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MEN'S HEALTH (R CARRION, SECTION EDITOR)

Conservative Non-surgical Options for Erectile Dysfunction

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Abstract

Purpose of Review This study aimed to review recent evidence on conservative non-surgical options for erectile dysfunction (ED) in men. A narrative review of the literature was performed. A comprehensive search in the MEDLINE, Embase, and Cochrane databases was done. Papers in English language, published from May 2017 until May 2022, were included. Papers reporting basic research or animal research were excluded, as long as reviews or meta-analyses. Congress reports, clinical cases, or clinical trials protocols with no results were also excluded.

Recent Findings We found a multitude of different treatment modalities for ED. We must take into account the type of patient, their comorbidities, the origin of their ED, and its severity in order to reproduce effective results using these therapies. Some of the treatments show good results with a good level of evidence (new IPDE5 formulations, intracavernous injections, shock wave therapy, hormonal theraphy, psycho-sexual theraphy). However, others (some new molecules, stem cell theraphy, platelet-rich plasma injections, oxygenation-based therapy, nutraceuticals), although some of them present promising results, require randomized studies with a larger number of patients and a longer follow-up time to be able to establish firm recommendations.

Summary Regarding the conservative treatment of erectile dysfunction, in recent years, some therapies have been consolidated as effective and safe for certain types of patients. On the other hand, other treatment modalities, although promising, still lack the evidence and the necessary follow-up to be recommended in daily practice.

Keywords Erectile dysfunction · Impotence · Conservative treatment · Non-surgical treatment

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection hard enough to permit satisfactory sexual intercourse [1]. According to the five-item International Index of Erectile Function questionnaire (IIEF-5) score, ED severity is classified on severe (score 1–7), moderate (8–11), mild-moderate (12–16), mild (17–21), and no ED (22–25) [2].

ED has become a major health concern even in younger men, causing a significant impact on men's quality of life [3]. Its prevalence varies on the different series published, but it is constantly high. In the Boston area, 52% of men between 40 and 70 years old were shown to suffer some grade of ED, according to the Massachusetts Male Aging Study (MMAS) [4]. Generally, ED can be considered as a natural part of aging, and its prevalence increases with age, ranging from 12% in those men < 59 years, 22% in men 60–69 years, and 30% in men > 69 years old, as per a population-based study of US health professionals [5]. In a cross-sectional real-life study performed among men asking for their first medical help for new-onset ED, 25% of patients were younger than 40 years old, with almost 50% of the younger men complaining of severe ED [6]. It is expected that by the end of 2025, the number of ED cases can rise to as high as 322 million across the world [7].

Treatment of ED has evolved along the years, with the introduction of sildenafil, the first 5-phosphodiesterase inhibitor (5-PDEi), as a major milestone in the late 1990s

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[8]. Since then, clinical practice guidelines have established different algorithms and recommendations, usually proposing therapeutic lines depending on the invasiveness of the treatments [9]. But recently, the European Association of Urology Guidelines on Sexual and Reproductive Health have proposed some changes in this paradigm [10]. Thereby, some treatments are no longer considered second-line options, and they can be offered to patients according to their preferences and their clinical situation, like intracavernous injections (ICI) or topical or intraurethral alprostadil. Also, some treatments previously considered experimental have recently been included in clinical practice guidelines according to their growing scientific evidence, like shockwave therapy. In the present paper, we aimed to comprehensively review the evidence on non-surgical treatments for ED of the last 5 years (2017–2022), focusing on the new developments.

Methods

Search Strategy

A non-systematic review of the literature was carried out using the MeSH terms "erectile dysfunction/drug therapy" or "erectile dysfunction/therapy," or using free language terms, erectile dysfunction and treatment or therap*, from May 2017 to May 2022. Language was limited to English. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [11] were used to guide reporting of the study. The search was initially carried out in the electronic database PubMed and identified a total of 1871 articles. The search was then limited separately to articles published in EMBASE and Cochrane (1512 publications). Both searches were subsequently compared, duplicates eliminated, and a final total of 2729 articles identified for review.

Eligibility Criteria

Only original papers of clinical prospective and retrospective studies assessing the outcomes of different conservative (non-surgical) therapies for ED in men > 18 years old were included for revision. Therefore, papers reporting basic research or animal research were excluded, as long as reviews or meta-analyses. Congress reports, clinical cases, or clinical trials protocols with no results were also excluded. Papers reporting the results of rehabilitation therapy for ED after radical pelvic surgery were not considered for revision.

Study Selection and Data Extraction

A total of 2729 papers were reviewed by two different experts in the field. After filtering for the previous inclusion/exclusion criteria, and excluding those not matching the search criteria in terms of date, language, and publication type, a total of 199 papers were finally considered for revision. The process of paper selection is represented in Fig. 1. Then, relevant data from these papers were extracted, considering the interventional type of treatment, type of ED, the number of patients included, the follow-up period, rate of success in correcting ED, the tool used to measure ED, adverse events, and satisfaction rate, if available. Each study was identified by the first author and year of publication.

Results

Psycho-sexual Therapy

A total of seven papers evaluating phyco-sexual interventions to treat DE were included, and their characteristics are resumed in Table 1.

Cognitive behavioral sexual therapy (CBST) is the most common intervention studied, with five out of the seven papers evaluating it. In four of them, only non-organic erectile dysfunction (NOED) patients were included, whereas in the remaining three, psycho-sexual therapy was studied in order to improve the results in any kind of ED. Six of the papers analyzed showed a significant and positive result of the psycho-sexual therapies in improving DE, according to

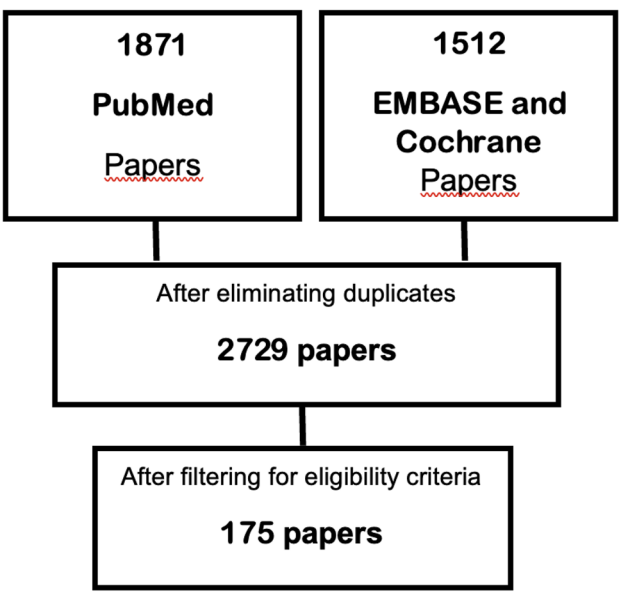

Fig. 1 Search flow diagram

Table 1 Results for psycho-sexual therapies

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Intervention	ED measurement tool	Results
Bilal and Abbasi 2022 [12•]	RCT	116 (35/34/35/33)	27	3	NOED	SC 50 mg/CBST/combination/placebo	IIEF-5	SC: + 1.65, p = 0.06; CBST: + 1.99, $p = 0.02$; Combination: + 2.31, ($p < 0.001$); against placebo group
Zhang et al. 2020 [13]	Prospective, observational	63 (33/30)	35	2	NOED	BPP + SC 100 mg/SC 100 mg	IIEF-5, EHS	IIEF-5: + 7.06 vs + 5.15 ($p = 0.04$) EHS ≥ 3, 27 pts vs EHS ≥ 3, 26 pts ($p = 0.06$)
Bilal and Abbasi 2020 [14]	Prospective, randomized	28 (13/15)	31	3	NOED	CBST/SC 50 mg	IIEF-5	IIEF-5: + 2.95 ($p = 0.01$)
Wang et al. 2020 [15]	Prospective	84 (42/42)	32	N/A	Any	CBST/nursing intervention	IIEF-5	IIEF-5: 20.26 vs 15.24 ($p < 0.05$)
Khan et al. 2019 [16]	Prospective	20 (10/10)	27	18	Any	PDE5i/CBST + PDE5i	IIEF	EF subscale: 16.8 vs 22.9 ($p < 0.05$)
Bossio et al. 2018 [17]	Observational	10	40	6	NOED	Mindfulness therapy	IIEF	EF subscale: + 2.42 ($p = 0.12$)
Khan et al. 2017 [18]	Prospective	60 (30/30)	27	N/A	Any	CBST + PDE5i/PDE5i	IIEF	EF subscale: + 6.39 vs + 4.05 ($p < 0.05$)

ED erectile dysfunction, *NOED* non-organic erectile dysfunction, *SC* sildenafil citrate, *CBST* cognitive behavioral sexual therapy, *PDE5i* phosphodiesterase-5 inhibitor, *EHS* erection hardness score, *IIEF* international index of erectile function, *DASS* Depression Anxiety Stress Scale, *SAS* Self-rating Anxiety Scale, *MHI* Mental Health Inventory, *SS* sexual satisfaction, Self-rating Depression Scale, *RCT* randomized controlled trial

the scores of the different questionnaires used. The study by Bossio et al. [17] found a positive but not significant effect of a mindfulness intervention in a small sample of 10 patients with NOED.

