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ORIGINAL ARTICLE

Efficacy of PDE5Is and SSRIs in men with premature ejaculation: a new systematic review and five meta-analyses

Yi Sun[1] · Lu Yang[1] · Yige Bao[1] · Zhenhua Liu[1] · Liangren Liu[1] · Qiang Wei[1]

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Abstract
Purpose To clarify the efficacy of phosphodiesterase-5 inhibitors (PDE5Is) and selective serotonin reuptake inhibitors (SSRIs) in men with premature ejaculation (PE).
Methods We searched the PubMed, Embase, and Cochrane Library databases to identify all randomized, controlled trials (RCTs) and compared the results, including intravaginal ejaculation latency time, satisfaction, intercourse per-week and side effects after treatment with PDE5I or SSRIs versus placebo, combined use of PDE5I with SSRIs versus PDE5I or SSRIs alone, and PDE5I versus SSRIs for treating PE.
Results The study inclusion criteria were met by 23 studies (ten RCTs with five crossover studies) involving 6145 patients. The data synthesized from these studies indicated that the efficacy of PDE5Is and SSRIs was better than that of placebo ($p < 0.00001$; $p < 0.00001$); however, more patients had side effects while taking PDE5Is and SSRIs ($p < 0.00001$; $p < 0.00001$). The efficacy of the combined treatment was significantly better than that of PDE5Is or SSRIs alone ($p < 0.00001$; $p < 0.00001$); however, more patients had side effects from the combined treatment than from SSRIs ($p = 0.0002$), with no significant difference in PDE5Is ($p = 0.5$). The efficacy of PDE5Is was better than that of SSRIs ($p = 0.006$), and no significant difference was observed in the frequency of side effects ($p = 0.93$).
Conclusions PDE5Is were significantly more effective than placebo or SSRIs for treating PE, while SSRIs were better than placebo. The combined treatment had better efficacy than PDE5Is or SSRIs alone.

Keywords Phosphodiesterase-5 inhibitor · Premature ejaculation · Selective serotonin reuptake inhibitors · Intravaginal ejaculation latency time · Randomized controlled trial

Abbreviations

PE	Premature ejaculation
IVELT	Intravaginal ejaculation latency time
SSRIs	Selective serotonin reuptake inhibitors
ED	Erectile dysfunction
AUA	American Urological Association
PDE5I	Phosphodiesterase type 5 inhibitor
IIEF	International Index of Erectile Function
MD	Mean difference
CI	Confidence interval
RR	Relative risk

Introduction

Premature ejaculation (PE) is a commonly encountered and troublesome male sexual dysfunction, with prevalence rates of more than 20% in the general community [1]. Some survey studies have revealed that 2.5% of men had an intravaginal ejaculation latency time (IVELT) of 1 min and 6% of 2 min [2]. Most studies have found that intravaginal ejaculation latency time (IVELT) is the most sensitive parameter for measuring the efficacy of PE treatment;

Yi Sun and Lu Yang contributed equally to this work and should share the co-first author.

✉ Lu Yang
wycleflue@163.com

✉ Qiang Wei
weiqiang933@126.com

[1] Department of Urology, West China Hospital of Sichuan University, No.37 Guoxue Xiang, Chengdu 610041, Sichuan, People's Republic of China

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Table 1 The condition of the studies and clinical details of the patients

References	Year	Age	Design	The definition of PE	Lifelong/acquired PE	Groups and amount of patients	Dosage	Usage	Duration	The criterion of NO ED
Salem et al. [3]	2017	25–50	Cross-over	IVELT <2 min	Lifelong PE	Paroxetin (60)/placebo (60)	20 mg	Diary	1 months	IIEF-EF ≥21
Moudi et al. [4]	2016	17–49	RCT	IVELT <1.5 min	Lifelong PE	Paroxetine (50)	10 mg	Diary	6 months	N M
						Tadalafil + paroxetine (50)	10 mg + 10 mg	Diary		
Polat et al. [5]	2014	20–41	RCT	N M	Lifelong PE	Tadalafil (50)	20 mg	On demand	3 months	N M
						Paroxetine (50)	20 mg	Diary		
						Tadalafil + paroxetine (50)	20 mg + 20 mg	On demand		
Gameel et al. [6]	2013	26–39	RCT	IVELT <2 min	≥1 year PE	Sildenafil (30)	50 mg	On demand	4 weeks	IIEF-EF ≥22
						Paroxetine (28)	20 mg	On demand		
						Placebo (27)	–	On demand		
Lee et al. [7]	2013	30–70	RCT	PEDT	Lifelong PE	Dapoxetine + mirodenafil (45)	30 mg + 50 mg	On demand	12 weeks	IIEF-EF ≥22
						Dapoxetine + placebo (31)	30 mg + placebo	On demand		
McMahon et al. [8]	2013	19–74	RCT	IVELT <2 min	Lifelong PE	Dapoxetine (221)	60 mg		18 weeks	After treatment
		21–77				Placebo (208)	60 mg			
Gokce et al. [9]	2010	18–50	Cross-over	IVELT <1 min	Lifelong PE	Vardenafil (17)/placebo (17)	10 mg/10 mg	On demand	7–15 days	IIEF-EF ≥26
Aversa et al. [10]	2009	18–35	Cross-over	IVELT <1 min PEDT	Lifelong PE	Vardenafil (30)/placebo (10)	10 mg/10 mg	On demand	8 weeks	IIEF-EF ≥22
Mathers et al. [11]	2009	N M	Cross-over	IVELT <1.5 min CMASH scale ≥4	≥1 year PE	Vardenafil (44)/sertraline (44)	10 mg/50 mg	On demand	6 weeks	IIEF-EF ≥25
Buvat et al. [12]	2009	39.6	RCT	IVELT <2 min		Dapoxetine (388)	30 mg		24 weeks	IIEF-EF ≥21
		40.5				Dapoxetine (389)	60 mg			
		40.1				Placebo (385)				
Mattos et al. [13]	2008	24–59	RCT	IVELT <1.5 min	Lifelong PE	Tadalafil + fluoxetine (15)	20 mg + 90 mg	On demand	12 weeks	IIEF-EF ≥26
						Fluoxetine + placebo (15)	90 mg + 20 mg	1/week		
						Tadalafil + placebo (15)	20 mg + 90 mg	On demand		
						Placebo + placebo (15)	110 mg	On demand		
Kaufman et al. [14]	2008	N M	RCT	PEDT	Lifelong PE	Dapoxetine (313)/placebo (167)	60 mg/60 mg	On demand	9 weeks	N M

Table 1 (continued)

