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Penile Rehabilitation Strategy after Nerve Sparing Radical Prostatectomy: A Systematic Review and Network Meta-Analysis of Randomized Trials

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Abbreviations and Acronyms

AE = adverse event
bns = bilateral nerve sparing
ED = erectile dysfunction
EF = erectile function
HBO_2 = hyperbaric oxygen therapy
IIEF = International Index of Erectile Function
IUA = intraurethral alprostadil
LPCa = localized prostate cancer
ns = nerve sparing
OD = on-demand
OeD = daily
ORP = open radical prostatectomy
PDE5Is = phosphodiesterase-5 inhibitors
PFMT = pelvic floor muscle training
PR = penile rehabilitation
PSV = penile vibratory stimulation
RALRP = robot-assisted laparoscopic radical prostatectomy
RCT = randomized controlled trial
RDCT = randomized, double-blind, controlled trial
RP = radical prostatectomy
SUCRA = surface under the cumulative ranking curve
uns = unilateral nerve sparing
VCD = vacuum constriction device
VED = vacuum erectile device

Purpose: Despite the advances in nerve sparing and minimally invasive radical prostatectomy, erectile dysfunction remains an important adverse event after radical prostatectomy. Penile rehabilitation strategies have been developed to expedite and improve erectile function recovery. However, the differential efficacy and the best penile rehabilitation strategy are unclear as yet. We conducted a systematic review and network meta-analysis to investigate and compare the efficacy of different penile rehabilitation strategies.

Materials and Methods: A systematic search was performed in May 2020 using PubMed® and Web of Science™ databases according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) extension statement for network meta-analysis. Studies that compared the erectile function recovery rate and adverse events between penile rehabilitation treatment groups (eg medications, devices and actions) and control group were included. We used the Bayesian approach in the network meta-analysis.

Results: A total of 22 studies (2,711 patients) met our eligibility criteria. Out of 16 different penile rehabilitation strategies and schedules vs placebo, only pelvic floor muscle training (OR 5.21, 95% CrI 1.24–29.8) and 100 mg sildenafil regular doses, ie once daily or nightly (OR 4.00, 95% CrI 1.40–13.4) were associated with a significantly higher likelihood of erectile function recovery. The certainty of results for 100 mg sildenafil regular dose was moderate, while pelvic floor muscle training had low certainty. The sensitivity analysis confirmed that the regular high dose of phosphodiesterase-5 inhibitors regardless of type vs placebo (OR 2.09, 95% CrI 1.06–4.17) was associated with a significantly higher likelihood of erectile function recovery with a moderate certainty. The on-demand doses of

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phosphodiesterase-5 inhibitors were not proven to be more beneficial than placebo. Secondary outcomes such as adverse events were not analyzed due to incomplete data in the literature. However, no serious adverse events were reported in any of the studies.

Conclusions: Sildenafil 100 mg regular dose is the best penile rehabilitation strategy to improve erectile function recovery rates after radical prostatectomy. Although pelvic floor muscle training has been shown to be effective in increasing the erectile function recovery rate, well designed randomized controlled trials with larger sample sizes are needed to confirm the presented early results. The on-demand dose of phosphodiesterase-5 inhibitors should not be considered as a penile rehabilitation strategy.

Key Words: erectile dysfunction, penis, urogenital surgical procedures, prostatic neoplasms, prostatectomy

The main treatments, with causative intent, for patients with nonmetastatic prostate cancer are radical prostatectomy and radiotherapy. Despite the advances in nerve sparing surgery techniques and minimally invasive approaches, erectile dysfunction remains a common adverse event that significantly affects the individual's and his partner's quality of life. Indeed, erectile dysfunction rates after radical prostatectomy are highly variable, ranging from 20%–90%,[1] and the prevalence of erectile dysfunction after robot-assisted radical prostatectomy and open retropubic radical prostatectomy is reported at 24% and 48%, respectively.[2] Even after a successful nerve sparing surgery, there is a period of neuropraxia that requires up to 2 years of recovery time after radical prostatectomy.[3,4] The erectile function recovery rate (to the baseline) without the use of medication has been estimated to be lower than 20%,[5] depending on several factors, including surgical technique, preoperative performance and patient age.

Penile rehabilitation programs have been developed to help improve the speed and amplitude of male EF recovery after RP. The concept of PR is the use of drugs, devices and activities alone or in combination to limit the neuropraxia recovery time.[1,6] Major efforts have been undertaken over the last 2 decades to translate this improved understanding of the pathophysiology underlying post-RP ED into effective PR strategies in order to alleviate or minimize damage and enhance the speed and amplitude of EF recovery. To this end, several randomized controlled trials have assessed different drugs, devices and activities.[7–27] Owing to heterogeneity among RCTs regarding PR strategies such as medication, dose, timing, outcomes and followup, there is no clear evidence or consensus regarding the optimal individualized PR efficacy and what the most effective PR strategy is.[28] The aim of this systematic review and network meta-analysis was to compare the current therapeutic options for PR that have been assessed in RCTs. Our goal was to identify the most effective treatment strategy to enhance the EF recovery rate.

MATERIALS AND METHODS

Literature Search

A protocol for this study was registered a priori on the International Prospective Register of Systematic Reviews (No. CRD42020206531). Our search was performed using electronic databases PubMed and Web of Science in May 2020. The systematic review and network meta-analysis of randomized controlled trials for PR treatments (with placebo and/or no treatment as the control arm) were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) extension statement for network meta-analysis.[29] The following search terms were used: "((""erectile dysfunction""[All Fields]) AND (""radical prostatectomy""[All Fields])) AND (""treatment""[All Fields] OR ""rehabilitation"" [All Fields]) AND (randomizedcontrolledtrial [Filter])." Manual searches of reference lists of relevant articles were also performed to identify additional studies. The primary outcome of interest was the proportion of patients who return to the baseline EF at the end of washout (the EF recovery rate), and the secondary outcome was AEs.

Inclusion and Exclusion Criteria

Studies were included if they investigated prostate cancer patients after RP ("patients") who had received a penile rehabilitation treatment ("intervention") compared with those treated with placebo and/or no treatment ("comparison") to assess the differential effects on the EF recovery rate and AEs ("outcomes") in a randomized controlled study only. We excluded observational studies, reviews, letters, editorials, meeting abstracts, replies from authors, case reports and articles not published in English. References of all papers included were scanned for additional studies of interest. Studies were included only if they involved patients who received placebo and/or no treatment as the control arm. Almost all RCTs included in this review excluded patients who had general risk factors of ED such as diabetes mellitus, arterial hypertension, ischemic heart disease and past history of pelvic irradiation, chemotherapy and endocrine disease.