Hormonal Therapy

Six papers studied the effect of testosterone therapy (TT) to improve ED as a single therapy in hypogonadal men [19–24], with different formulations. All of them showed a benefit of the TT, according to the scores of the IIEF-EF or the IIEF-5. The remaining paper compared the results of TT alone or in combination with tadalafil 10 mg on alternate days [25], in a randomized, crossover study with 29 patients. It demonstrated higher satisfaction rates in the combination group.

5-PDE5i

Forty papers investigating the effects of PDE5is were identified. The results are resumed in Table 2.

Topical Drugs

Two papers analyzed the use of topical alprostadil to treat ED. In one of them [66], 71 patients were randomized to receive 300 µg of alprostadil over the glans, as the standard administration route, or within the urethral meatus, as an alternative administration route. The results showed that the alternative administration route achieved better results in terms of IIEF-5 score (+ 3.8 vs + 6.3, $p < 0.001$), and positive response to sex encounter profile (SEP)-2 (10 vs 27, $p < 0.001$), with no differences in the profile safety. The paper by Garrido-Abad et al. [67] evaluated the efficacy of topical alprostadil alone or in combination with maximum doses of PDE5i in patients non-responding to PDE5i alone. Those in the combination group presented higher IIEF-5 scores after the treatment (12.4 vs 17.1, $p < 0.001$), whereas those in the alprostadil alone group showed no significant improvement (12.2 vs 12.7, $p = 0.148$).

A randomized, placebo-controlled trial by Ralph et al. [68] assessed the efficacy of a novel topical gel containing

Table 2 Results for PDE5i

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Efficacy of PDE5i									
Lee et al. 2022 [26]	RCT	129 (43/43/43)	60	2	Any	Any	Mirodenafil ODF 50 mg vs 100 mg vs placebo on-demand	IIEF-5, SEP	IIEF-5: +3.19 vs +4.71 vs +1.88 ($p=0.086$, $p=0.026$; against placebo group) SEP-2: +29.99% vs +34.36% vs 25.45% ($p=0.09$, $p=0.078$; against placebo group) SEP-3: +43.46% vs +41.22% vs +24.12% ($p=0.006$, $p=0.043$; against placebo group)
Kumar et al. 2022 [27]	Randomized, non-inferiority clinical study	220 (111/109)	37	3	Any	IIEF-EF < 26	Avanafil 100 mg/200 mg vs sildenafil 50 mg/100 mg on-demand	IIEF	EF subscale: + 14.6 vs + 12.9 ($p=0.002$)
Cui et al. 2021 [28]	Randomized, controlled, double-cycle crossover trial	60 (30/30)	44	2 doses with 7 days washout in between	Any	Mild-moderate ED (IIEF-5 8–21)	Sildenafil 60 mg vs placebo	Duration of penile tip rigidity ≥ 60% (RigiScan®)	RigiScan®: 6.5 vs 0.5 min ($p<0.001$)
Sangkum et al. 2021 [29]	Randomized, controlled crossover study	120 (60/60)	64	2	Any	Any	Sildenafil orally disintegrating strips 50 mg twice a week vs tablet 100 mg once a week	IIEF-5, EHS	IIEF-5: +3.56 vs +3.38 ($p<0.001$) (comparison $p=0.899$) EHS: +0.42 vs +0.54 ($p<0.001$) (comparison $p=0.953$)
Jiang et al. 2021 [30]	RCT	218 (72/74/72)	40	3	Any	IIEF-5 ≤ 21	Avanafil 100 mg vs avanafil 200 mg vs placebo on-demand	IIEF, SEP	EF subscale: + 8.2 vs + 8.1 vs + 4.8 ($p=0.003$, $p=0.006$ against placebo group; $p=0.795$ 100 mg vs 200 mg) SEP 2: +22.3% vs +22.1% vs 5.4% ($p=0.005$, $p=0.025$; against placebo group; $p=0.499$ 100 mg vs 200 mg) SEP 3: +42.6% vs +38.1% vs +22.7% ($p=0.005$, $p=0.02$; against placebo group; $p=0.566$ 100 mg vs 200 mg)

Table 2 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Elkamshoushiet al. 2021 [31]	RCT	140 (70/70)	61	1	OED	IIEF-5 5–21	Avanafil 50 mg vs placebo daily	IIEF-5	IIEF-5: +4 vs + 0.5 ($p < 0.001$)
Law et al. 2020 [32]	RCT	50 (27/23)	60	2	Any****		Pentoxifyl-line 400 mg thrice daily orally + silde-nafil 100 mg on-demand vs placebo + silde-nafil 100 mg on-demand	IIEF	IIEF-5: 14.11 vs 14.87 ($p = 0.673$) EF subscale: 17.33 vs 18.43 ($p = 0.539$)
Pavone et al. 2020 [33]	Open-label uncontrolled study	65	64	3	PostRP ED	Any	Sildenafil ODF 100 mg twice a week	IIEF-5, SEP	IIEF-5: + 10 ($p < 0.001$) SEP 2: + 25% ($p < 0.001$) SEP 3: + 36% ($p < 0.001$)
Demirci et al. 2019 [34]	Retrospective	143 (30 mild-moderate ED/33 severe ED/80 control)	48	N/A	Any	Any	Tadalafil 5 mg daily	IIEF-5	IIEF-5: mild-moderate + 6.5 ($p < 0.001$), severe + 12 ($p < 0.001$)
Pattanaik et al. 2019 [35]	RCT	82 (41/41)	32	1	OED**	+ + +	Tadalafil 10 mg vs placebo daily	IIEF-5	IIEF5: +4.5 vs + 3.7 ($p = 0.22$)
Jiang et al. 2018 [36]	Prospective, randomized, open-label study	635	44	24	Any	Any	Tadalafil 2.5 mg vs 5 mg daily 3 months, then all patients 5 mg 21 months	IIEF, SEP	EF subscale at 12th month: 2.5 to 5 mg + 8 ($p < 0.001$), 5 mg + 7.9 ($p < 0.001$) SEP-2 at 3rd month: 2.5 mg + 30.6% ($p < 0.001$), 5 mg + 33.8% ($p < 0.001$) SEP 3 at 3rd month: 2.5 mg + 41.1% ($p < 0.001$), 5 mg + 43.6% ($p < 0.001$)
Lee et al. 2018 [37]	Single group, open-labeled, before-and-after prelimi-nary trial	40	53	2	Any	Any	Tadalafil 5 mg daily	IIEF-5	IIEF-5: + 3.33 ($p < 0.001$)
Cocci et al. 2017 [38]	Prospective	139	67	2.5	Any	IIEF > 16	Sildenafil 100 mg tablet 4 weeks, 2 weeks washout, then sildenafil 75 mg ODF 4 weeks; on-demand	IIEF	EF subscale: 25.41 vs 24.67 (− 0.74) ($p < 0.01$)

Table 2 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Park et al. 2017 [39]	RCT	158 (40/40/39/39)	56	2	Any	IIEF 11–25	Avanafil 50 mg vs 100 mg vs 200 mg vs placebo on-demand	IIEF, SEP	EF subscale: + 4.9 vs + 6.8 ($p < 0.001$) vs + 9.1 ($p < 0.001$) vs + 3.2; against placebo SEP 2: + 18.7% vs + 22.9% ($p < 0.05$) vs + 26.9% ($p < 0.001$) vs + 10.6%; against placebo SEP 3: + 22.3% vs + 44.9% vs + 52.9% ($p < 0.05$) vs + 32.1%; against placebo
Li et al. 2017 [40]	Retrospective	3674 (977/2697)	42	N/A	Any	Any	Sildenafil 50 mg vs 100 mg on-demand	IIEF	IIEF (severity): normal 42% vs 38.9%, mild 49.6% vs 51.9%, moderate 6.7% vs 7.7%, severe 1.7% vs 1.4% ($p > 0.05$)
Li et al. 2017 [41]	Prospective	86 (43/43)	23	3	NOED	Severe ED	Tadalafil 5 mg vs de-escalation (20 > 10 > 5 mg), daily	IIEF-5, SEP, EHS	IIEF-5: + 6.15 vs + 8.65 ($p < 0.05$) SEP score: + 1.91 vs + 2.53 ($p < 0.05$) EHS: + 1.01 vs + 1.43 ($p < 0.05$)
ED + PE									
Gharib 2022 [42]	RCT	160 (80/80)	36	3	Any	Any	Tadalafil 5 mg daily vs placebo	IIEF-5	IIEF-5: + 7.27 vs + 1.87 ($p < 0.001$)
Tuken 2019 [43]	Single-arm, open-label clinical study	53	45	1	Any	Any	Dapoxetine/Sildenafil 30/50 mg on-demand	IIEF	EF subscale: + 11.43 ($p < 0.001$)
ED + LUTS									
Sebastianelli et al. 2021 [44]	Prospective	50 (31 with MetS/19 without MetS)	65	3	Any	IIEF-5 < 22	Tadalafil 5 mg + tamsulosin 0.4 mg daily	IIEF-5	IIEF-5: + 3.7 vs + 4.9 ($p = 0.353$)
Sebastianelli et al. 2021 [45]	Prospective	50 (25/25)	66	6	Any	IIEF-5 < 22	3 months tamsulosin 0.4 mg + tadalafil 5 mg then 3 months monotherapy tadalafil vs tamsulosin	IIEF-5	IIEF-5: − 1.64 vs − 4.4 ($p = 0.003$)

