A
Paroxetine, sertraline, nefazodone and placebo	Waldinger et al. 2001 [29]	Paroxetine: 12 Sertraline: 12 Nefazodone: 12 Placebo: 12	NR	"There were no statistically significant differences between the active treatment groups and placebo with respect to nonsexual side effects."	NR	3 and 1 subjects with paroxetine and sertraline, respectively	N/A

*Reported as the percentage of total days on treatment a given AE occurred.
†Number of completers.
‡Dapoxetine qd group was included for withdrawal assessments only.
§Reported only for the dapoxetine prn arm.
AE = adverse event; NR = not reported; N/A = not applicable; prn = as needed; qd = daily.

and mild somnolence (n = 3) with tramadol [8]. Tramadol was generally tolerated in the open-label study, with gastric upset being the most common AE [9]. No serious AEs or AE-related discontinuations were reported in either study. These AEs are similar to what has been reported with tramadol in other populations. A recent meta-analysis [54] of 11 controlled studies of tramadol in more than 1,000 patients with osteoarthritis reported that the most common AEs were nausea, vomiting, dizziness, somnolence, tiredness, and headache, and approximately 20% of patients receiving tramadol or tramadol/acetaminophen experienced nonserious AEs. Although tramadol is reported to have a lower risk of dependence than traditional opioids, its use as an on-demand treatment for PE is limited by the potential risk of addiction [55]. In community practice, dependence does occur, but appears to be minimal [56]. Adams and colleagues [57] reported abuse rates of 0.7% for tramadol compared with 0.5% for nonsteroidal anti-inflammatory drugs and 1.2% for hydrocodone, based on application of a dependency algorithm as a measure of persistence of drug use.

Combination Therapies

There are limited data regarding the safety and tolerability of combination treatments for PE. In the study that evaluated fluoxetine, tadalafil, and fluoxetine plus tadalafil, the overall incidence of AEs was higher with the combination (40%) compared with either drug alone (fluoxetine, 33%; tadalafil, 26%) or placebo (12%); common AEs with fluoxetine plus tadalafil included somnolence, nausea, palpitation, and muscle soreness [23].

Dapoxetine

Similar AE profiles have been reported across the phase III trials of dapoxetine [20]. In the integrated analysis of these studies [31], AEs occurred in 651/1,857 (35.1%), 760/1,616 (47.0%), 1,270/2,106 (60.3%), and 341/502 (67.9%) subjects with placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn, and dapoxetine 60 mg qd, respectively. The most common AEs with dapoxetine included nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis. Nausea was the most common AE associated with discontinuation. Sexual function AEs occurred in a low percentage of subjects across groups.

Severe or serious AEs occurred infrequently (~3% and ≤1%, respectively), and most AEs were of mild to moderate severity [31]. Across trials, AE-related discontinuation occurred in 1.7–4.0% and 5.1–10.0% of subjects receiving dapoxetine 30 and 60 mg, respectively, most commonly because of nausea, dizziness, and diarrhea. Syncope (including loss of consciousness), which appeared to be vasovagal in nature and generally occurred within 3 hours of the first dose, was reported in 0.05%, 0.06% and 0.23% of subjects with placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively [31]. Syncope occurred more frequently when dapoxetine was administered at one of the study sites (onsite [0.31%] vs. offsite [0.08%]), appeared to be related to syncope-associated onsite study procedures (e.g., blood draws or orthostatic maneuvers) and occurred almost exclusively with dapoxetine 60 mg, with only one reported episode with the 30-mg dose. Similar observations have been reported with other SSRIs, and these events resolved without sequelae.

Dapoxetine is the only agent for which studies have been adequately powered and designed to assess SSRI class-related effects in a PE population. Dapoxetine was not associated with treatment-emergent anxiety (measured by the Hamilton Anxiety Scale), depression (measured by the Montgomery-Åsberg Depression Rating Scale and the Beck Depression Inventory II), or suicidality [31]. Abrupt discontinuation of dapoxetine was not associated with an increased incidence of withdrawal syndrome compared with placebo or continued therapy (measured by the Discontinuation-emergent Signs and Symptoms Checklist) [31].

Discussion

This review is limited by the author's attempt to retrospectively apply the contemporary ISSM definition of lifelong PE to previously conducted intervention studies that employed differing inclusion/exclusion criteria and study endpoints. The attempt to approximate data from studies enrolling a heterogenous population of both lifelong and acquired PE to the ISSM definition of lifelong PE is somewhat balanced by the recently published post-hoc analysis of dapoxetine phase 3 baseline and treatment outcome data suggesting that there are substantial similarities in baseline IELT, PROs and response to dapoxetine between both PE sub-populations [46].

While many of the well-designed studies of oral agents in PE included in this review may be considered to have at least partially met the ISSM criteria for lifelong PE for their study populations, few used validated PRO measures for control over ejaculation and PE-related distress or bother, or

included detailed prospective reporting of SSRI class-related AEs. All of these studies were conducted prior to the existence of the ISSM definition of lifelong PE and the development of PE inventories; however, these elements have been included in most earlier criteria, such as those proposed by the DSM-IV-TR [58], the American Urological Association [59], and the International Consultation on Urological Diseases [60].