Study Selection

Unfortunately, there is significant heterogeneity in the literature in terms of definitions of ED after RP, and a significant number of studies do not clearly state their definitions of ED or return to normal sexual function. Consequently, we selected RCTs that used the most utilized and accepted questionnaire to assess EF before and

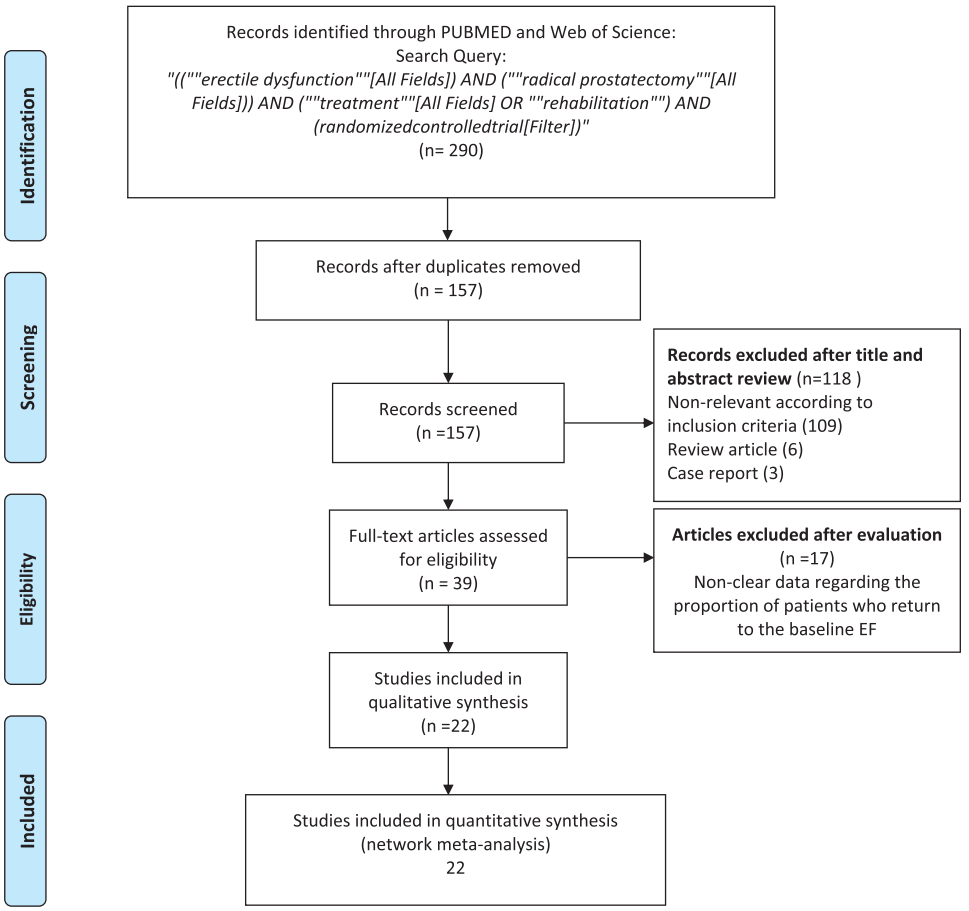

Figure 1. Selection process of articles to assess penile rehabilitation treatment effects on erectile function recovery rate

after RP. According to the International Index of Erectile Function questionnaires such as the IIEF-5, IIEF-EF (erectile function domain) and IIEF, we defined "sufficient for intercourse" as men with IIEF-5 >17, IIEF-EF ≥22 and IIEF >19. All of these thresholds (ie IIEF-5 >17, IIEF-EF ≥22 and IIEF >19) are mentioned as a mild ED and indeed, these cutoffs were previously identified as a reliable score for defining EF recovery after nsRP.[1,30] Therefore, we defined a return to sexual function as return to baseline IIEF-5, IIEF-EF and/or IIEF scores. Initial screening was performed independently by 2 investigators based on the titles and abstracts of the article to identify eligible and ineligible reports. Reasons for exclusions were noted. Potentially relevant reports were subjected to a full text review, and the relevance of the reports was confirmed after the data extraction process. Disagreements were resolved via consensus with the coauthors and referring to the senior author.

Data Extraction

Two investigators independently extracted the following information from the included articles: first author's name, publication year, period of patient recruitment, number of patients, treatment dosage and duration, age, study design, study funding and/or support, IIEF-5, IIEF-EF and/or IIEF scores before RP and after RP and PR treatment (at the end of washout) and AEs. Subsequently, the number of potent patients with eligible scores before RP, the number of potent patients who returned to the baseline scores and AEs rate were retrieved. In 9 cases where RCTs used only mean scores of the questionnaire as an outcome; we contacted the corresponding authors for additional details. All discrepancies regarding data extraction were resolved by consensus with the coauthors or referring to the senior author.

Methodological Quality

The risk-of-bias evaluation for each study was assessed according to the Cochrane Collaboration tool for assessing risk of bias, version 2.[31] This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The risk-of-bias of each study was assessed independently by 2 authors. Disagreements were resolved by consultation with the coauthors or referring to the senior author. The Risk-of-Bias VISualization tool (R Project for Statistical Computing, Vienna, Austria) was used to create risk-of-bias plots.[32]

Statistical Analysis

We conducted a network meta-analysis using random and fixed effect models with a Bayesian approach for the direct and indirect treatment comparisons with placebo or no treatment as the common comparator arm.[33,34] We performed 2 sensitivity analyses. As regards the Fourth

Table 1. *Characteristics of RCTs included in systematic review and network meta-analysis*