References	Year	Age	Design	The definition of PE	Lifelong/acquired PE	Groups and amount of patients	Dosage	Usage	Duration	The criterion of NO ED
Hosseini et al. [15]	2007	21–43	RCT		Lifelong PE	Fluoxetine (48)/fluoxetine + sildenafil (43)	20 mg	On demand	4 months	IIEF
							20 mg + 50 mg	On demand		
Wang et al. [16]	2007	20–51	RCT	IVELT <2 min	Lifelong PE	Sildenafil (59)/paroxetine (49)	50 mg/20 mg	O D/Diary	6 months	IIEF-EF ≥21
Atan et al. [17]	2006	20–52	RCT	PEDT	9–60 months	Sildenafil (20)/placebo (20)	50 mg/50 mg	O D/Diary	2 months	N M
Pryor et al. [18]	2006	18–65	RCT	IVELT <2 min	Lifelong PE/acquired PE	Dapoxetine (876)	30 mg	Diary	12 weeks	N M
						Dapoxetine (870)	60 mg			
						Placebo (872)				
McMahon et al. [19]	2005	18–65	RCT	IVELT <2 min	Lifelong PE	Sildenafil (66)/placebo (60)	50–100 mg/100 mg	On demand	8 weeks	IIEF-EF ≥21
Zhang et al. [20]	2005	18–42	RCT	IVELT <2 min	Lifelong PE	Sertraline (36)	50 mg	Diary	12 weeks	IIEF
						Sertraline + sildenafil (36)	50 mg + 50 mg	Diary + O D		
Salonia et al. [21]	2002	19–46	RCT	IVELT <1 min	Lifelong PE	Paroxetine (33)	20 mg	Diary	6 months	IIEF-EF ≥14
						Paroxetine + sildenafil (36)	20 mg + 50 mg	Diary + O D		
Waldinger et al. [22]	2001	18–65	RCT	IVELT <1 min	Lifelong PE	Paroxetine (12)	20 mg	Diary		
						Sertraline (12)	50 mg	Diary		
						Placebo (12)	Identical capsules	Diary		
Chris et al. [23]	1999	20–51	Cross-over	IVELT <1 min	N M	Paroxetine (42)	10 mg + 20 mg	Diary + O D	17 weeks	N M
						Placebo (42)	10 mg + 20 mg	Diary + O D		
Yilmz et al. [24]	1999	22–56	RCT	UEFM	N M	Fluoxetine (20)	20 mg	Diary	1 months	N M
		24–58				Placebo (20)	20 mg	Diary		
Biri et al. [25]	1998	21–54	RCT	PEDT	N M	Sertraline (22)/placebo (15)	50 mg/50 mg	Diary	4 weeks	N M

PEDT premature ejaculation diagnostic tool, *IIEF-EF* score of erectile function domain of International Index of Erectile Function, *O D* on demand, *CMASH* Center for Marital and Sexual Health questionnaire, *IPE* Index Of Premature Ejaculation, *N M* no mention, *UEFM* uncontrolled ejaculation on the few minutes

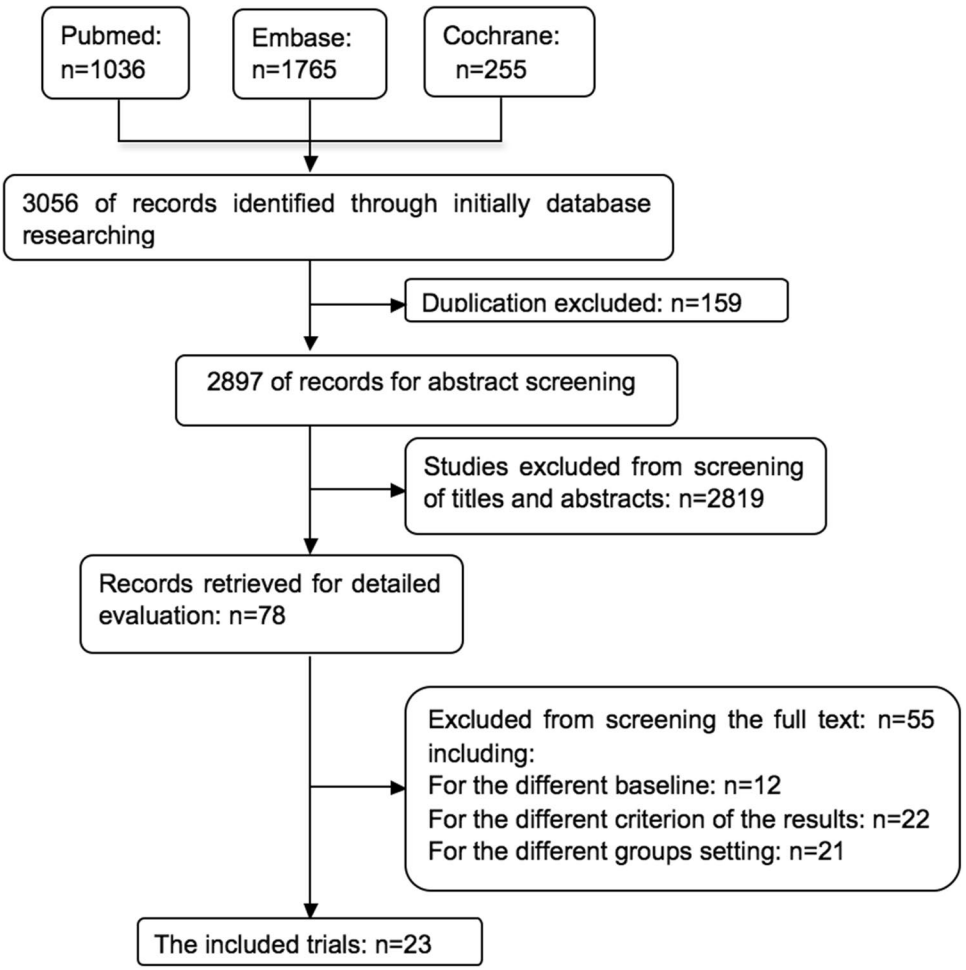

Fig. 1 The flow diagram of the searching

in addition, the satisfaction score and intercourse per week are also important for the examination of sexual activities [3–25]. There are several treatment options provided for patients, including sexual education, behavioral therapy and pharmaceutical treatment [26]. Selective serotonin reuptake inhibitors (SSRIs) have emerged as an effective treatment for patients with PE whether or not these patients suffer from depression [27]. In men with both PE and erectile dysfunction (ED), the American Urological Association (AUA) recommends phosphodiesterase type 5 inhibitors (PDE5Is) as the first line to treat patients' ED [28]. Although some basic research has proposed several possible mechanisms for the effects of PDE5Is in patients with PE, [29] evidence as to whether PDE5I inhibitors are effective in the treatment of PE remains controversial [29]. Therefore, we reviewed five meta-analyses to test and demonstrate the efficacy and side effects of PDE5Is and SSRIs in patients with PE.

Methods

Inclusion and exclusion criteria

Men with primary PE but not ED, older than 18-year-old and having stable monogamous heterosexual relationships with the same sexual partner for more than 6 months were eligible. In this study, we included five studies that defined PE as IVELT <1 min, [9, 10, 15, 21, 23, 35] IVELT <2 min, [3, 6, 8, 12, 16, 18–20] IVELT <1.5 min, [4, 11, 13] PEDT, [7, 10, 14, 17, 25] and others [5, 24]. In addition, the International Index of Erectile Function (IIEF) domain scores were used to determine ED. The exclusion criteria were a history of medical or psychiatric illness, current physical illness (e.g., diabetes or liver disease), vascular disease, current substance abuse (e.g., alcohol or drug abuse), prior surgery, and use of drugs that could affect sexual function or cause other sexual disorders (e.g., low libido, urethritis, cystitis, urogenital tract malignancy, or other urinary disease). Patients with ED were excluded.