Table 2 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Sebastianelli et al. 2019 [46]	Prospective	75 (50/25)	66	3	Any	IIEF-5 < 22	Tadalafil 5 mg + tamsulosin 0.4 mg vs tadalafil 5 mg + placebo daily	IIEF-5	IIEF-5: + 5.7 vs + 6.1 ($p = 0.255$)
Zhang et al. 2019 [47]	RCT	857 (337/346/174)	62	3	Any	Any	Placebo vs tadalafil 5 mg vs tamsulosin 0.2 mg daily	IIEF, SEP	EF subscale: + 1.88 vs + 5.24 vs + 2.64 ($p < 0.001$) SEP-2: + 10.9% vs + 23.83% vs + 6.84% ($p < 0.001$) SEP-3: + 15.96% vs + 36.62% vs + 17.42% ($p < 0.001$)
Amano et al. 2018 [48]	Prospective	81	66	12	Any	Any	Tadalafil 5 mg daily	SHIM	SHIM: + 3.25 ($p < 0.01$)
Özkıdık et al. 2018 [49]	Retrospective	208 (104 dutasteride/104 control)	61	N/A	Any	IIEF < 17	Tadalafil 10 mg/20 mg on-demand	IIEF	IIEF: + 9.3 vs + 10 ($p = 0.59$)
Kim et al. 2017 [50]	RCT	510 (169/170/171)	62	3	Any	IIEF-EF < 25	Tadalafil/tamsulosin 5 mg/0.4 mg or 5 mg/0.2 mg vs tadalafil 5 mg daily	IIEF	EF subscale: + 9.17 vs + 9.49 ($p = 0.588$) + 9.66 vs + 9.25 (0.39) ($p = 0.4576$)
Specials cohorts									
Lee et al. 2022 [51]	RCT	68 (45/23) andropause patients	60	6	Any	Any	Tadalafil 5 mg daily vs placebo	IIEF-5	IIEF-5: + 6.56 ($p = 0.003$) vs + 2.22 ($p = 0.003$)
Du et al. 2021 [52]	RCT	80 (40/40) hyperlipidemia patients	60	3	Any	Mild-moderate ED (IIEF-5 8–21)	Atorvastatin calcium 20 mg vs tadalafil 10 mg	IIEF-5	IIEF-5: + 0.23 ($p = 0.00$) vs + 4.11 ($p = 0.00$)
Jagdish et al. 2021 [53]	RCT	140 (70/70) cirrhosis patients	46	3	Any	Any	Tadalafil 10 mg daily vs placebo	IIEF, SEP-2, SEP-3	IIEF-5: + 7.5 ($p = 0.001$) vs + 3.5 ($p = 0.001$) SEP-2: + 35% vs + 8.6% ($p = 0.001$) SEP-3: + 37.3% vs + 11.1% ($p = 0.001$)

Table 2 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Verri et al. 2021 [54]	Randomized, double-blind, prospective and crossover study	50 hypertensive patients	57	3	Vasculogenic ED	IIEF-5 ≤ 21	Sildenafil 50 mg twice daily vs placebo in two 30-day periods with a 30-day washout between them	IIEF, SEP-3	IIEF: + 3.5 ($p = 0.0001$) SEP-3: 66%vs 98%
Thakur et al. 2019 [55]	Prospective, observational	25 cirrhosis patients	45	1	Any	Any	Tadalafil 10 mg once daily	IIEF	IIEF: + 6.9 ($p = 0.001$)
Bolat et al. 2018 [56]	Retrospective	63 (31/32) diabetic patients	61	3	Any	Any	Tadalafil 5 mg once a day vs tadalafil 20 mg on-demand	IIEF, EHS, MSHQ	IIEF: ≤ 65 years: + 3 ($p = 0.001$) vs + 2.3 ($p = 0.04$); > 65 years: + 3.2 ($p = 0.001$) vs + 0.9 ($p = 0.09$) EHS: + 1 ($p = 0.001$) vs 0.9 ($p = 0.001$) MSHQ: + 3.1 ($p = 0.001$) vs + 4.8 ($p = 0.02$)
Bolat et al. 2017 [57]	Retrospective	30 hemodialysis patients	48	3	Any	Any	Tadalafil 5 mg twice weekly	IIEF, EHS	IIEF: + 7.6 ($p = 0.01$) EHS: + 12.1 ($p = 0.01$)
Miscellaneous									
Wang et al. 2021 [58]	Cross-sectional	378 (93 non-responders/285 responders)	33	N/A	Any	Any	Sildenafil 100 mg or tadalafil 20 mg on-demand	N/A	Predictors of response: history of drinking (OR = 3.152) spousal noncooperation (OR = 2.994) number of stable sex partners (OR = 0.358), duration of ED (OR = 3.356) and depression (OR = 3.689), ($p < 0.05$)
Zhang et al. 2021 [59]	Prospective, observational	136 (73 responders/63 on-responders)	39	3	OED	IIEF-5 < 21	Sildenafil 50 or 100 mg, on demand	PSV (IMT)	PSV, cm/s: 24.07 ± 10.25 vs 2 0.34 ± 9.59 ($p = 0.015$) IMT, mm: 0.17 ± 0.06 vs 0.26 ± 0.80, $p = 0.001$
Boeri et al. 2020 [60]	Prospective, observational	446 (253 normoglycemia/105 prediabetes/88 diabetes)	58	3	Any	Any	PDE5i	IIEF	IIEF: + 8 ($p = 0.001$) vs + 6 ($p = 0.001$) vs + 8 ($p = 0.001$)
Rocca et al. 2020 [61]	Prospective, observational	28 (24 responders/4 non-responders)	48	3	Any	Any	Sildenafil ODF	IIEF	IIEF: + 5.1 ($p = 0.007$)

Table 2 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Kızılay et al. 2020 [62]	Retrospective, observational	131 (51/73)	35/52	3	Any	Any	Tadalafil 5 mg daily	IIEF	IIEF: +4.62 ($p=0.029$) vs 2.17 ($p=0.029$) Predictors of response: testosterone level ($p=0.026$) and BDI score ($p=0.034$)
Jamaluddin et al. 2019 [63]	Prospective, observational	282 (86 non-responders/134 responders)	37	1.5	Any	Any	Tadalafil 10 mg daily	IIEF-6 (hs-CRP levels)	IIEF-6: −1.3 vs +9.9 ($p<0.001$) hs-CRP levels: median 2 mg/L vs 1.5 mg/L ($p=0.034$) Predictors of response: shorter duration of ED ($p=0.008$), non-vasculogenic origin ($p=0.025$), higher IIEF-6 score at baseline ($p=0.013$)
Lacchini et al. 2018 [64]	Prospective, observational	143 (71 post-prostatectomy ED/72 vasculogenic ED)	60	N/A	Post-RP and vasculogenic ED	Any	Sildenafil 50 mg or 100 mg	IIEF-5	IIEF-5: +5 ($p=0.025$) vs +7 ($p=0.025$)
Ogrede et al. 2018 [65]	Retrospective, observational	148 (32 non-responders/40 partially responders/72 complete responders)	56	3	Any	Any	Vardenafil 10 mg ODT twice a week	PSV	PSV 30 cm/s >: 5.6% vs 1.9% vs 92.6% ($p=0.00$)

BDI Beck's Depression Inventory, *ED* erectile dysfunction, *MetS* metabolic syndrome, *NOED* non-organic erectile dysfunction, *ODF* oro-dispersable film, *ODT* oro-dispersable tablet, *PDE5i* phosphodiesterase-5 inhibitor, *EHS* erection hardness score, *IMT* intima-media thickness, *IIEF* International Index of Erectile Function, *LUTS* lower urinary tract symptoms, *MSHQ* Male Sexual Health Questionnaire, *PE* premature ejaculation, *PSV* peak systolic velocity, *SEP-2/3* Sexual Encounter Profile question 2/3, *SHIM* Sexual Health Inventory for Men, *RCT* randomized controlled trial; *RP*, radical prostatectomy

0.2% of glyceryl trinitrate (GNT), and is currently under investigation to become an agent to treat ED. It is supposed to have a fast absorption, minutes-length erection, and satisfactory safety profile. Treated patients showed a slight but significant higher score in the IIEF-EF comparing with those receiving placebo (19.6 vs 18.5, $p=0.0132$), with a greater increase in the mild ED group (23.1 vs 21.3, $p<0.001$).