Reference/Yr	Design/Funding/Support	Stage/ Age (yrs)	Baseline EF Score	No. Pts/Controls at Start, End	Intervention	Control	Outcome	Surgery Type	Followup (mos)
de Lira et al, 2019	RCT/none	LPCa/ 45–75	IIEF ≥17	9/9, 9/9	PFMT	Usual post-RP care	Recovery rate IIEF-5 ≥17	ORP	3
Mulhall et al, 2018	RDCT/company funded	LPCa/ ≤65	IIEF ≥24	62/69, 37/43	2–3 mg Tacrolimus daily	Placebo	Recovery rate IIEF ≥24	bns Open	24
Ki jo et al, 2018	RCT None.	LPCa/ ≥50	IIEF-5 ≥17	60/62, 58/62	100 mg Sildenafil early	Delayed sildenafil 100 mg	Recovery rate IIEF-5 ≥17	bns RALRP	12
Chiles et al, 2017	RDCT/none	LPCa/ ≤65	IIEF-EF ≥26	50/50, 40/43	Hyperbaric oxygen therapy	Air	Recovery rate IIEF-EF ≥22	bns RALRP	18
Mulhall et al, 2016*	RDCT/company funded	LPCa/ <68	IIEF ≥22	139/142/141, 139/141/141	5 mg Tadalafil OeD, 20 mg tadalafil OD	Placebo	Recovery rate IIEF ≥22	bns RP	9
Kim et al, 2015	RDCT/company funded	LPCa/ <62	IIEF-EF ≥22	49/48, 37/37	50 mg Sildenafil OeD	Placebo	Recovery rate IIEF-EF ≥22	ns RP	13
Fode et al, 2014	RCT/company funded	LPCa/ 46–76	IIEF-5 ≥17	42/41, 30/38	PFMT+PVS	PFMT	Recovery rate IIEF-5 ≥17	ns RALRP	12
Montorsi et al, 2014*	RDCT/company funded	LPCa/ ≤68	IIEF ≥22	139/143/141, 98/112/105	5 mg Tadalafil OeD, 20 mg tadalafil OD	Placebo	Recovery rate IIEF ≥22	bns RP	12
Moncada et al, 2014*	RDCT/company funded	LPCa/ ≤68	IIEF ≥22	139/143/141, 137/140/137	5 mg Tadalafil OeD, 20 mg tadalafil OD	Placebo	Recovery rate IIEF ≥22	bns RP	12
Pavlovich et al, 2012	RCT/company funded	LPCa/ ≤65	IIEF-EF ≥25	50/50, 36/38	50 mg Sildenafil nightly	50 mg On-demand sildenafil	Recovery rate IIEF-EF ≥22	ns RALRP or ns laparoscopic RP	13
Jones et al, 2013	RCT/research grant from National Cancer Institute	LPCa/ ≤65	IIEF ≥22	25/25, 15/20	Aerobic training	Usual post-RP care	Recovery rate IIEF-EF ≥22	bns RALRP or bns ORP	12
Prota et al, 2012	RCT/research grant from Fundacao de Amparo a Pesquisa do Estado de Sao Paulo, Brazil	LPCa/ ≤72	IIEF-5 >20	26/26, 17/16	PFMT	Usual post-RP care	Recovery rate IIEF-5 >20	ORP	12
Bannowsky et al, 2012*	RCT/not clear	LPCa/ 52–71	IIEF-5 ≥19	12/12/12, 12/12/12	5 mg Vardenafil OeD, 10 mg vardenafil OeD	Placebo	Recovery rate IIEF-5 ≥19	uns ORP	12
Aydogdu et al, 2011	RCT/none	LPCa/ 50–65	IIEF-EF ≥26	32/33, 32/33	20 mg Tadalafil 3 days/wk for 6 mos	Placebo	Recovery rate IIEF-EF ≥26	bns RP	12
McCullough et al, 2010	RCT/not clear	LPCa/ ≤70	IIEF-EF ≥26	139/73, 97/59	Intraurethral prostaglandin E1 125–250 μg	50 mg Sildenafil nightly	Recovery rate IIEF-EF ≥26	bns RP	11
Pace et al, 2010	RCT/none	LPCa/ 50–71	IIEF-EF ≥26	20/20, 20/20	Flexible dose 50 mg or 100 mg sildenafil nightly	Placebo	Recovery rate IIEF-EF ≥26	ns RP	6
Padma-Nathan et al, 2008*	RDCT/company funded	LPCa/ 18–71	Normal perioperative EF	40/41/42, 23/28/25	50 mg Sildenafil nightly, 100 mg sildenafil nightly	Placebo	Recovery rate	bns RP	12
Montorsi et al, 2008*	RDCT/company funded	LPCa/ 18–64	IIEF-EF ≥26	210/208/210, 116/135/127	5–10 mg Vardenafil nightly, 5–20 vardenafil mg OD	Placebo	Recovery rate IIEF-EF ≥22	bns RP	13.5
McCullough et al, 2008*	RDCT/company funded	LPCa/ 18–70	Normal perioperative EF	17/18/19, 17/18/19	50 mg Sildenafil OeD, 100 mg sildenafil OeD	Placebo	Recovery rate	bns RP	11
Bannowsky et al, 2008	RCT/none	LPCa/ 54–75	IIEF-5 ≥17	23/18, 23/18	25 mg Sildenafil nightly	Placebo	Recovery rate IIEF-5 ≥17	bns/uns RP	13
Köhler et al, 2007	RCT/none	LPCa/ ≤65	IIEF-5 ≥17	17/11, 17/11	VCD	Placebo	Recovery rate IIEF-5 ≥17	bns/uns RP	12
Raina et al, 2006	RCT/not clear	LPCa/ 50–71	IIEF-5 ≥17	74/35, 60/35	VCD	Placebo	Sufficient erections for vaginal intercourse	bns/uns RP, nonns RP	9

* Study with 2 intervention groups.

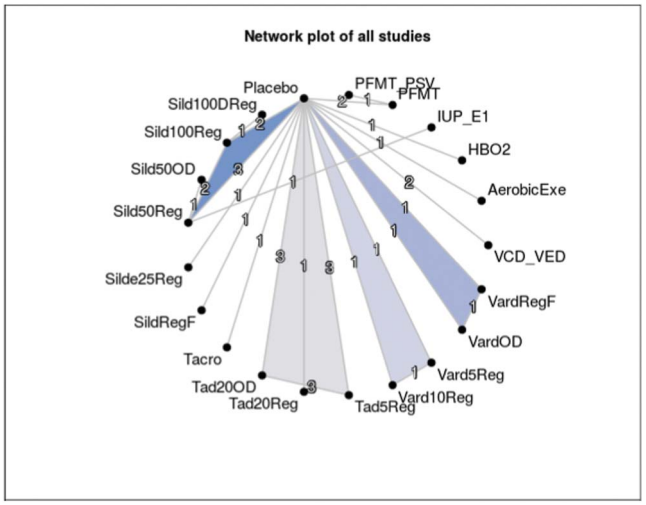

Figure 2. Network plot of RCTs that assessed penile rehabilitation treatment effects on erectile function recovery rate. Numbers indicate number of studies. *D,* delay. *F,* flexible. *Reg,* regular. *Sild,* sildenafil. *Tad,* tadalafil. *Tacro,* tacrolimus. *Vard,* vardenafil.