Table 2 The efficiency of the drugs

Authors	Drug	Baseline IVELT	Treatment IVELT	Baseline satisfied	Treatment satisfied	Intercourse/week (Pro)	Intercourse/week (Aft)
Salem et al. [3]	SSRIs	1.17 ± 0.30	17.09 ± 8.2	–	–	–	–
	Placebo	1.17 ± 0.30	1.07 ± 0.35	–	–	–	–
Moudi et al. [4]	SSRIs	–	4.8 ± 1.0	9/50	11/50	1.08 ± 0.6	–
	Combination	–	5.3 ± 2.0	9/50	14/50	1.12 ± 0.6	–
Polat et al. [5]	Combination	1.19 ± 0.67	2.92 ± 1.00	–	–	–	–
	PDE5I	1.14 ± 0.36	1.83 ± 0.62	–	–	–	–
	SSRIs	1.01 ± 0.50	1.96 ± 1.12	–	–	–	–
Gameel et al. [6]	PDE5I	1.99 ± 0.49	3.81 ± 1.15	1.17 ± 0.75	4.10 ± 0.84	–	–
	SSRIs	1.16 ± 1.63	3.11 ± 1.08	1.04 ± 0.64	3.25 ± 0.25	–	–
	Placebo	1.02 ± 0.51	1.35 ± 0.54	1.04 ± 0.64	1.18 ± 0.72	–	–
Lee et al. [7]	Combination	3.90 ± 3.86	11.3 ± 8.92	–	–	–	–
	SSRIs	4.90 ± 5.39	9.10 ± 8.18	–	–	–	–
McMahon et al. [8]	SSRIs	1.11 ± 0.55	5.2 ± 5.78	–	–	–	–
	Placebo	1.11 ± 0.53	3.4 ± 3.54	–	–	–	–
Gokce et al. [9]	PDE5I	–	3.16 ± 4.70	–	–	–	–
	Placebo	–	1.04 ± 1.43	–	–	–	–
Aversa et al. [10]	PDE5I	0.60 ± 0.30	4.50 ± 1.10	7 ± 2	15 ± 1	–	–
	Placebo	0.70 ± 0.30	0.90 ± 1.00	10 ± 1	8 ± 2	–	–
Mathers et al. [11]	PDE5I	0.59	5.01 ± 3.69	–	–	–	–
	SSRIs	0.59	3.20 ± 1.89	–	–	–	–
Buvat et al. [12]	SSRIs 30 mg	0.6 ± 0.27	2.5 ± 5.26	–	–	–	–
	SSRIs 60 mg	0.5 ± 0.28	2.8 ± 3.66	–	–	–	–
	Placebo	0.5 ± 0.26	1.3 ± 2.12	–	–	–	–
Mattos et al. [13]	Combination	0.82 ± 0.32	3.11 ± 2.65	–	–	–	–
	PDE5I	0.94 ± 0.31	3.89 ± 1.75	–	–	–	
	SSRIs	0.83 ± 0.43	5.60 ± 3.75	–	–	–	–
	Placebo	0.83 ± 0.31	1.13 ± 0.77	–	–	–	–
Kaufman et al. [14]	SSRIs	–	–	1.4 ± 0.83	2.5 ± 1.11	–	–
	Placebo	–	–	1.5 ± 0.79	2.0 ± 1.01	–	–
Hosseini et al. [15]	Combination	0.55	5.10 ± 9.10	6	9.3	1	3.2
	SSRIs	0.50	4.30 ± 6.70	6	7.2	1	2.5
Wang et al. [16]	PDE5I	1.09 ± 0.32	6.21 ± 1.86	2.42 ± 0.90	6.60 ± 1.16	0.86 ± 0.75	2.39 ± 1.30
	SSRIs	1.11 ± 0.45	4.93 ± 1.36	2.60 ± 1.02	5.80 ± 1.36	0.81 ± 0.88	1.84 ± 1.1
Atan et al. [17]	PDE5I	–	–	–	–	–	–
	Placebo	–	–	–	–	–	–
Pryor et al. [18]	SSRIs 30 mg	0.62 ± 0.32	2.19 ± 3.54	1.65 ± 1.02	2.21 ± 1.05	–	–
	SSRIs 60 mg	0.61 ± 0.29	2.67 ± 3.42	1.72 ± 1.05	2.32 ± 1.06	–	–
	Placebo	0.61 ± 0.26	1.28 ± 1.67	1.66 ± 1.03	1.70 ± 1.06	–	–
McMahon et al. [19]	PDE5I	0.96 ± 0.48	2.60 ± 0.16	–	3.1 ± 0.2	–	–
	Placebo	1.04 ± 0.48	1.63 ± 2.16	–	2.2 ± 0.1	–	–
Zhang et al. [20]	Combination	0.56 ± 0.11	5.60 ± 0.12	8.8 ± 1.1	13.8 ± 1.3	1.0 ± 0.2	2.1 ± 0.2
	SSRIs	0.59 ± 0.12	3.90 ± 0.15	8.9 ± 1.2	10.8 ± 1.1	0.9 ± 0.2	1.9 ± 0.3
Salonia et al. [21]	Combination	0.35 ± 0.03	5.30 ± 0.02	3.0	9.0	1 ± 0.2	2.3 ± 0.3
	SSRIs	0.33 ± 0.04	4.20 ± 0.03	3.0	8.3	0.9 ± 0.1	1.7 ± 0.3
Waldinger et al. [22]	SSRIs(p)	0.29 ± 0.02	1.80 ± 0.02	–	–	–	–
	SSRIs(s)	0.23 ± 0.02	0.84 ± 0.01	–	–	–	–
	Placebo	0.25 ± 0.02	0.30 ± 0.02	–	–	–	–
Chris et al. [23]	SSRIs	0.5	4.88 ± 1.31	–	–	–	–
	Placebo	0.5	0.65 ± 0.26	–	–	–	–

Table 2 (continued)

Authors	Drug	Baseline IVELT	Treatment IVELT	Baseline satisfied	Treatment satisfied	Intercourse/week (Pro)	Intercourse/week (Aft)
Yilmz et al. [24]	SSRIs	1.2 ± 1.0	6.6 ± 7.7	–	–	–	–
	Placebo	1.1 ± 1.1	1.5 ± 1.3	–	–	–	–
Bibr et al. [25]	SSRIs	0.68 ± 0.21	5.42 ± 4.36	–	–	–	–
	Placebo	0.73 ± 0.34	1.91 ± 1.56	–	–	–	–

The gastrointestinal upset include nausea, diarrhea, lack of appetite and dyspepsia

SSRIs(*p*) paroxetine, *SSRIs*(*s*) sertraline, *Pro* before treatment, *Aft* after treatment

Literature search and data sources

We searched the PubMed (updated to April 2017), Embase® (updated to April 2017), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases. The initial search process was designed to find all trials involving the terms phosphodiesterase-5 inhibitor, premature ejaculation, and selective serotonin reuptake inhibitor. The reference lists from the retrieved documents were also searched. Computer searches were supplemented by a manual search. Two authors (Y.S. and L.Y.) independently screened all of the citations and abstracts selected by the search strategy to identify potentially eligible studies.