Shockwave Therapy

A number of 29 papers analyzing the results of different regimes of shockwave therapy in the management of ED were identified. Their results are resumed in Table 3.

Stem Cells

A total of 10 papers evaluating the utility of stem cells for ED were found. Great heterogenicity was found in respect to the type of stem cell used: in four [114–117], they used bone marrow cells, whereas in the other six, they used mesenchymal stem cells [118–123]. Additionally, other paper studied the effect of stem cell-derived bioactive molecules to restore erectile function (EF) [124]. In all of them, ED is evaluated according to IIEF-5, and in half of them, they also include an assessment of penile hemodynamics with a color Doppler ultrasound. The number of patients included is low in all of them (5-40), 8 papers being pilot phase I studies. Only one [119] is a randomized single-blinded clinical trial, in which 20 diabetic, PDE5i non-responder patients were administered either intracavernosal autologous mesenchymal stem cells or placebo. In the treatment group, mean IIEF-5 score was 7.2 ± 2.1, 9.2 ± 3.4, and 10.6 ± 4.7 before, 3 months, and 6 months after the injection, respectively ($p=0.01$). This follow-up time is common in most of the studies, with the exception of the one by Yiou et al. [117], with a mean follow-up of 62.1 ± 11.7 months, in which a slow decline on EF was observed after the improvement in the first year. This trend was also observed in other papers with lower follow-up times [120, 122].

Phytotherapy/Nutraceuticals

Twenty-six papers investigating the effect in DE of different phytotherapy or nutraceutical agents have been identified. Nineteen studies analyzed the effect of as many substances in mild ED or special-to-treat patients [125–142]. Most of them showed a positive effect of these substances as a single therapy or, most commonly, as a concomitant treatment added to a standard oral therapy.

Three papers investigated the utility of L-arginine for patients with ED. Gallo et al. [143] demonstrated that the combination of L-arginine and oral daily tadalafil 5 mg was superior to both therapies alone (IIEF-EF: +7.1 vs +3.1 vs +6, respectively, $p<0.0001$). Similar results were reported by Abu El-Hamd et al. [144] (SHIM: +13.69 vs +10.33 vs 12.27, $p<0.0001$), who also found that treatment with L-arginine, tadalafil, or its combination conducted to a significative increase in testosterone levels in all patients, in contrast to placebo (+2.37 vs +9.04 vs +11.23 nmol/L for L-arginine, tadalafil, and combination groups, respectively; $p<0.0001$). In a recent study, Menafra et al. [145] showed that supplementation with high doses of L-arginine alone for 3 months conducted to an increase in the score of the IIEF-6 (+4, $p<0.0001$) and in the peak systolic volume (PSV) (+4.6 cm/s, $p<0.0001$) in contrast to placebo.

Tribulus terrestris is a plant originating from Bulgaria that is considered to be an herbal steroid. Its effect in ED in hypogonadal men has been investigated by GamalEl Din et al. [146], where they found an improvement in IIEF-5 score (+5.4, $p<0.0001$) and in the testosterone levels (+0.58 nmol/L, $p<0.0001$), compared to placebo. Kamenov et al. [147] conducted a RCT in a cohort of 180 patients with mild or moderate ED who were treated with *Tribulus* or placebo. After 12 weeks, they found a significant difference in IIEF scores for the treatment group (+4.75 vs 1.97, $p<0.0001$).

The response to vitamin D supplementation in patients with ED and deficiency of this element has been studied in two papers, both comparing the effect of regular tadalafil intake only or in combination with vitamin D. Demirci et al. [148] found better scores in IIEF-EF in the combination group after 3 months (+13 vs +8, $p=0.01$), similarly to Ali et al. [149] that found a higher improvement in IIEF-5 scores in the combination group compared to tadalafil only (+8.44 vs +5.72, $p=0.012$).

Platelet-Rich Plasma Injections

Intracavernosal therapy with platelet-rich plasma (PRP) was assessed in 6 papers in the last years. Their results are presented in Table 4.

Effect of Previously Known Molecules on ED

The effect of different established drugs for other indications has been studied in several papers, including mirabegron, aspirin, bupropion, cabergoline, and levotiroxin.

Mirabegron is a selective β3 adrenergic receptor agonist that is supposed to cause relaxation of the vascular smooth muscle cells of the corpora cavernosa [156]. Its effect on ED has been studied in two recent articles. In the first, a pilot study by Karakus et al. [157], 20 patients with DE and lower urinary tract symptoms (LUTS) were administered mirabegron for 12 weeks. After this period, 38.5% of the patients

Table 3 Results for shockwave therapy

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Shockwave therapy alone									
Chung et al. 2022 [69]	RCT	60 (30/30)	56	6	Any	IIEF-5 ≥ 12	Li-ESWT 12 sessions (2/week) vs sham therapy	IIEF-5, EHS	IIEF-5: + 4 vs + 0 ($p = 0.001$) EHS: + 1.3 vs + 0 ($p = 0.001$)
Geyik 2022 [70]	Retrospective	41	52	6	Any	IIEF-EF < 26	Li-ESWT 10 sessions (1/week × 2, 6-months rest period)	IIEF-EF	EF subscale: + 6.44 vs + 3.66 ($p = 0.001$)
Chung and Cartmill 2021 [71•]	Prospective	30	56	60	Vasculogenic ED [27] and PostRP ED [3]	Any	Li-ESWT 12 sessions (2/week)	IIEF-5, EDITS	IIEF-5: + 1.7 ($p > 0.05$) EDITS > 50%: 48%
Akande et al. 2021 [72]	Descriptive cross-sectional study	22	54	6	Vasculogenic ED	SHIM < 12	Li-ESWT 6 sessions (3/week × 2, 4-week rest period)	IIEF-EF	EF subscale: + 2.5
Lei et al. 2021 [73]	Prospective	78 (46/32)	32	3	Any	Any	Li-ESWT 6 sessions (2/week × 2, 3-week rest period) vs sildenafil 100 mg on demand	IIEF-5, EHS	IIEF-5: + 7.43 vs + 8.26 ($p > 0.05$) EHS: + 1.06 vs + 1.29 ($p > 0.05$)
Ortac et al. 2021 [74]	RCT	66 (44/22)	41	12	Vasculogenic ED	IIEF-EF: 17–25	ESWT 4 sessions (1/week) vs sham therapy	IIEF-EF	EF subscale: + 2.35 vs + 0.14 ($p = 0.003$)
Palmieri et al. 2021 [75]	Prospective	106	58	1	Vascular PDE5i-refractory ED	Any	Li-ESWT 6 sessions (2/week)	IIEF-EF, EHS	EF subscale: + 8.6 ($p = 0.0001$) EHS: + 1.2
Vinay et al. 2021 [76]	RCT	76 (40/36)	60	6	Vascular PDE5i-refractory ED	IIEF < 26	Li-ESWT 4 sessions (1/week) vs sham therapy	IIEF, EHS	IIEF: + 1 vs 0 ($p = 0.25$) EHS > 2: + 20% vs − 11% ($p = 0.028$)
Huang et al. 2020 [77]	Prospective	35	37	1	OED	IIEF-5 < 21 EHS ≤ 3	Li-ESWT 4 sessions (1/week)	IIEF-5	IIEF-5: + 4.53 ($p = 0.003$)
Kalyvianakis et al. 2020 [78]	Prospective, randomized, four parallel-arm, open-label study	89	57	6	Vasculogenic ED	IIEF-EF < 26	Li-ESWT 12 sessions: A: 2/week EFD 0.05 mJ/mm^2, B: 3/week EFD 0.05 mJ/mm^2, C: 2/week EFD 0.10 mJ/mm^2, D: 3/week EFD 0.10 mJ/mm^2	IIEF-EF, SEP-3	EF subscale: + 5.3 vs + 4.5 vs + 5.6 vs + 5.9 SEP-3: + 32.4% vs + 31.4% vs + 34.9% vs + 47.1%