International Consultation for Sexual Medicine recommendation that the effects of on-demand phosphodiesterase-5 inhibitors are not more than placebo as a PR treatment,[28] the first sensitivity analysis was conducted with a Bayesian approach for the direct and indirect treatment comparisons with placebo, no treatment and/or on-demand dose of PDE5Is as the comparator arm. Owing to that PDE5Is are the most frequent PR strategies across the literature, we assessed only PDE5Is studies as the second sensitivity analysis. We categorized RCTs that used PDE5Is regardless type of PDE5Is to the regular high dose (100 mg sildenafil, 20 mg tadalafil and 10 mg vardenafil), the regular low dose (50 mg and 25 mg sildenafil, 5 mg tadalafil, 5 mg vardenafil), the regular flexible dose (50−100 mg sildenafil and 5−10 mg vardenafil) and any on-demand dose. The second sensitivity analysis was performed with a Bayesian approach for the direct and indirect PDE5Is treatment comparisons with placebo or no treatment. The odds ratio was used to denote the results with a 95% credible interval, indicating the strength of association between treatments and outcomes. In Bayesian statistics, a credible interval is an interval within which an unobserved value falls with a particular probability. Pooled ORs and their 95% CrIs were also calculated. Statistical significance was established with a 2-sided $p < 0.05$ or a 95% CrI that did not include a value of 1. All treatments were ranked according to the SUCRA probability. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of the proportion of patients. All Bayesian statistical calculations were performed using the MetaInsight software[34] from gemtc (Network Meta-Analysis Using Bayesian Methods version 0.8-2) and BUGSNET (Bayesian Inference Using Gibbs Sampling to Conduct NETwork Meta-Analysis) version 1.0.3 (R Project for Statisical Computing).[35] Statistical significance was set at $p < 0.05$. The certainty assessment of the network meta-analysis results was performed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to rate the certainty of evidence from network meta-analysis.[36]

RESULTS

Search Results

Our initial search identified 290 publications, and after the elimination of duplicates, 157 publications were available. A total of 118 articles were excluded after screening the titles and abstracts, and a full text review was performed for 39 articles. Figure 1 illustrates the selection process flowchart.

Characteristics of Studies Included

Based on the selection criteria, we identified 22 articles comprising 2,711 patients for this systematic review and network meta-analysis.[7−27,37] Extracted data from the 22 studies are outlined in table 1. All studies included localized prostate cancer patients who underwent nerve sparing open, laparoscopic or robot-assisted radical prostatectomy. All studies were published between 2006 and 2019; they included a total of 831 patients treated with placebo and/or no treatment and 1,880 patients treated with medications, device and/or action such as a PR treatment.

Network Meta-Analysis

The network of eligible comparisons is graphically represented in network plots in terms of the EF recovery rate (ie the proportion of patients who experienced a return to the baseline EF at the end of washout) in figure 2. A network meta-analysis of 16 different PR treatments (eg medication type, medication dose, devices or actions) was conducted for the primary outcome of the EF recovery rate. Compared with placebo, only pelvic floor muscle training (OR 5.21, 95% CrI 1.24−29.8) and 100 mg sildenafil regular doses, ie once daily or nightly (OR 4.00, 95% CrI 1.40−13.4), were associated with a significantly higher likelihood of returning to baseline EF, respectively. The certainty of result for sildenafil 100 mg (regular dose) was moderate, while PFMT had a low certainty due to publication bias and the small sample size of 2 RCTs. The main results of the network meta-analysis and the certainty assessment of results are mentioned in table 2 and figure 3. Based on Bayesian analysis and analysis of the treatment ranking according to the SUCRA, it was highly likely that PFMT and sildenafil 100 (regular dose) were the best PR treatments (table 2). Vardenafil (on-demand dose) and tadalafil (on-demand dose) had the same and lower ranking compared to placebo, respectively.

In the first sensitivity analysis, all PR treatments were compared with placebo, no treatment and/or

Table 2. *Summary of network meta-analysis results regarding best penile rehabilitation treatment*

Classification	Intervention	OR Effect on EF Recovery Rate Compared to Placebo (95% CrI)	Certainty
Beneficial effect	PFMT	5.21 (1.24, 29.8)	Low
	100 mg Sildenafil regular dose	4.00 (1.40, 13.4)	Moderate
No beneficial effect	5 mg Vardenafil regular dose	3.27 (0.49, 25.6)	Low
	Sildenafil regular flexible dose	2.61 (0.45, 17.3)	Low
	10 mg Vardenafil regular dose	2.22 (0.33, 19.5)	Low
	25 mg Sildenafil regular dose	2.07 (0.47, 10.4)	Low
	50 mg Sildenafil regular dose	1.94 (0.82, 5.35)	Moderate
	VED/VCD	1.59 (0.53, 5.24)	Moderate
	20 mg Tadalafil regular dose	1.38 (0.38, 5.16)	Low
	5 mg Tadalafil regular dose	1.14 (0.66, 1.91)	Moderate
	Vardenafil OD	1.02 (0.44, 2.36)	Moderate
	20 mg Tadalafil OD	0.92 (0.52, 1.56)	Moderate
	HBO_2	0.79 (0.25, 2.31)	Moderate
	Vardenafil regular flexible dose	0.77 (0.33, 1.84)	Moderate
	2–3 mg Tacrolimus	0.66 (0.21, 1.95)	Moderate
	Aerobic training	0.38 (0.07, 1.79)	Moderate

*Lighter colors indicate higher rank of best treatment according SUCRA probability. Cells with same color have same rank.