Data extraction

Data were extracted independently by two authors (Y.S. and YG.B.) using a pre-designed data extraction form. The data extraction included the data source, eligibility, methods, participant characteristics, interventions, and results. The two authors subsequently met to discuss their findings, and the information was subsequently entered into RevMan software, version 5.1.4. Any discrepancies among the extracted data were resolved by discussion. If disagreements persisted after discussion, they were resolved in consultation with a third author (Q.W.).

Interventions and comparisons

We evaluated five meta-analyses and compared two groups in each of the meta-analyses. In the first meta-analysis, the experimental group was administered PDE5Is (sildenafil, tadalafil, vardenafil, and avanafil), and the control group received placebo. In the second meta-analysis, the experimental group was administered SSRIs (fluoxetine, dapoxetine, sertraline, and paroxetine), and the control group received placebo. In the third meta-analysis, the two groups took PDE5Is alone or a combination of PDE5Is and SSRIs. In the fourth meta-analysis, the two groups took SSRIs alone or a combination of PDE5Is and SSRIs. In the fifth meta-analysis, the groups took PDE5Is or SSRIs. The outcome measurements were IVELT, sexual satisfaction scores, side effects, and other indices.

Outcome measurements

We used IVELT, sexual activity satisfaction and intercourse per week as the major efficacy measurements and the number of patients with side effects after treatment as the side effect measurement. Side effects included headache and dizziness, fatigue, decreased libido, gastrointestinal upset, palpitations, nasal congestion, erectile dysfunction and flushing. The patients were asked to record their ejaculation times with a stopwatch during sexual intercourse to measure IVELT. The sexual satisfaction scores for each patient were recorded before and after the treatment. Moreover, the per-week numbers of instances of intercourse were recorded before and after the treatment. The data were analyzed using SPSS software (SPSS Inc., Chicago, IL, USA) with the General Linear Model procedure, and the mean and standard deviation were calculated. The number of patients who developed side effects was also recorded.

Quality assessment

The quality of the studies included was assessed by two authors (Y.S. and L.Y.), according to the Cochrane Collaboration Reviewer's Handbook and the Quality of Reporting of Meta-analyses guidelines [30, 31]. The quality items were the generation of random sequences, blinding methods, allocation concealment, description of withdrawals and dropouts, and intent-to-treat analysis.

Data analysis

The analysis of the meta-analyses data was performed using RevMan software, version 5.1.4. Continuous outcomes are presented as the weighted mean difference (MD) with 95% confidence interval (CI). Dichotomous data were presented

Table 3 The efficiency and side effects of the drugs

Authors	Drug	Total	Headache and dizziness	Fatigue	Decreased libido	Gastrointestinal upset	Palpitation	Nasal congestion	Erectile dysfunction	Flushing
Moudi et al. [4]	SSRIs	12/50	4/50	–	2/50	5/50	–	–	–	0/50
	Combination	23/50	11/50	–	0/50	4/50	–	–	–	8/50
Polat et al. [5]	Combination	12/50	5/50	0/15	–	3/50	4/50	–	–	3/50
	PDE5I	12/50	5/50	0/15	–	0/50	4/50	–	–	3/50
	SSRIs	15/50	0/50	15/50	–	2/50	0/50	–	–	0/50
Gameel et al. [6]	PDE5I	–	20/30	–	–	17/30	–	–	–	9/30
	SSRIs	–	11/28	–	–	6/28	–	–	–	3/28
	Placebo	–	0/27	–	–	0/27	–	–	–	0/27
Lee et al. [7]	Combination	26/45	14/45	–	–	8/45	4/45	–	–	2/45
	SSRIs	18/31	8/31	–	–	8/31	1/31	–	–	1/31
McMahon et al. [8]	SSRIs	74/221	21/221	–	–	35/221	–	3/221	–	0/221
2013	Plcebo	49/208	15/208	–	–	6/208	–	7/208	–	3/208
Gokce et al. [9]	PDE5I	7/17	–	–	–	–	–	–	–	–
	Placebo	4/17	–	–	–	–	–	–	–	–
Aversa et al. [10]	PDE5I	3/30	3/30	–	–	0/30	–	–	–	0/30
	Placebo	0/10	0/10	–	–	0/10	–	–	–	0/10
Mathers et al. [11]	PDE5I	7/44	3/44	–	0/44	0/44	–	1/44	–	3/44
	SSRIs	7/44	0/44	–	1/44	3/44	–	0/44	–	0/44
Buvat et al. [12]	SSRIs 30 mg	218/388	105/388	22/388	–	134/388	–	21/388	8/388	–
	SSRIs 60 mg	265/389	55/389	26/389	–	108/389	–	24/389	12/389	–
	Placebo	148/385	42/385	8/385	–	17/385	–	13/385	8/385	–
Mattos et al. [13]	Combination	6/15	0/15	3/15	–	2/15	1/15	–	–	0/15
	PDE5I	4/15	3/15	0/15	–	0/15	2/15	–	–	2/15
	SSRIs	5/15	0/15	6/15	–	1/15	0/15	–	–	0/15
	Placebo	2/15	0/15	0/15	–	1/15	0/15	–	–	0/15
Kaufman et al. [14]	SSRIs	301/313	90/313	–	–	105/313	–	–	4/313	10/313
	Placebo	108/167	22/167	–	–	9/167	–	–	6/167	0/167
Hosseini et al. [15]	Combination	29/43	12/43	–	2/43	8/43	–	–	–	7/43
	SSRIs	16/48	6/48	–	3/48	7/48	–	–	–	0/48
Wang et al. [16]	PDE5I	19/59	7/59	0/59	–	2/59	–	5/59	–	5/59
	SSRIs	17/49	4/49	3/49	–	6/49	–	0/49	–	0/49
Atan et al. [17]	PDE5I	9/20	5/20	–	–	0/20	–	–	0/20	4/20
	Placebo	0/20	0/20	–	–	0/20	–	–	0/20	0/20
Pryor et al. [18]	SSRIs 30 mg	216/876	78/876	–	3/876	–	–	–	25/876	–
	SSRIs 60 mg	379/870	113/870	–	6/870	–	–	–	33/870	–
	Placebo	90/872	42/872	–	0/872	–	–	–	13/872	–

Table 3 (continued)