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Kim et al. 2020 [79]	RCT	81	64	1.75	OED	IIEF-EF 11–25	Li-ESWT 6 sessions (2/week × 2, 3-week rest period) vs sham therapy	IIEF-EF, EHS	EF subscale: + 5.1 ($p = 0.001$) vs − 2.2 ($p = 0.001$) EHS ≥ 3: + 36.9% vs − 11.6
Lurz et al. 2020 [80]	Non-randomized prospective clinical trial	22	63	1	Vasculogenic ED	IIEF 11–25	Li-ESWT 6 sessions (1/week)	IIEF, EDITS	IIEF: + 5 ($p = 0.01$) EDITS: + 12 ($p = 0.74$)
Patel et al. 2020 [81]	RCT	87 (45/42)	52	6	Any	IIEF 11–25	Li-ESWT 5 sessions (consecutive days) vs 6 sessions (3/week)	IIEF-EF	EF subscale: + 2.7 vs + 2.7
Sramkova et al. 2020 [82]	RCT	60 (30/30)	54	3	Vasculogenic ED	IIEF-5 ≤ 21	Li-ESWT 4 sessions (2/week) vs sham therapy	IIEF-5, EHS	IIEF-5: + 8 (p 0.001) vs + 2.4 ($p = 0.001$) EHS: + 1.5 ($p = 0.001$) vs + 0.6 ($p = 0.0$ 001)
Wang et al. 2020 [83]	Prospective	45 (7/38)	60	4	Any	Any	Li-ESWT 8 sessions (2/week)	IIEF	IIEF: + 6 vs + 6 ($p = 0.000$)
Wu et al. 2020 [84]	Retrospective	48 (24/24)	66	1.5	Vasculogenic ED	Any	fSWT vs rWT 6 sessions (1/week)	SHIM	SHIM: + 6.2 ($p = 0.001$) vs + 6.8 ($p = 0.001$)
Fojecki et al. 2018 [85]	Randomized, controlled, double-cycle crossover trial	95 (52/43)	65	12	Vasculogenic ED	IIEF-EF ≤ 25	Linear Li-ESWT 5 sessions (1/week) vs Sham therapy. After 4 weeks break, Linear Li-ESWT 5 sessions (1/week) in both	IIEF-EF	EF subscale: + 3.1 vs + 1.9 ($p = 0.4$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Kalyvianakis et al. 2018 [86]	RCT	42 (21/21)	56	6	Vasculogenic ED	IIEF-EF < 26	Li-ESWT: 6 sessions (1/week) +, after 6 months, 6 sessions (2/week) vs 12 sessions (2/week) +, after 6 months, 6 sessions (1/week)	IIEF-EF, SEP-2, SEP-3	Phase 1: EF subscale: + 3.1 vs + 5.1 ($p = 0.31$) SEP-2: + 2.6% vs + 10.4% ($p = 0.32$) SEP-3: + 10.9% vs + 25.5% ($p = 0.02$) Phase 2: EF subscale: + 1.8 vs + 1.7 ($p = 0.57$) SEP-2: + 1.3% vs − 3% ($p = 0.83$) SEP3: + 14.9% vs + 0.3% ($p = 0.48$)
Katz et al. 2018 [87]	RCT	21	54	6	Any	IIEF-EF 11–25	Li-ESWT 5 sessions daily vs 1 session every 2 day for 2 weeks	IEEF-EF	EF subscale: no significant difference vs + 4.2 ($p = 0.0028$)
Kitrey et al. 2018 [88]	Retrospective, observational	156	59	24	Any	Any	Li-ESWT 12 sessions (2/week × 2, 3-week rest period)	IIEF-EF	Clinically effective response: 34%
Ayala et al. 2017 [89]	Retrospective	710	58	1	OED	EHS ≤ 3	Li-ESWT 5 sessions (1/week)	EHS	% Patients with EHS ≥ 3 + 10.1%
Tsai et al. 2017 [90]	Prospective, observational	52	63	3	PDE5i non-responding ED	EHS ≤ 2	Li-ESWT 12 sessions (1/week)	IIEF-5, EHS	EHS: + 1 ($p = 0.001$) IIEF-5: + 5.8 ($p = 0.001$)
Kalyvianakis and Hatzichristou 2017 [91]	RCT	46 (30/16)	54	12	Vasculogenic ED	IIEF-EF < 26	Li-ESWT 12 sessions (2/week × 2, 3-week rest period) vs sham therapy	IIEF-EF	EF subscale: minimal clinically important differences: 75% vs 25% ($p = 0.008$)
Combination with PDE5i									
Gallo et al. 2022 [92]	Prospective, observational	100 (50/50)	50	12	Any	IIEF-EF: 11–25	Li-ESWT 6 sessions (1/week) + tadalafil 5 mg + L-arginine 2.500 mg vs Li-ESWT 6 sessions (1/week) + placebo	IIEF-EF, EHS	EF subscale: + 5.6 vs + 3 ($p = 0.03$) EHS: + 0.91 vs + 0.64 ($p = 0.08$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Mykoniatis et al. 2022 [93]	RCT	50 (25/25)	57	6	Vasculogenic ED	IIEF-EF: 17–25	Li-ESWT 6 sessions (2/week) + tadalafil 5 mg/24 h vs placebo	IIEF-EF, SEP-3	EF subscale: + 5.9 vs + 4.1 ($p = 0.003$) SEP-3: + 32.1 vs + 21.7 ($p = 0.016$)
Sandoval-Salinas et al. 2022 [94]	RCT	80 (40/40)	48	2.5	Any	IIEF-EF: 11–21	rWT 6 sessions (1/week) + sildenafil 25 mg daily vs sham therapy + sildenafil 25 mg daily	IIEF-EF	EF subscale: + 0.8 vs + 2.7 ($p = 0.28$)
Vena et al. 2021 [95]	Prospective	21	56	6	Any	Any	Li-ESWT 6 sessions (1/week) + tadalafil 2.5 mg daily	IIEF-EF	EF subscale: + 6 ($p = 0.02$)
Lau et al. 2021 [96]	Prospective	19	57	6	Any	Any	Li-ESWT 6 sessions (1/week) or 12 sessions (2/week) + PDE5i or TRT	IIEF-5, EHS	IIEF-5: + 5.3 ($p = 0.001$) EHS: + 0.82 ($p = 0.02$)
Special cohorts									
Daneshwar and Nordin 2022 [97]	Prospective	50	42	1	ED with CPPS	Any	Prior: levofloxacin/ciprofloxacin 500 mg/12 h + tamsulosin 0.4 mg/24 h Li-ESWT 10 sessions (2/week) + tadalafil 5 mg daily	IIEF, SHIM	IIEF: + 4.06 ($p = 0.036$) SHIM: + 1.74 ($p = 0.130$)
Ergün and Akyüz 2022 [98]	Retrospective	116	57	3	ED with DM PDE5i non-responders	IIEF-5: 5–8	Li-ESWT 12 sessions (2/week/×2, 3-week rest period) + PDE5i therapy for 3 months	IIEF-5, EHS	IIEF-5: + 0.27 ($p = 0.61$) EHS: + 0.02 ($p = 0.79$)
Ladegaard et al. 2021 [99]	RCT	38 (20/18)	63	3	ED following nerve-sparing RP	IIEF-5 < 22	ESWT 5 sessions (1/week) vs sham	IIEF-5, EHS	IIEF-5: + 3.45 vs + 0.65 ($p = 0.026$) EHS: + 0.5 vs − 0.17 ($p = 0.019$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Shendy et al. 2021 [100]	RCT	42 (21/21)	48	3	ED with type 2 DM neuropathy	Mild to moderate ED	Li-ESWT 12 sessions (2/week/×2, 3-week rest period) + PFE vs sham therapy + PFE	IIEF, doppler	EF subscale: + 4.75 ($p < 0.001$) vs + 0.65 ($p = 0.194$) PSV (cm/s) (Right): + 12.66 (< 0.001) vs + 3.74 ($p < 0.001$) (comparing $p < 0.001$) PSV (cm/s) (left): + 12.21 (< 0.001) vs + 4.48 ($p = 0.048$) (comparing $p < 0.001$)
Verze et al. 2020 [101]	Matched-pair comparison study	156 (78/78)	57	6	ED with type 2 DM	Any	Tadalafil 5 mg daily 12 weeks + Li-ESWT 12 sessions (2/week) vs tadalafil 5 mg daily 12 weeks	IIEF-5	IIEF-5: + 3.8 vs + 1.8 ($p < 0.001$)
Zasieda 2020 [102]	Prospective	42 (22/20)	N/A	6	Corporal veno-occlusive erectile dysfunction on the background of hypogonadotropic hypogonadism	IIEF-5 < 17	ChG 5000 UI weekly + ICA 50 mg/day + Focused LISWT 12 sessions (2/week) vs ChG 5000 UI weekly + ICA 50 mg/day	IIEF-5, Doppler	IIEF-5: mild 77% vs 60% ($p = 0.226$), mild-moderate 23% vs 20% ($p = 0.829$), moderate 0% vs 20% ($p = 0.027$) PSV: 54.10 cm/s vs 49.62 cm/s ($p = 0.631$) EDV: 2.8 cm/s vs 5.2 cm/s ($p = 0.021$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Yamaçake et al. 2019 [103]	RCT	20 (10/10)	54	12	Vasculogenic ED, with history of kidney transplant at least 6 months prior to the study	IIEF-5 < 21	Li-ESWT 6 sessions (2/week) vs sham therapy	IIEF-5, EHS, Doppler	IIEF-5 (4^{th} month): + 6.3 vs + 1.61 ($p = 0.018$) EHS (4^{th} month): + 0.6 vs + 0.4 ($p = 0.724$) PSV (4^{th} moth): − 0.9 cm/s vs − 3.1 cm/s ($p = 0.853$)
Wang et al. 2019 [104]	Prospective	43 (12 PDE5i non-responders)	33	6	ED with pelvic fractures associated with urethral injury	EHS ≤ 2 or IIEF-5 ≤ 21	Tadalafil 5 mg daily. Non-responders [12•]: Li-ESWT 6 sessions (1/week)	IIEF-5, EHS	Li-ESWT responders ($n = 5$): IIEF-5 + 6.8 ($p = 0.021$), EHS + 2.4 ($p < 0.001$) Li-ESWT non responders ($n = 7$): IIEF-5 + 0.4 ($p = 0.790$), EHS + 0 ($p = 1$)
Miscellaneous									
Ghahhari et al. 2022 [105]	Retrospective	94	57	12	Any	IIEF-5: 11–25	Li-ESWT 8 sessions (1/week)	IIEF-5, SHIM, EHS	IIEF-5: + 5.49 ($p < 0.0001$) SHIM: + 5.47 ($p < 0.0001$) EHS: + 1.18 ($p < 0.0001$)
Oginski et al. 2022 [106]	Prospective	50	60	6	PDE5i non-responding ED	Any	Li-ESWT 6 sessions (1/week)	IIEF-5, EHS	IIEF-5: 3^{rd} month + 4 ($p = 0.003$), 6^{th} month + 0.5 ($p > 0.05$) EHS: 3^{rd} month + 1, 6^{th} month + 1 ($p < 0.001$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Adeldaeim et al. 2021 [107]	Prospective	425 (220 responders/205 non-responders	55	30	Vasculogenic ED	Any	Li-ESWT 6 sessions (1/week)	N/A	Predictors of response: age ($p=0.0001$), DM ($p=0.001$), HTA ($p=0.001$), smoking ($p=0.001$), BMI ($p=0.001$), hyperlipidemia ($p=0.001$), pre-treatment SHIM ($p=0.001$), duration of ED ($p=0.001$)
Caretta et al. 2021 [108]	Retrospective	111	54	6	Any	Any	Li-ESWT 6 sessions (1/week)	IIEF-5, doppler	IIEF-5: + 3.7 ($p<0.001$) PSV: + 17.4 cm/s ($p<0.001$) EDV: − 2.2 cm/s ($p<0.008$)
Geyik 2021 [109]	Retrospective	184 (93/91)	49	6	Any	IIEF-EF < 26	Li-ESWT 5 sessions (1/week) vs 5 sessions (1/week) + PRP	IIEF-EF	EF subscale: + 9.5 vs + 8.5 ($p=0.001$)
Tzou et al. 2021 [110]	Retrospective	69	55	12	Any	EHS ≤ 2	Li-ESWT 12 sessions (1/week)	IIEF-5, EHS	IIEF-5: + 5.10 ($p<0.001$) EHS: + 0.80 ($p<0.001$)
Musa et al. 2020 [111]	Prospective	52 (33 responders/19 non-responders)	51	18	Vasculogenic ED, PDE5i non-responders	Any	Li-ESWT 12 sessions (2/week/×2, 3-week rest period)	N/A	Predictors of response: age ($p=0.031$), ED duration ($p<0.001$), ED severity ($p=0.02$)
De Oliveira et al. 2019 [112]	Prospective	25	61	3	Any	IIEF-5 < 22	Li-ESWT 6 sessions (1/week)	IIEF-5, doppler	IIEF-5: + 3.3 ($p<0.001$) PSV: + 6.6 cm/s ($p<0.001$) EDV: − 1.3 cm/s ($p=0.015$)