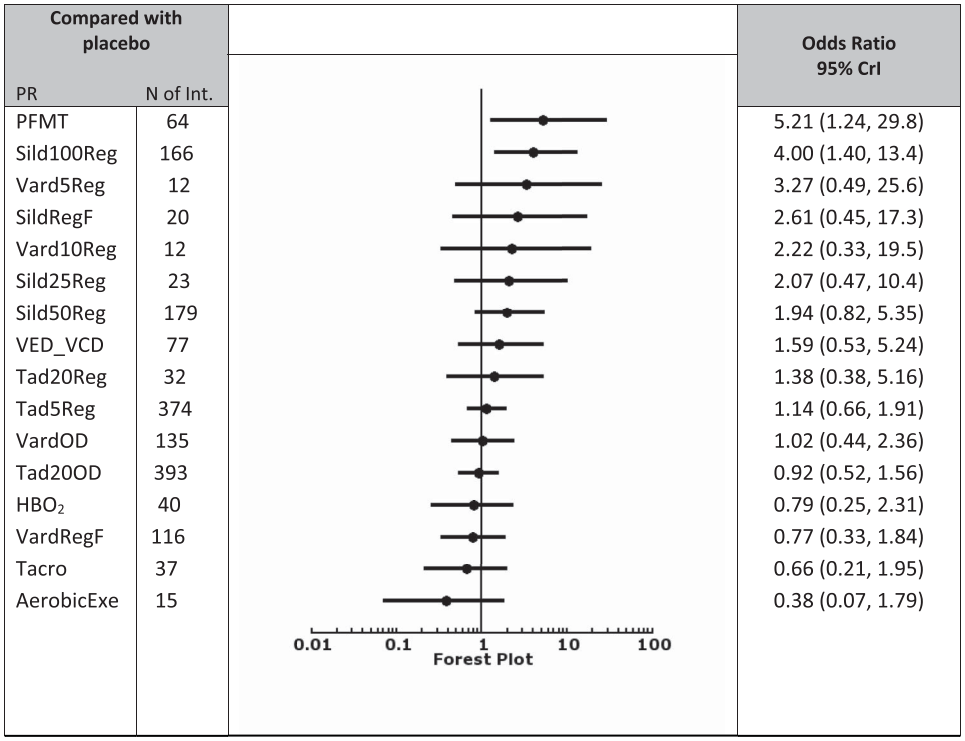

Figure 3. Forest plot of Bayesian random effect consistency model for all studies compared to placebo and/or no treatment. *D*, delay. *F*, flexible. *Reg*, regular. *Sild*, sildenafil. *Tad*, tadalafil. *Tacro*, tacrolimus. *Vard*, vardenafil. *Exe*, exercise. *Int*, interventions.

on-demand doses of PDE5Is, as stated in the Materials and Methods section. We found that PFMT (OR 5.54, 95% CrI 1.16–40.6) and sildenafil 100 mg (regular dose) (OR 3.21, 95% CrI 1.51–6.94) were both associated with a significantly higher likelihood of the baseline EF recovery. Figure 4 shows a summary of the sensitivity analysis results. Based on Bayesian analysis and analysis of the treatment ranking (SUCRA), it was highly likely that PFMT, vardenafil 5 mg (regular dose) and sildenafil 100 mg (regular dose) were the best PR treatments. In the second sensitivity analysis, we only analyzed PDE5I studies categorized to regular high dose, regular low dose, regular flexible dose or any on-demand dose regardless of the type of PDE5I, as stated in the Materials and Methods section. We found that only the regular high dose of PDE5Is (OR 2.09, 95% CrI 1.06–4.17) was associated with a significantly higher likelihood of the baseline EF recovery and, moreover, the regular high dose of PDE5Is was the best in the ranking analysis. Figure 5 shows a summary of the second sensitivity analysis results.

The secondary outcome was not reached and performing a network meta-analysis was not feasible due to incomplete reported data in the included studies. All reported AEs are summarized in table 3. No serious AEs were reported in any study. Moreover, 10 of 22 studies did not report any data regarding the PR treatment AEs and/or discontinuation due to AEs.[7,11,13,15,17–19,21,24,25]

Bias Assessment

Risk of bias assessment for the RCTs included was performed following the Cochrane recommendations; the results are presented in figure 6. The main risk of bias was observed in domain 2 (ie bias due to deviations from intended interventions). Indeed, blinding participants and personnel were not possible for some of the PR treatments such as PFMT or vacuum erectile or constriction devices VED/VCD.[7,13,17,26,27] Moreover, some studies, that used oral medications as a PR treatment were not blinded RCTs.[9,18,20,25,37] Missing data regarding the discontinued treatment and the reason of discontinuation (eg AEs) were observed in RCTs,[16,17,19–22,25,26] and therefore there was bias in the selection of reported results (ie domain 5). There was heterogeneity across RCTs in terms of nerve sparing surgery; 12 studies included bilateral ns surgeries, and 8 studies only mentioned that they included ns surgeries and/or they included both unilateral and bilateral ns surgeries.

DISCUSSION

Although PR is an integral part of patient management after RP, the evidence to support its efficacy and the best treatment strategy to promote

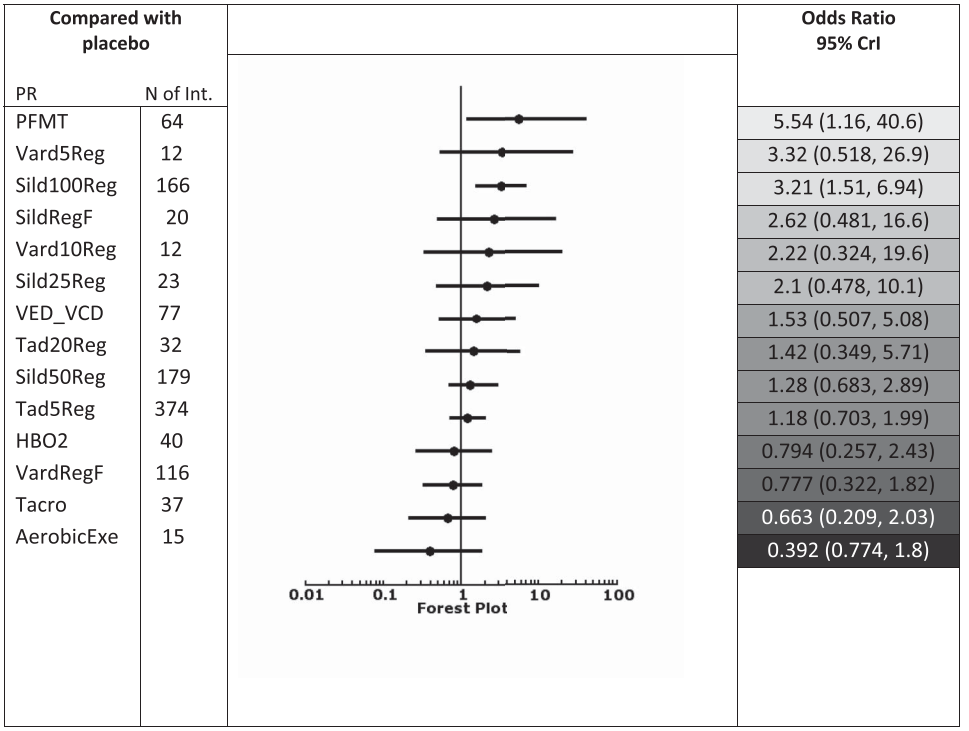

Figure 4. Forest plot of Bayesian random effect consistency model for all studies compared to placebo, no treatment and/or on-demand dose of phosphodiesterase 5 inhibitors. Lighter colors represent higher rank of best treatment according SUCRA probability. Cells with same color have same rank. *D*, delay. *F*, flexible. *Reg*, regular. *Sild*, sildenafil. *Tad*, tadalafil. *Tacro*, tacrolimus. *Vard*, vardenafil. *Exe*, exercise. *Int*, interventions.