Authors	Drug	Total	Headache and dizziness	Fatigue	Decreased libido	Gastrointestinal upset	Palpitation	Nasal congestion	Erectile dysfunction	Flushing
McMahon et al. [19]	PDE5I	30/66	10/66	–	–	3/66	–	3/66	–	10/66
	Placebo	2/60	1/60	–	–	1/60	–	0/60	–	0/60
Zhang et al. [20]	Combination	22/36	8/36	–	–	8/36	–	–	–	5/36
	SSRIs	13/36	4/36	–	–	7/36	–	–	–	0/36
Salonia et al. [21]	Combination	22/36	8/36	–	1/36	6/36	–	–	–	6/36
	SSRIs	12/33	4/33	–	2/33	5/33	–	–	–	0/33
Waldinger et al. [22]	SSRIs(p)	0/12	–	–	0/12	–	–	–	0/12	–
	SSRIs(s)	0/12	–	–	0/12	–	–	–	0/12	–
	Placebo	0/12	–	–	0/12	–	–	–	0/12	–
Chris et al. [23]	SSRIs	7/42	0/42	–	2/42	3/42	–	–	0/42	–
	Placebo	2/42	0/42	–	0/42	0/42	–	–	2/42	–
Yilmz et al. [24]	SSRIs	–	–	–	3/20	–	–	–	–	–
	Placebo	–	–	–	1/20	–	–	–	–	–
Biri et al. [25]	SSRIs	12/22	11/22	–	–	3/22	–	–	–	–
	Placebo	7/15	6/15	–	–	1/15	–	–	–	–

The gastrointestinal upset includes nausea, diarrhea, lack of appetite and dyspepsia

Erectile dysfunction

SSRIs(*p*) paroxetine, SSRIs(*s*) sertraline

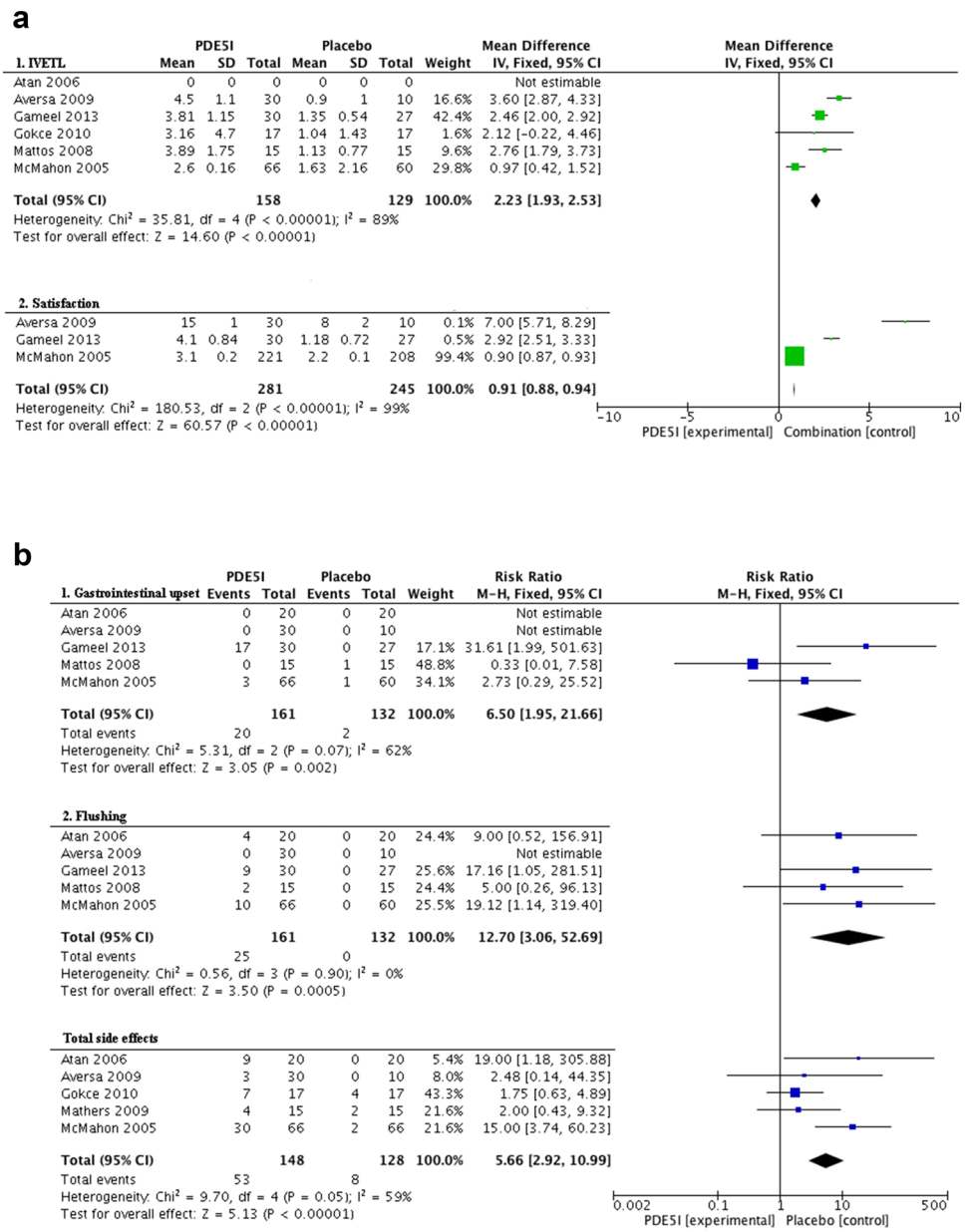

Fig. 2 The efficiency and complications of PDE5i versus the placebo

as the relative risk (RR) with 95% CI. The analysis of the meta-analyses was performed using a fixed effects or random effects method. The fixed effects method was used to combine the results when no significant heterogeneity was present. The random effects method was applied when heterogeneity was present. Statistical heterogeneity among the trials was evaluated using the I^2 test, with significance set at $p < 0.05$. Publication bias was evaluated using a funnel plot. In addition, sensitivity analysis was performed if low quality trials were included in the analysis.

Results

Description of the included studies

A total of 3056 reports were initially identified from the database and manual searching. After removing redundant publications, reviews and meta-analyses, and scanning the titles and abstracts of unrelated records, 2978 reports were excluded from the study. After referring to the full texts, 12 articles with different baselines, 22 articles with different results criteria, and 21 articles with different group settings were excluded. Finally, 23 publications (randomized control