Table 3 (continued)

Author/year	Type of study	*N* (groups)	Age (mean)	Follow-up (months)	Type of ED	Severity of ED	Intervention	ED measurement tool	Results
Vita et al. 2019 [113]	Prospective	20	59	3	Vasculogenic ED, PDE5i non/poor-responders	Any	Li-ESWT 6 sessions (1/week). After a 3-week break, 4 non-responders/poor responders received another 6 weekly sessions	IIEF-5, RS	IIEF-5: +2.8 ($p=0.04$) RS ≥ 3: 55% (*n*: 11) ($p<0.0001$)

ChG recombinant chorionic gonadotropin, *CPPS* chronic pelvic pain syndromes (CPPS), *ED* erectile dysfunction, *EDITS* Erectile Dysfunction Inventory of Treatment Satisfaction, *EHS* erection hardness score, *fSWT* focused shockwave therapy, *NOED* non-organic erectile dysfunction, *PDE5i* phosphodiesterase-5 inhibitor, *EHS* erection hardness score, *ICA* extract of *Epimedium brevicornum*, *IMT* intima-media thickness, *IIEF* International Index of Erectile Function, *LUTS* lower urinary tract symptoms, *MSHQ* Male Sexual Health Questionnaire, *PFE* pelvic floor muscle exercise, *PRP* platelet-rich plasma, *PSV* peak systolic velocity, *RCT* randomized controlled trial, *RS* rigidity score, *rWT* radial wave therapy, *SEP-2/3* Sexual Encounter Profile question 2/3, *SHIM* Sexual Health Inventory for Men, *TRT* testosterone replacement therapy

improved the IIEF-5 score ≥ 4 points, whereas in 61.5 there was no variation. These results were widely studied in a RCT by Elbaz et al. [158], in which 55 patients with ED and LUTS were randomized to receive mirabegron and doxazosin (treatment group) or tolterodine and doxazosin (control) for 12 weeks. The found a significant difference in IIEF score improvement between both groups (+15 vs +3, $p<0.05$).

Aspirin has also been evaluated as a potential treatment for ED, given its antiplatelet action. In a paper by Bayraktar and Albayrak [159], 184 patients with vasculogenic ED were randomized to take aspirin 100 mg daily for 6 weeks or placebo. They found significant differences in IIEF-EF (+7.2 vs +2, $p<0.0001$), and in the SEP 2 and 3. The same group published later the results of a study in which 336 patients were randomized to take aspirin 100 mg daily, tadalafil 5 mg daily, both drugs, or placebo for 6 weeks [160]. They found similar improvements in IIEF-EF scores in all treatment groups, with a weaker increment in the placebo group (+7.2, +7.3, +7.5, $p<0.0001$ vs +2.0, $p=0.0204$).

Bupropion is an antidepressant with a dual reuptake inhibitor of dopamine and norepinephrine mechanism, and it has been hypothesized to have a benefit on DE. Ghoreishi et al. [161] studied its effects on a cohort of 40 patients with chronic kidney disease, who were randomized to treatment or placebo. After a 10-week period, changes in the IIEF were higher in the treatment than in the control group (+2.75 vs +0.35, $p<0.005$). Similarly, Yee et al. [162] studied the effect of bupropion against placebo on a randomized cohort of 80 male patients on methadone with ED for 6 weeks. Significant changes in the IIEF score (+8.37, $p=0.02$) and in the total plasma testosterone level (+4.03 nmol/L, $p=0.01$) were observed.

The effect of adding cabergoline to daily tadalafil was compared to daily tadalafil alone in a group of 580 patients diagnosed with psychogenic ED in a paper by Mohammad et al. [163]. They found that 92.7% of the patients in the combination group improved the EF, in contrast with a 53.6% of the patients in the tadalafil group ($p<0.05$). Cannarella et al. [164] found that levothyroxine improved arterial ED in patients with subclinical hypothyroidism, according to IIEF-5 score (20.2 in the treatment group, no changes in the control group, $p<0.05$). Also, a subanalysis of a systolic blood pressure intervention trial [165] found that an intensive treatment of high systolic blood pressure (goal of < 120 mmHg), in contrast to a standard treatment (goal of < 140 mmHg), had very small impact on ED, according to IIEF-5.

ICI of Vaso-active Agents

A total of six papers analyzing the effect of different types of intracavernosal botulinum toxin injections were evaluated, and the results are resumed in Table 5.