satisfactory unassisted erection remain inconclusive.[1,28] Since 1997, when Montorsi et al reported their first study over PR,[38] many RCTs have evaluated PR strategies. Indeed, there are many different choices including medications (eg oral, injectable, intraurethral), devices and action (eg PFMT and aerobic exercise) with different schedules, dosages, frequencies and timing. None of previous studies were able to recommend the best PR treatment and its optimal delivery regimen.[1,6,39]

The present network meta-analysis included 22 RCTs that compared the treatment efficacy of 16 PR strategies in terms of EF recovery rate. The results suggested that 100 mg sildenafil regular dose (ie once daily or nightly) was most likely to increase EF recovery rate at the end of washout. We found that other PDE5Is with different doses (eg fixed, flexible) and schedules (eg on-demand, regularly) have no efficacy in expediting the EF recovery rate. The main results were confirmed by the findings of the

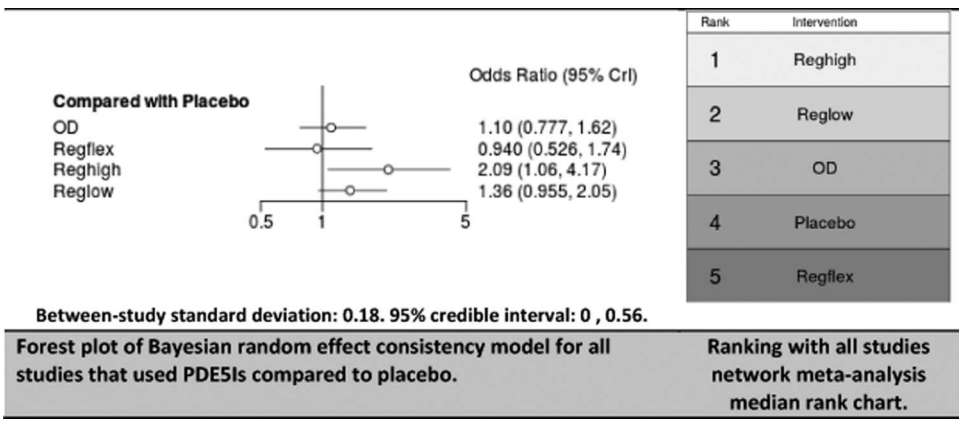

Figure 5. Summary of Bayesian sensitivity network meta-analysis. Pooled analysis of all studies that used PDE5Is compared to placebo regardless type of PDE5Is. *Regflex*, regular flexible dose. *Reghigh*, regular high dose. *Reglow*, regular low dose.

Table 3. *Summary of penile rehabilitation adverse events*

Reference Study, Yr/Penile Rehabilitation Type	Reported Adverse Events	No. Pts/Controls	No. Adverse Events in Pts/Controls
de Lira et al, 2019/PFMT	Not available	9/9	Not available
Mulhall et al, 2018/2—3 mg tacrolimus	No symptoms or signs of immunosuppression; 36% of pts needed tacrolimus dose adjustment due to AEs; no severe AEs such as symptomatic hyperkalemia or permanent creatinine elevation	37/43	Not available
Ki jo et al, 2018/100 mg sildenafil	Facial flushing was most commonly reported adverse event but it was transient + mild in severity; no pt had headache, blurred vision or serious AE	58/62	9/4
Chiles et al, 2017/HBO_2	Barotrauma related to hyperbaric compression was most commonly reported AE; 2 pts withdrew from study due to complications of otic barotrauma	40/43	1/2
Mulhall et al, 2016/5 mg tadalafil*	Not available	139/141/141	Not available
Kim et al, 2015/50 mg sildenafil	3 Pts discontinued due to AEs	37/37	Not available
Fode et al, 2014/PFMT+PSV	Not available	30/38	Not available
Montorsi et al, 2014/5 mg tadalafil*	19.4% of Pts in all groups discontinued studies due to AEs (regular dose in 41, on-demand in 31, placebo in 36).	98/112/105	55/62/50
Moncada et al, 2014/5 mg tadalafil*	Not available	137/140/137	Not available
Pavlovich et al, 2012/50 mg sildenafil	26 Pts discontinued treatment (14 nightly, 12 on-demand), of whom 2 discontinued treatment due to AEs (headache/blurred vision in 1, blurred vision in 1)	36/38	3/0
Jones et al, 2013/aerobic training	No serious AEs	15/20	Not available
Prota et al, 2012/PFMT	Not available	17/16	Not available
Bannowsky et al, 2012/5—10 mg tadalafil*	Not available	12/12/12	Not available
Aydogdu et al, 2011/20 mg tadalafil	Not available	32/33	Not available
McCullough et al, 2010/ Intraurethral prostaglandin E1 or 50 mg sildenafil	Main AEs were penile burning or discomfort with IUA, + headache + flushing with sildenafil; 30% of IUA pts + 19% of sildenafil pts discontinued study due to AEs	97/59	Not available
Pace et al, 2010/50 or 100 mg sildenafil	Not available	20/20	0/0
Padma-Nathan et al, 2008/50—100 mg sildenafil*	Most commonly reported AEs were dyspepsia, headache, flushing, abnormal vision + rhinitis; 2 pts in 50 mg sildenafil group discontinued due to AEs	23/28/25	23/20/6
Montorsi et al, 2008/5 or 10 mg vardenafil*	Most common AEs were headache, flushing + nasopharyngitis. 5% of Pts on placebo, 8% on vardenafil nightly and 6% on vardenafil on-demand discontinued study due to AEs	116/135/127	59/69/28
McCullough et al, 2008/50—100 mg sildenafil*	Not available	17/18/19	Not available
Bannowsky et al, 2008/25 mg sildenafil	Not available	23/18	Not available
Köhler et al, 2007/VED or VCD	No pt withdrew in first 6 mos of study	17/11	Not available
Raina et al, 2006/VED or VCD	18% of Pts discontinued study due to AEs; common AEs were discomfort, social inconvenience, penile bruising	60/35	14/0

* Three-arm studies with 2 intervention groups.