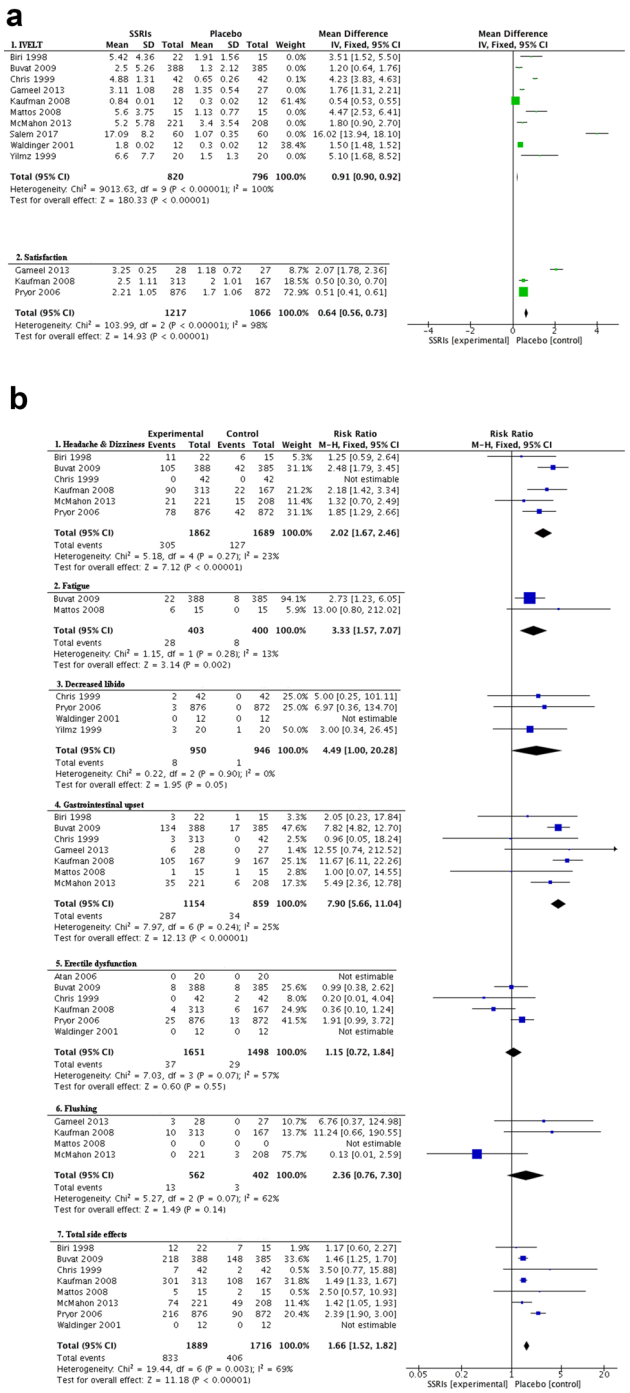

Fig. 3 The efficiency and complications of SSRIs versus the placebo

trials, RCTs, with five crossover studies) involving 6145 patients were included in this study. The conditions of these studies and the clinical details of the patients are presented in Table 1. The search flow diagram is presented in Fig. 1.

No significant differences were detected in the baseline information between the groups in the five meta-analyses. Six placebo-controlled trials involving 287 patients were included in the first meta-analysis. Eleven studies with 3364 patients who were taking either an SSRI or placebo as a control were included in the second meta-analysis. Two placebo-controlled trials involving 130 patients were included in the third meta-analysis. Seven placebo-controlled trials involving 538 patients were included in the fourth meta-analysis. The final meta-analysis included six trials with 408 patients either on a combined therapy of PDE5Is and SSRIs or SSRIs alone. All three meta-analyses measured efficacy with IVELT, satisfaction and intercourse per week (Table 2). In addition, side effects were also analyzed (Table 3). Our review of the funnel plots showed no publication bias.

PDE5I versus placebo

Six studies compared IVELT, satisfaction and side effects between PDE5I and placebo groups. Treatment with PDE5Is was significantly more effective based on IVELT than placebo (MD 2.23; 95% CI 1.93–2.53; $p < 0.00001$; Fig. 2a). In addition, the satisfaction score with PDE5Is was significantly better than with placebo (MD 0.91; 95% CI 0.88–0.94; $p < 0.00001$; Fig. 2a). The rates of occurrence of side effects were 35.81 and 6.25% in the PDE5I and placebo groups, respectively. The PDE5I group had more serious complications than those in the placebo group (RR 5.66; 95% CI 2.92–10.99; $p < 0.00001$; Fig. 2b).

SSRIs versus placebo

Eleven studies compared IVELT, satisfaction and side effects between SSRIs and placebo groups. Treatment with SSRIs was significantly more effective based on IVELT than placebo (MD 0.91; 95% CI 0.90–0.92; $p < 0.00001$; Fig. 3a). In addition, the satisfaction score with PDE5Is was significantly better than with placebo (MD 0.64; 95% CI 0.56–0.73; $p < 0.00001$; Fig. 3a). The rates of occurrence of side effects were 44.10 and 23.66% in the PDE5I and placebo groups, respectively. The SSRI group had more serious complications than those in the placebo group (RR 1.66; 95% CI 1.52–1.82; $p < 0.00001$; Fig. 3b).

PDE5Is alone versus combination of PDE5I and SSRIs

Two studies compared IVELT and side effects between PDE5I and combination treatment groups. Treatment with the combination of two drugs was significantly more effective based on IVELT than PDE5Is alone (MD −1.11; 95% CI −1.43 to −0.78; $p < 0.00001$; Fig. 4a). The rates of occurrence of side effects were 7.69 and 4.62% in the PDE5I and combination groups, respectively. There were no significant differences between the two groups (RR 1.57; 95% CI 0.43–5.77; $p = 0.50$; Fig. 4b).