There is a wide disparity in AE reporting amongst studies of oral agents. By convention, AEs are reported retrospectively by the subject at the next trial visit, and are recorded and rated by the investigator using Medical Dictionary for Regulatory Activities [61] coding by their relation to the trial drug. However, trial visits may be up to 4 weeks apart, prompting concerns regarding the reliability of subject recall of the AE frequency, severity, duration and/or temporal relation to administration. Prospective reporting of AEs within 24 hours in a subject diary using a validated questionnaire, such as the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale for psychotropic/neuroleptic drugs, has been suggested [16,61].

A wide range of diagnostic criteria were used for PE in these clinical trials. Few trials enrolled men who approximately met the ISSM criteria. While all of the studies included here implemented an IELT threshold in their enrollment criteria, different thresholds were applied (i.e., <1 minute, ≤2 minutes); differences in baseline IELT may have a profound impact on the apparent magnitude of IELT increases with treatment. Further, no more than a handful of studies incorporated both an IELT threshold and PRO measures for control over ejaculation and PE-related distress or bother [11,12,14,21,27], leaving only IELT as the main outcome measure for contrasting efficacy results between studies.

The wide variability among PE study designs also complicates their comparison and interpretation. Studies have ranged in length from 4 to 24 weeks, and the impact of treatment duration on outcomes is unclear. Various methods were used for reporting IELT outcomes, including arithmetic mean, geometric mean, or fold-increase from baseline. Further, a wide range of validated and unvalidated PRO instruments have been used, complicating the comparison of PRO results between studies. There is a need for consensus on the appropriate use and application of PRO measures to ensure interpretability of results across trials.

Administration schedules also varied among studies. As mentioned above, in the studies of SSRI antidepressants included in this review, chronic daily dosing was used. SSRIs were developed for daily use in chronic diseases, and their pharmacokinetic profiles are characteristic of agents intended to remain at therapeutic concentrations for extended periods of time. Daily administration of these agents results in the chronic blockade of serotonin transport, leading to the desensitization of presynaptic 5-HT1A autoreceptors and postsynaptic 5-HT1B/ID autoreceptors and resultant greater increases in 5-HT neurotransmission [62–65], a principal factor thought to contribute to both the therapeutic and adverse effects of these agents. Daily dosing also results in significant accumulation (approximately eightfold with paroxetine [66] and twofold with sertraline [67]. PDE-5 inhibitors, tramadol, and dapoxetine are all intended for and evaluated with on-demand administration. In contrast to long-acting SSRIs, dapoxetine has a rapid pharmacokinetic profile; maximum plasma concentrations are reached approximately 1 hour after oral administration and fall to less than 5% of this peak within 24 hours [68].

Current understanding of the safety and tolerability of SSRIs, PDE-5 inhibitors, α_1-antagonists, and tramadol in the treatment of PE relies heavily on results from studies in other patient populations (e.g., depression, ED, BPH, and chronic, severe musculoskeletal pain). In addition, men with many of the approved indications for these treatments are excluded from PE trials, despite the fact that men with PE frequently have comorbid conditions such as depression or ED. Further study is necessary to determine the safety and tolerability of these agents in a PE population and in men with PE and comorbid conditions.

The ISSM criteria for lifelong PE provide an evidence-based definition of PE that can be used as a standard in future trial design; in contrast, no evidence-based definition of acquired PE has been put forth. The ISSM was unable to define acquired PE because of a lack of sufficient normative data [15]. As noted recently by Jannini [69], clinical trials of dapoxetine contained men with acquired PE as well as men with lifelong PE, and dapoxetine was shown to be effective in both groups. These trials typically included stopwatch-measured IELT and validated PRO measures of control over ejaculation and distress or bother related to PE; therefore, information from these trials may provide some insight into the clinical picture of acquired PE.

Conclusions

Improvements in PE with treatment should be evaluated based on the characteristics that define the condition. According to the new ISSM criteria, the parameters of importance are IELT, control over ejaculation, and negative psychological consequences such as distress, bother, frustration, and sexual avoidance. This systematic review of well-designed trials in PE demonstrated that many agents, particularly SSRI antidepressants and dapoxetine, are effective and well tolerated for the treatment of men with PE. Evidence for the effectiveness of PDE-5 inhibitors, α_1-receptor antagonists, and tramadol is currently weak and none are currently recommended as treatment for PE with the exception of treatment of comorbid ED in men with acquired PE. While most studies now report stopwatch-measured IELT, the ISSM lifelong PE criteria of control-over-ejaculation and PE-related negative personal psychological consequences of distress and/or bother have been used in only a small number of studies as enrollment criteria or outcome measures using validated PRO instruments. Because of the wide variation among studies in the reporting of data, direct comparisons between trials and agents are not feasible at this time.

Perhaps because some of these studies have been small, reporting of AEs has been inconsistent across trials, and known class-related safety effects have rarely been evaluated. Currently, dapoxetine has the largest efficacy and safety database for use in men with PE, and it is the only agent for which SSRI class-related effects have been studied in a PE population.

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