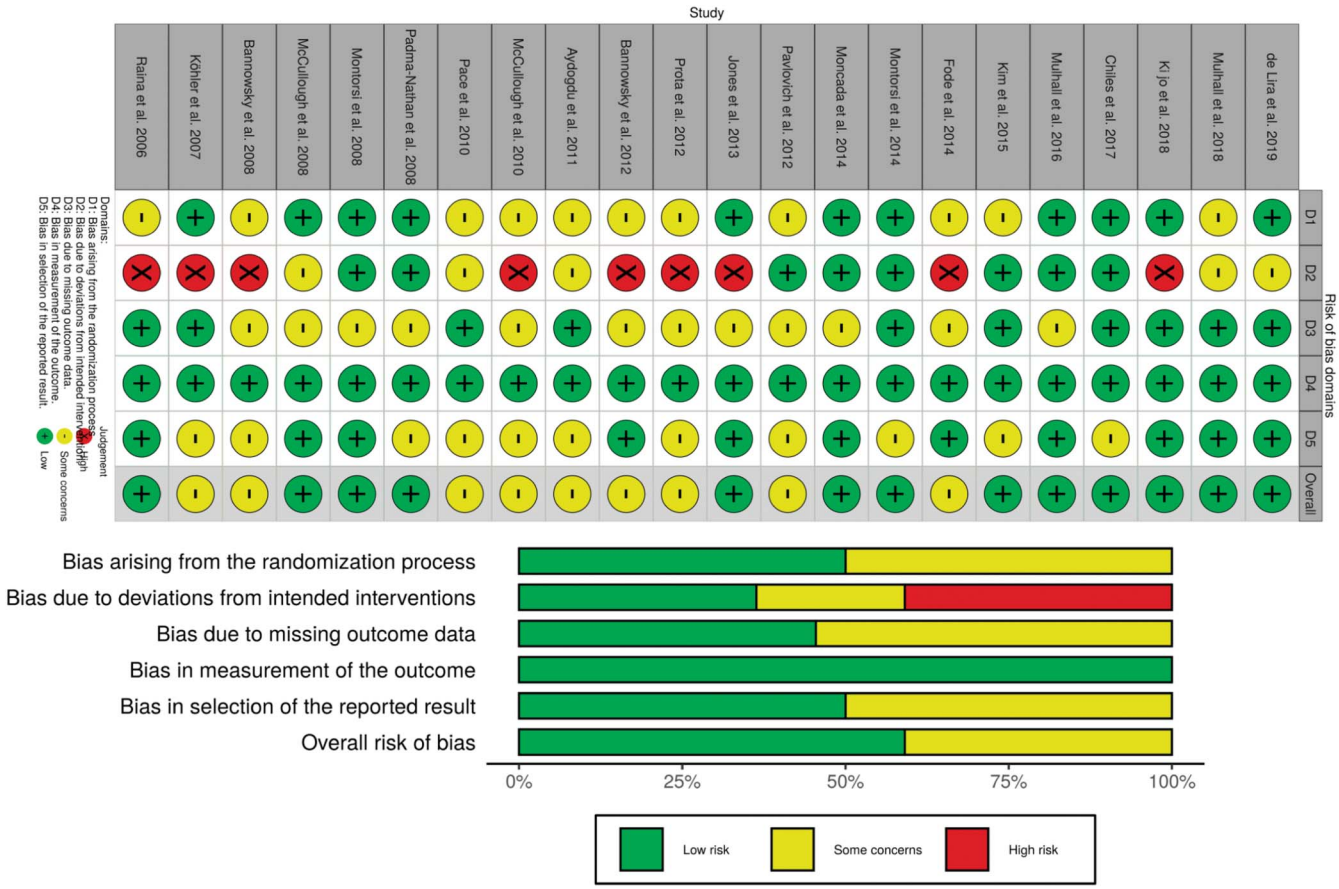

Figure 6. Risk of bias assessment for all studies included in systematic review and network meta-analysis

first sensitivity analysis and confirmed sildenafil 100 mg (regular dose) as the best PR treatment, according to the estimated OR, SUCRA ranking and the certainty of results. Moreover, we found in the second sensitivity analysis that the regular high dose of PDE5Is regardless of the type (ie 100 mg sildenafil once daily or nightly, 20 mg tadalafil 3 days per week and 10 mg vardenafil once daily) could significantly increase the EF recovery rate at the end of washout, but on the other hand, the regular low dose, regular flexible dose and any on-demand dose of PDE5Is could not show such efficacy.

Both the last International Consultation for Sexual Medicine[28] and the last update of the American Urological Association Guideline on Erectile Dysfunction[40] reported that the PDE5Is data remained unproven to recommend as an erectile function rehabilitative protocol (level of evidence 3 and grade of recommendation C). The results of this network meta-analysis including 22 RCTs and 2 sensitivity analyses could provide useful recommendations to guide clinical practice. The regular high dose of PDE5Is and especially sildenafil 100 mg once daily or nightly could be recommended as an effective PR strategy after ns RP (fig. 7).

Oral PDE5Is are a practical treatment of ED due to their simple oral administration, safety, side effect profile, tolerance and efficacy. Therefore, they are often considered as the mainstay of ED management and are the most commonly assessed drug as a PR strategy after RP. The Fourth International Consultation for Sexual Medicine recommended by level 1 and grade A evidence that treatment with on-demand PDE5Is is better than leaving the patients without treatment.[28] However, according to ORs of the main and second sensitivity analyses and moreover, the results of SUCRA probability treatment ranking, the on-demand doses of PDE5Is were not more effective than placebo. Our result is the same direction as the AUA Guideline on Erectile Dysfunction,[40] which recommends that the early administration of on-demand dose of PDE5Is does not improve later responses to these medications compared to early administration of placebo. Additionally, in the first sensitivity analyses with the on-demand dose groups being delineated as the control group (ie similar to placebo and/or no treatment), PFMT and 100 mg sildenafil (regular dose) remained the best PR treatment. This could reflect the similar effect of on-demand dose of PDE5Is and placebo in the network meta-analysis results.