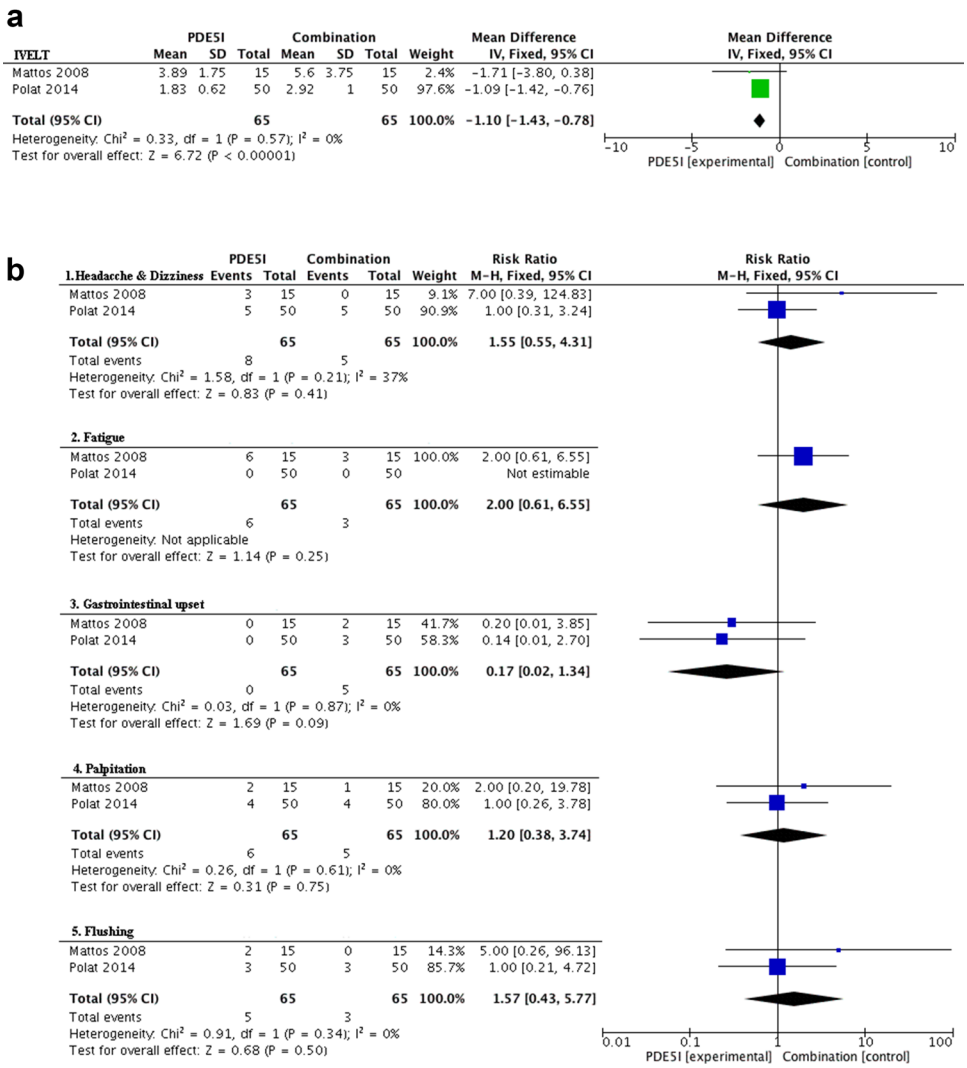

Fig. 4 The efficiency and complications of PDE5Is alone versus combination of PDE5I and SSRIs

SSRIs alone versus combination of PDE5I and SSRIs

Seven studies investigated IVELT, intercourse per week and side effects between SSRIs and combination groups. In these RCTs, combination treatment was significantly more effective than SSRI treatment (MD −1.12; 95% CI −1.13 to −1.11; $p < 0.00001$; Fig. 5a), and the intercourse per week was also better in the combination group than in the SSRI group (MD −0.10; 95% CI −0.15 to −0.04; $p = 0.0007$; Fig. 5a). The rates of occurrence of side effects were 34.21 and 50.91% in the SSRI and combination groups, respectively. The SSRI group had less serious complications than those in the combination group (RR 0.68; 95% CI 0.56–0.83; $p = 0.0002$; Fig. 5b).

PDE5I versus SSRIs

Six studies investigated IVELT, satisfaction and the side effects between SSRI and PDE5I groups. In these RCTs, PDE5I treatment was significantly more effective than SSRIs treatment (MD −0.37; 95% CI −0.63 to −0.11; $p = 0.006$; Fig. 6a). In addition, the satisfaction score with PDE5Is was significantly better than with SSRIs (MD −0.84; 95% CI 0.57–1.10; $p < 0.00001$; Fig. 6a). The rates of occurrence of side effects were 26.79 and 25.95% in the PDE5I and SSRI groups, respectively. No significant differences were observed between the two groups (RR 1.02; 95% CI 0.71–1.45; $p = 0.93$; Fig. 6b).

Side effects of the three treatments

Drug-related side effects in the PDE5I, SSRI, and the combination treatment groups included headache and dizziness (12.31, 29.42, and 18.53%, respectively), fatigue (0, //9.16, and 4.62%, respectively), decreased libido (0, 0.84, and 0%, respectively), gastrointestinal upset (nausea, diarrhea, lack of appetite, and dyspepsia; 8.85, 22.61, and 14.18%,

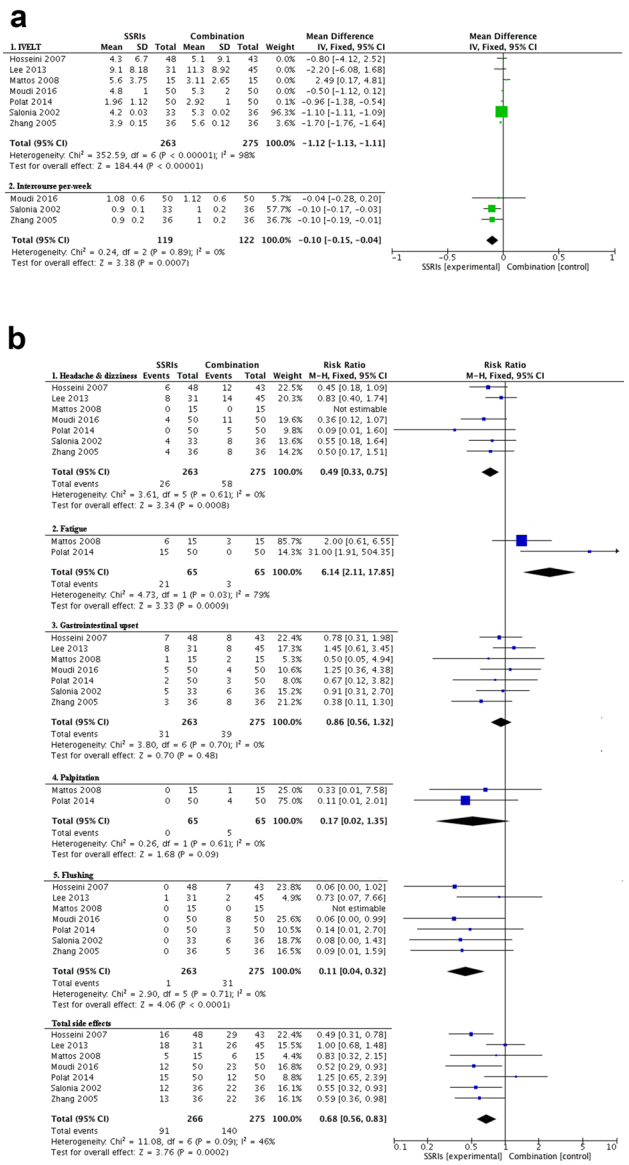

Fig. 5 The efficiency and complications of SSRIs alone versus combination of PDE5I and SSRIs

respectively), palpitations (9.23, 0, and 7.69%, respectively), nasal congestion (5.83, 0 and 0%, respectively), erectile dysfunction (0, 2.24 and 0%, respectively) and flushing (11.37, 1.44, and 11.27%, respectively).

Discussion

Although PE is a common sexual dysfunction, the exact causes of PE remain unclear [6]. Several mechanisms have been demonstrated for this problem, including organic and psychogenic factors. Animal and human psycho-pharmacological studies have suggested that there are changes related to central serotonergic neurotransmission in PE, 5-hydroxytrypta-mine-2C receptor hyposensitivity and/or 1A receptor hypersensitivity, which seem to be possible mechanisms [6]. As we all know, various treatments are useful for PE, and behavioral psychosexual therapy is commonly agreed to be the primary choice [32], but the efficacy might not continue after behavioral therapy. In addition, anesthetic agents are also a treatment for PE, but their side effects include penile numbness, which can induce the side effect of loss of erection [33]. Moreover, tramadol has also been used to treat PE; however, it can cause nausea, vomiting, dyspepsia, headache, somnolence, and dizziness [33].