Besides, other ICI were studied in three more papers. Taşkapu et al. [172] demonstrated that adding clomiphene

Table 4 Results for platelet-rich plasma injections

Author/year	Type of study	Age (mean)	*N* (groups)	Follow-up	Type of ED	Intervention	ED measurement tool	Results
Zaghloul et al. 2022 [150]	Prospective	48	51	8 weeks	Diabetic and non-diabetic ED	Tadalafil 5 mg daily + Vardenafil 20 mg on demand + Intracavernosal platelet-rich plasma injection	IIEF-5, EHS, duplex studies	IIEF-5: diabetic 8.04 vs 12.1 ($p = 0.003$), non-diabetic 10.2 vs 14.8 ($p = 0.001$). EHS: improved 41.7% in diabetic and 62.5% in non-diabetic
Wong et al. 2021 [151]	Prospective	55	30	11 weeks	Any	Intracavernosal platelet-rich plasma injection	IIEF-5. EHS, SEP2 and SEP3, GAQ1	IIEF-5: 12 ± 5.1 vs 16.59 ± 5.5 ($p < 0.001$). EHS: +0.72 ($p < 0.001$)
Taş et al. 2021 [152]	Prospective	54	31	6 months	Associated to metabolic syndrome	Intracavernosal platelet-rich plasma injection	IIEF	EF: 18 vs 20 ($p < 0.001$)
Poulios et al. 2021 [153•]	RCT	58	60 (30/30)	6 months	Vascular	Intracavernosal platelet-rich plasma injection/placebo	IIEF, EDITS, MCID, SEP	EF: improved 3.9 in patients treated compared to placebo ($p < 0.001$). SEP: improved 28.6% ($p < 0.001$). EDITS: 63.2 ± 24.6 vs 32.8 ± 24 ($p < 0.001$)
Zaghloul et al. 2021 [154]	Prospective	50	34	3 months	Any	Intracavernosal platelet-rich plasma injection	IIEF-5	IIEF-5: 7.7 ± 2.7 vs 13.2 ± 6.8 ($p < 0.001$)
Matz et al. 2018 [155]	Prospective	46	5	15.5 months	Any	Intracavernosal platelet-rich fibrin matrix injection	IIEF-5	IIEF-5: +4.14

EDITS Erectile Dysfunction Inventory of Treatment Satisfaction, *MCID* Minimal Clinically Important Difference, *RCT* randomized controlled trial

citrate to alprostadil 10 or 20 µg in late-onset hypogonadism men offered great results in ED scores (IIEF-EF + 11.07, EHS + 1.52, $p < 0.001$). Bernie et al. [173] compared a classical empirical approach algorithm of ICI to a new, risk-based approach, not observing significant differences in multiple domains of sexual function. A retrospective study by Bearelly et al. [174] showed that a cohort of 105 patients treated with different ICI combinations presented good response to their ED after a mean duration of therapy of 8.4 years, according to the IIEF-EF scores (+ 11.8, $p < 0.05$).

Oxygenation-Based Therapies

The effect on ED of both continuous positive airway pressure (CPAP) and hyperbaric oxygen therapy (HBOT) has been investigated. The results for these therapies are resumed in Table 6.

Other Physical Therapies

Finally, four articles were classified under the epigraph of "other physical therapies." Two papers referred to the effect of electrostimulation (ES) in the management of ED. The first [183] was a RCT that compared a group of 15 young patients (39.17 ± 6.21) who received ES with another 15 who were proposed to aerobic exercise. After 6 weeks, the ES group presented a better score in the IIEF-5 compared to the exercise group (20.83 vs 14.33, $p = 0.001$). Similarly, the second paper [184] compared ES against a control group in a cohort of 22 patients, finding better significative ($p < 0.05$) scores in the IIEF-5 and EHS for the treatment group.

One paper [185] presented the results of a novel therapy of low-intensity pulsed ultrasound (LIPUS) in treating mild to moderate ED. A total of 120 patients were randomized to LIPUS [80] or sham treatment. They defined success as an improvement in the IIEF-5 ≥ 2 points, being the response after the complete therapy of 71.01% of patients in the LIPUS arm compared to 17.65% in the sham group ($p < 0.05$).

Finally, Juho et al. [186] presented a study in which they evaluated the efficacy of a far-infrarred textile on the underwear of 30 patients with vasculogenic ED, who were randomized to wear the assessed underwear or a regular one. Although an improvement on the IIEF-5 score, the PSV, and the end diastolic flow was observed, it did not reach statistical significance.

Discussion

Studies related to psycho-sexual therapy are quite heterogeneous, most dealing with psychogenic ED in young patients. Cognitive behavioral therapy is the most studied treatment modality. Treatment combining cognitive-behavioral therapy and PDE5is achieves improvements in ED, as well as a significant reduction in anxiety and depression compared to PDE5is monotherapy [12•, 13, 16, 18]. A pilot study [17], with a reduced number of patients ($n = 10$) and no control group, studied the use of mindfulness-based group therapy in situational ED. No significant improvements in ED or overall satisfaction were appreciated. According to the analyzed data, it seems that psycho-sexual therapy, and specifically cognitive behavioral therapy (CBT), may be a useful treatment for the treatment of psychogenic ED in young patients, improving the effect of oral therapies in some cases and reducing anxiety and depression associated with the disease.

Hormone replacement therapy, both in monotherapy [19–24] and in combination with PDE5is [25], has shown significant benefits in the treatment of EF in patients with hypogonadism. This represents a reminder of the need of requesting testosterone levels in the study of patients with ED and offers hormonal treatment if needed.

With regard to classical oral treatments of 5-phosphodiesterase inhibitors, there have been no major developments in the last 5 years. In fact, we have only found in this review a single study on a new molecule: mirodenafil [26]. Sildenafil, vardenafil, tadalafil, and avanafil are still the most used PDE5is. Trials comparing the efficacy and safety of PDE5is are still lacking, with available data suggesting similar efficacy and safety profiles [27, 58]. Many publications report the effectiveness of daily tadalafil therapy, but there is still little published evidence comparing its efficacy versus on-demand use for the treatment of erectile dysfunction [56]. We found quite a few publications that study the recent new formulations: orodispersible tablets (ODT) [65], orodispersible films (ODF) [26, 33, 38, 61], and orally disintegrating strips [29]. These may be an advantage for patients who have difficulty swallowing tablets and for those who will benefit of a rapid onset of action, because of the more discreet route of administration which some patients may prefer.

The application of alprostadil inside the urethra has shown greater efficacy compared to classic topical administration with a similar safety profile [66, 67]. In addition, the combination therapy of alprostadil administered intraurethral together with 5-phosphodiesterase inhibitors [67] showed better results in the treatment of ED compared to inhibitors in monotherapy.

Regarding low-intensity shockwave therapy (Li-ESWT), there are very heterogeneous studies, even if they study the same treatment modality. This is due to several factors such as the diversity of treatment protocols (energy, type of focus, duration of sessions, number of sessions, etc.), the different devices used, the combination or not of other therapies, and the different evaluation methods. Due to this great heterogeneity regarding different energies and administration

Table 5 Results for botulinum toxin

Author/year	Type of study	Age (mean)	*N* (groups)	Follow-up	Type of ED	Intervention	ED measurement tool	Results
Giuliano et al. 2022 [166]	Retrospective	56.6	54	9 months	Any	IncobotulinumtoxinA 100 UI ICI + PDE5-is/PGE1 ICIs	IIEF-EF	1st injection: 52% responders, EF + 8. 2nd injection: 76% responders, EF + 9
Giuliano et al. 2022 [167]	Retrospective	53	123	7 months	Any	OnabotulinumtoxinA 100 UI or AbobotulinumtoxinA 250/500 UI ICI + PDE5-is/PGE1-ICI	IIEF-EF	55.2% responders, EF + 9
Moradi et al. 2022 [168]	RCT	49	40 (20/20)	6 weeks	Vascular	AbobotulinumtoxinA 50 UI/100 UI	IIEF, SHIM, EHS	EF: + 1 vs + 4.3 (both $p < 0.0001$); SHIM: + 0.9 vs + 4 (both $p < 0.0001$); EHS: + 0.2 ($p = 0.26$) vs + 0.5 ($p < 0.0001$)
Abdelrahman et al. 2021 [169]	RCT	54.3	70 (35/35)	12 weeks	Any	OnabotulinumtoxinA 100 UI ICI/Placebo	SHIM	+ 2.86 vs − 0.12 ($p < 0.001$)
El-Shaer et al. 2021 [170•]	RCT	56	176 (62/59/55)	6 months	Any	OnabotulinumtoxinA 100 UI ICI/50 UI/Placebo	SHIM, PSV	SHIM: + 6 vs 0 vs 0 ($p < 0.001$); PSV: + 17.5 cm/s vs + 6.5 vs + 0.2 ($p < 0.001$)
Giuliano et al. 2019 [171]	Retrospective	55.1	47	6 weeks	Any	AbobotulinumtoxinA 250/500 UI ICI + PDE5-is or PGE1-ICI	IIEF-EF	+ 4.7 vs + 5.6