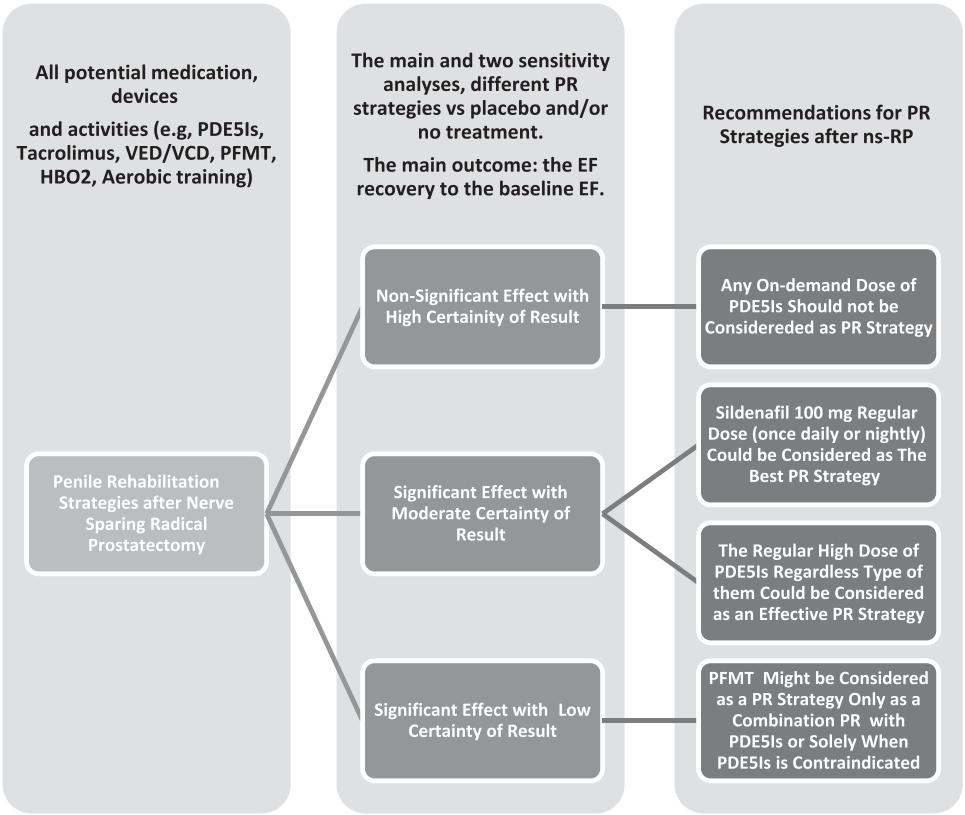

Figure 7. Recommendations for penile rehabilitation strategy according to present network meta-analysis

The goal of early PR treatment is the prevention of cavernosal tissue hypoxia. However, the use of tacrolimus as a PR treatment has a different rationale point. Immunophilin ligands such as tacrolimus were shown to be neuroprotective/neuro-regenerative in animal nerve injury models.[8] As a PR treatment strategy, probably, tacrolimus has not the efficacy to increase the EF recovery rate. Moreover, it requires close observation and dose adjustment for immunosuppression events and/or electrolyte disturbances.[8]

To our knowledge, this analysis is the first to evaluate the pharmacological and nonpharmacological PR strategies in comparison with placebo and/or no treatment. Among nonpharmacological PR treatments, PFMT was most likely to increase EF recovery rate; others, such as HBO_2 therapy and aerobic exercise were not more effective than placebo. PFMT was likely more efficacious than sildenafil 100 (regular dose) according to the estimated OR and the SUCRA treatment ranking (table 2). However, PFMT had a low certainty of result due to risk of bias assessment and the small sample size (51) of 2 RCTs that directly assessed PFMT vs usual post-RP care.[7,17] Sildenafil 100 (regular dose), had, in turn, a moderate certainty of result.

Although VED/VCD had a higher ranking than placebo, the effect estimation of VCD/VED was not statistically significant (OR 1.59, 95% CrI 0.53–5.24). Vacuum devices were used mostly in a combination with PDE5Is in the RCTs as a PR treatment. Qin et al reported in their systematic review and meta-analysis that VED/VCD plus PDE5Is had significantly increased the IIEF-5 mean score compared to PDE5Is alone (mean difference 4.76, 95% CI: 3.28–6.24). However, the EF recovery rate was not considered as an outcome, and moreover placebo and/or no treatment were not used as a control group.[39]

AEs and the rate of discontinued treatment due to AEs are important end points in the assessment of PR strategies. Unfortunately, the current data are spare to allow a quantitative evidence synthesis. PDE5Is were mostly used as a PR treatment in RCTs and the usual side effects of PDE5Is were reported in these studies. However, the rate of discontinuation of PR treatment due to AEs was not high among these studies. Three RCTs that used 100 mg sildenafil once daily or nightly (regular doses) as a PR strategy did not report that patients discontinued treatment due to AEs. Moreover, vardenafil and tadalafil were previously assessed by Montorsi et al, in 2 different studies, as a PR treatment.[14,23] The discontinued rate due to AEs was not different between the 3 arms of each study (ie regular dose, on-demand dose and placebo). Compared to sildenafil 50 mg (regular dose), a higher discontinuation rate with IUA AEs (19% vs 30%) was reported by McCullough et al.[20] It seems

that commonly prescribed daily doses of IUA (500 or 1,000 μg) could result in an unacceptably high discontinuation rate.

Although our systematic review and network meta-analysis has several robust elements, it is not without limitations that should be acknowledged. First, there was inconsistency in outcome assessment tools among studies that assessed the efficacy of PR treatments such as self-reported potency and whether EF questionnaires were validated or not. Second, there was an inconsistency in the reported scores such as mean score and mean difference score and/or total score of each patient before and after receiving PR treatment. These limitations affected all previous systematic reviews and meta-analyses. However, the first limitation was resolved by including studies that used IIEF questionnaire as an accepted outcome assessment tool.[28] The second limitation was resolved by contacting the corresponding authors—when possible—for the complementary data that were not report in the published articles. Unfortunately, there were still some missing data due to unanswered requests. Another important limitation was the company support and/or funding for the RCTs. Ten of 22 RCTs were funded by companies. Such RCTs are more likely to report positive outcomes, and consequently bias in the selection of the reported results is highly possible. Moreover, it is likely that negative trials have not been published, thereby skewing the landscape even further.

CONCLUSIONS

Our results showed that an early initiation of 100 mg sildenafil regular dose (ie once daily or nightly) after nsRP is the best PR strategy to enhance the EF recovery rate. Moreover, the regular high dose of PDE5Is regardless of type could significantly increase the EF recovery rate. The on-demand dose of PDE5Is should not be considered and recommended as a PR strategy. PFMT might be considered as a combination therapy with 100 mg sildenafil (the regular high dose of PDE5Is) or solely when there is a contraindication for PDE5Is. PFMT is promising as a PR treatment due to the effect estimation and the fact that it has no side effects. Future, well designed RCTs with a larger sample size and lowered risk of bias are needed to compare PFMT with no treatment, as well as with the regular high dose of PDE5Is such as 100 mg sildenafil to establish its definitive role in the PR therapeutic landscape.

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