The PDE5Is have been used as a single application and in combination with serotonergic drugs for ED since 2001, and they inhibit presynaptic reuptake of serotonin [11]. Several possible mechanisms might explain the efficacy of PDE5Is in PE [33]. Not only peripheral but also the central mechanisms are likely important; however, although reduced sympathetic tone and smooth muscle dilatation are speculated mechanisms, the role of each factor in retarding ejaculation remains unknown [33]. Further, some researchers have demonstrated that the potential role of PDE5Is in the treatment of PE without ED remains controversial [7]. In addition, among pharmacologic agents for the treatment of PE is dapoxetine, an SSRI, which is rapid acting with a short half-life and is an approved drug [7]. However, one of its common side effects is delayed ejaculation, and other complications include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhea, perspiration, decreased libido, anorgasmia, and anejaculation [29]. Moudi et al. compared the PDE5Is alone and PDE5Is combined with SSRIs in patients complaining of premature ejaculation [4]. The results of this study showed that IELT at the 3- and 6-months follow-ups, in the group with combination therapy, was higher than that in the PDE5I alone group [4]. Moreover, the mean fold increases in the IELT in the PDE5Is plus SSRIs group were also greater than that in the SSRIs only group over 12 weeks [7].

There have been several meta-analysis studies of the efficiency of PDE5Is and SSRIs in treatment of the PE, but these studies included only a few studies, while our study included 23 studies. We demonstrated in the first meta-analysis that PDE5Is increased IVELT and satisfaction compared to placebo; however, more side effects were observed. We found in the second meta-analysis that the efficacy of SSRIs was better than that of placebo with more serious complications. In the third meta-analysis, we found much greater improvement in IVELT in patients who administered the combined PDE5I and SSRI treatment than in patients administered PDE5Is alone, without more side effects detected. In the fourth meta-analysis, we found much greater improvement in IVELT and intercourse per week in patients who administered

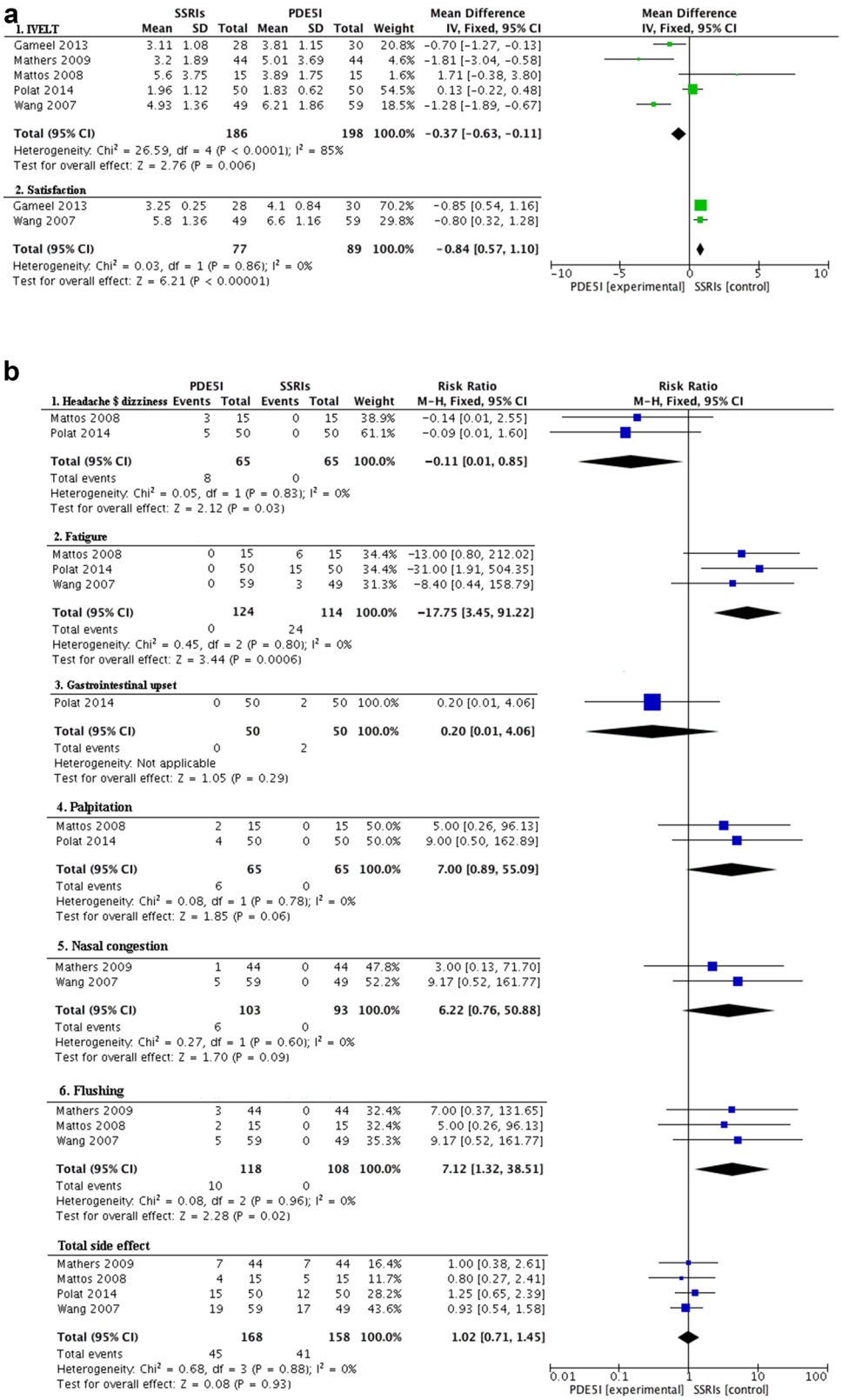

Fig. 6 The efficiency and complications of SSRIs versus PDE5I

the combined PDE5I and SSRI treatment than in patients administered SSRIs alone, with more side effects. In the last meta-analysis, we found that the improvements in IVELT and satisfaction were better with PDE5Is than SSRIs. Therefore, the use of PDE5Is as a single application and in combination with SSRIs seems to be the most

efficient treatment for treating PE, given the additional side effects.

Some limitations of our study should be discussed. There is currently no universally agreed upon definition for primary PE. One study recently defined PE as ejaculation that always or nearly always occurs prior to or within approximately 1 min of vaginal penetration from the first sexual experience or a clinically significant reduction in latency time, often to approximately 3 min or less (acquired PE), the inability to delay ejaculation in all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [34]. In this study, we used five different definitions from 23 articles because there is no validated definition of PE. Only if a truly objective diagnosis of PE were made would the search for the best treatments be able to continue. In addition, in this study, the various authors used sildenafil, [6, 15–17, 19–21] vardenafil, [9–11] or tadalafil [4, 5, 13] as PDE5Is, whereas they used sertraline, [11, 20, 22, 25] fluoxetine, [13, 15, 24] dapoxetine, [8, 12, 14, 18] or paroxetine as SSRIs [3–7, 21–23]. Therefore, we used different medications and doses in our study, but the different medications have similar mechanisms. In a future study, we will continue to examine the different treatments in PE and include more indices.

Author contributions YS: Protocol development; Data collection or management; Data analysis; Manuscript writing. LY: Data collection or management; Data analysis; Manuscript writing. YB: Data collection or management; Data analysis. ZL: Data analysis; Manuscript writing. LL: Data analysis. QW: Protocol development; Manuscript editoring.

Compliance with ethical standards

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Conflict of interest Authors declare that they have no competing interests.

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