PDE5-is phosphodiesterase type 5 inhibitors, *PGE1 ICIs* prostaglandin E1 intracavernosal injections, *RCT* randomized controlled trial, *EHS* erection hardness score *PSV* peak systolic velocity, *SHIM* sexual health inventory for men

Table 6 Results for oxygenation-based therapies

Author/year	Type of study	Age (mean)	*N* (groups)	Follow-up	Type of ED	Intervention	ED measurement tool	Results
Apergis et al. 2021 [175]	Prospective, controlled	47	87 (62/25)	12 months	Any	CPAP/No treatment	IIEF-15	IIEF-EF: 25.9 vs 21.8 ($p<0.001$)
Coban et al. 2020 [176]	Observational	47	54	3 months	Any	CPAP	IIEF-15	IIEF-EF: + 1.59 ($p=0.014$)
Sen et al. 2020 [177]	Observational	60	43	5 weeks	Any	HBOT	IIEF-15	IIEF-EF: + 4.8 ($p<0.001$)
Schulz et al. 2019 [178]	Observational	52	64	6–12 months	Any	CPAP	IIEF-5	IIEF-5: moderate ED + 3.5 ($p<0.05$), severe ED + 7 ($p<0.01$)
Pascual et al. 2018 [179]	RCT	54	77 (42/35)	3 months	Any	CPAP/No treatment	IIEF-15, SEAR	IIEF-EF: + 4.6 ($p=0.002$) vs + 2.1 ($p=0.024$) SEAR: + 4 ($p=0.147$) vs + 3 ($p=0.178$)
Melehan et al. 2018 [180]	RCT	55	61 (31/30)	12 weeks	Any	CPAP/sham// Vardenafil 10 mg daily/ placebo	IIEF-15, Rigiscan®	CPAP/sham: IIEF-EF: + 4.4 vs + 0.6 ($p=0.04$); Rigiscan®: CPAP increased the number of sleep-related erections ($p=0.007$), no change in tumescence or rigidity Vardenafil/ placebo: IIEF-EF: + 5.5 vs + 2.2 ($p=0.15$); Rigiscan®: Vardenafil did not significantly change any parameters
Sahin et al. 2018 [181]	Observational	59	50	5 weeks	Any	HBOT	IIEF-15	IIEF-EF: + 3.76 ($p<0.001$)
Hadanny et al. 2018 [182]	Observational	59	30	6 weeks	Non-surgery-related ED	HBOT	IIEF-15, perfusion MRI	IIEF-EF: + 10.5 ($p<0.001$) Perfusion MRI: angiogenesis + 153.3 of K-trans values in the corpus cavernous ($p<0.0001$)

CPAP continuous positive airway pressure, *HBOT* hyperbaric oxygen therapy, *SEAR* Self-esteem and Relationship test *RCT* Randomized controlled trial, *SERS* Self-Esteem and Relationship Satisfaction, *IIEF* International Index of Erectile Function

protocols, several articles strive to compare different treatment modalities [78, 81, 86, 87, 105]. The results proved to be comparable in the different evaluators' treatment methods, without statistically significant differences. Li-ESWT is a clinically effective and safe treatment for erectile dysfunction regardless of generator type, source, emitted shock wave morphology, and treatment protocol [105, 107, 110, 113]. Most common inhibitor included in the Li-ESWT protocol is tadalafil [92, 93, 95, 104]. The preferred dose is 5 mg daily. Most of the studies showed a significant improvement in EF and penile rigidity, which was greater when the use of Li-ESWT was combined with PDEis, without reporting significant changes in its safety profile. Several publications [76, 104, 111] conclude that Li-ESWT is also effective in patients refractory to PDE5is, being able to directly improve their EF in some and make them respond to oral treatment in others. Results are better in younger patients, with ED of vascular origin, with fewer comorbidities, and with mild or moderate ED [107, 108, 111]. Long-term loss of efficacy has been reported, suggesting the need for follow-up and the possibility of repeating therapy [71•, 88, 107]. Li-ESWT appears to be an effective and safe method for the treatment of erectile dysfunction in diabetic patients [100, 101, 109]. Other studies demonstrated the efficacy and safety of Li-ESWT treating ED in patients with chronic pelvic pain syndrome [97], post-prostatectomy [99], pelvic fractures with urethral damage [104], and renal transplant patients [103].

The vast majority of available studies on stem cell therapy (SCT) had a small sample size, had no control group, and had other relevant methodological limitations. Due to the heterogeneity present in the studies regarding the type, the optimal dose, or the route of administration of SCT, the comparison of results is very difficult. Despite encouraging initial results in terms of efficacy and safety, these issues do not yet allow firm conclusions to be drawn.

The use of nutraceuticals as a treatment for erectile dysfunction is controversial. Patients may perceive this type of therapy as more natural and safer. In addition, they can be obtained without a prescription and bought online and lack adequate health controls [187]. The use of nutraceuticals in erectile dysfunction has a very ancient history and has its roots in traditional Chinese medicine and Ayurvedic medicine [188]. Promising improvements in EF have recently been described with different nutraceuticals: L-arginine [143–145], *Tribulus terrestris* [146, 147], vitamin D [148, 149], panax ginseng [126], L-citrulline [127, 128], muira puama [133], and *Ginkgo biloba* [125]. However, the available studies on the subject are methodologically heterogeneous and generally of low quality, often reporting contradictory results, so recommendations on its use have not yet been established [9, 10].

We found 6 papers that analyze the effect of intracavernous injections PRP for the treatment of erectile dysfunction. Only one of the papers [153•] is a double-blind, randomized, placebo-controlled clinical trial. It is also the one that analyzes a greater number of patients ($n = 60$), obtaining a significant improvement in EF and patient satisfaction. Most studies [150, 151, 154, 155] reported statistically and clinically significant improvements in EF. In addition, smoking status, HbA1C, and severity of ED before treatment were strengthened as negative predictors of response to treatment [150, 154]. In general, no significant adverse effects were reported in any of the studies, the most frequent being mild pain at the injection site and mild penile bruising [151]. Therefore, analyzing the limited data available, it suggests that PRP can be used successfully for the treatment of ED. However, the available data is limited by its small sample size, short follow-up, and/or lack of controls. We also do not have standardized methods to prepare PRP or standardized treatment protocols.

In the last 5 years, the effect on EF of several drugs used for the treatment of other pathologies has been studied. Published papers include mirabegron [156, 157], aspirin [159, 160], bupropion [161, 162], cabergoline [163], and levothyroxine [164]. Most of the studies, although they analyzed different and special populations, found a significant difference in the improvement of ED. Only a few works did not find significant differences [160, 165]. It remains to be determined and it can be discussed whether the improvement in EF in some cases is due directly to the effect of the molecule or to the improvement of the underlying pathology of the patient (e.g., LUTS, hypothyroidism).

The use of intracavernous injections of botulinum toxin for the treatment of ED has recently been studied. We found three retrospective studies [166, 167, 171], and three double-blind randomized clinical trials [168, 169, 170•]. An improvement in the EF of patients was demonstrated, improving the results at high doses [168, 170•]. However, this therapy, although promising, still lacks long-term results, unlike the classic vaso-active drugs for the treatment of ED [174].

We have found five studies evaluating the effect of CPAP on EF [175, 176, 178–180]. In total, they include 318 patients with a follow-up time of between 3 and 12 months. Only one of the works is a clinical trial against placebo [180]. The correct use of CPAP improved both EF, sexual desire, general sexual satisfaction, self-esteem, relationship, and treatment, as well as drowsiness and quality of life. This improvement in EF was clinically significant in all but one study [176]. In addition, a trend of correlation between improvement in EF and hours of CPAP use was reported [175, 179].

Three papers have also been published [177, 181, 182] that evaluate the efficacy of hyperbaric therapy on EF. Significant improvements in IIEF and absence of adverse effects were reported. Unfortunately, all three are prospective pilot

studies with a very short follow-up time (5-6 weeks). Innovatively, one of the works also demonstrates a significant improvement in angiogenesis measured by perfusion magnetic resonance imaging [182]. Therapies based on improving tissue oxygenation also seem promising therapies for the treatment of ED; however, the evidence is still scarce and long-term follow-up studies are lacking.

Conclusion

Numerous publications related to the conservative treatment of ED have been carried out. The significant rate of discontinuation of available therapies and the paucity of curative options prompted research on possible new treatments. In some cases, we must take into account the type of patient, their comorbidities, the origin of their ED, and its severity in order to reproduce effective results using these therapies. Some of these new treatments show good results with a good level of evidence (new PDE5i formulations, intracavernous injections, Li-ESWT, hormonal therapy). However, others (some new molecules, SCT, PRP, oxygenation-based therapies), although they present promising results, require better quality studies to establish firm recommendations.

Compliance with Ethical Standards

Conflict of Interest The authors do not have existing conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were performed in accordance with all applicable ethical standards including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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