THE JOURNAL OF
SEXUAL MEDICINE

ERECTILE FUNCTION

REVIEW

The Potential Role of Arginine Supplements on Erectile Dysfunction: A Systemic Review and Meta-Analysis

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ABSTRACT

Introduction: The efficacy and safety of arginine supplements in erectile dysfunction (ED) remain debatable.

Aim: To assess the potential role of arginine supplements on ED as alternatives to phosphodiesterase inhibitors.

Methods: Studies published up to April 2018 that evaluated the efficacy of arginine supplements were identified from multiple databases (Google Scholar, PubMed, Medline, Embase, Kiss, DBpia, and Cochrane databases). Studies comparing arginine supplements with placebo or no treatment; focusing only on patients with mild to moderate severity of ED; and presenting outcomes such as improvement rate, International Index of Erectile Function (IIEF) score, and adverse effects were included. Subgroup analysis for arginine alone and arginine in combination with other substances was further conducted to increase interpretability.

Main Outcome Measure: The strength of the association between arginine supplements and ED was assessed using relative odds ratios and weighted mean differences with 95% CI.

Results: In total, 10 randomized controlled trials met the inclusion criteria, reporting the outcomes of 540 patients with ED. The analysis demonstrated that arginine supplements with dosage ranging from 1,500 to 5,000 mg significantly improved ED compared with placebo or no treatment (odds ratios, 3.37 [1.29, 8.77], $P = .01$, $I2 = 44$). Arginine supplements also caused significant improvements in the IIEF subdomain scores of overall satisfaction, intercourse satisfaction, orgasmic function, and erectile function, whereas the IIEF sexual desire score remain unchanged. The adverse effect rate in the arginine-treated group was 8.3%, and that in the placebo group was 2.3%, none of which were severe.

Clinical Implications: Arginine supplements can be recommended to patients with mild to moderate ED.

Strength & Limitations: The strength of this study is that it is the first meta-analysis to assess the potential role of arginine supplements in ED compared with placebo or no treatment. A limitation is that the treatment dosage and duration varied among studies, which may have contributed to study heterogeneity.

Conclusion: The results of our systematic review and meta-analysis provide evidence on the effectiveness of arginine supplements for mild to moderate ED. **Rhim HC, Kim MS, Park Y-J, et al. The Potential Role of Arginine Supplements on Erectile Dysfunction: A Systemic Review and Meta-Analysis. J Sex Med 2019;16:223–234.**

Key Words: Erectile Dysfunction; L-Arginine; Pycnogenol; Yohimbine

INTRODUCTION

Erectile dysfunction (ED), a common condition among men worldwide, is defined as the inability to achieve or maintain an erection sufficient for a satisfactory sexual performance.[1] The prevalence of ED increases with age,[2] and ED affects 52% of men between 40 and 70 years old.[3] The worldwide prevalence of ED is expected to increase to 322 million men by the year 2025.[4] Along with age, endocrine dysfunctions are also known to affect ED, whereas hypothyroidism, diabetic mellitus, gynecomastia, and low levels of testosterone are substantially, or at least partially, associated with ED.[5–9] Although ED is not life-threatening, it should not be overlooked because it may influence interpersonal relationships and impact a couple's relationship in a negative fashion.

Penile erection is a dynamic vascular process that involves relaxation of arterial and trabecular smooth muscle in the corpus

Received July 26, 2018. Accepted December 6, 2018.

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https://doi.org/10.1016/j.jsxm.2018.12.002

cavernosum, thereby increasing arterial blood flow to the penis.[10] Nitric oxide (NO) is considered to be the primary mediator of penile erection and derives from 2 different cell types. NO is produced by neuronal NO synthase (NOS) from non-adrenergic, non-cholinergic nerve terminals of the penis and by endothelial NOS (eNOS) from endothelial cells of penile arteries. The release of NO from neuronal NOS activates NO production in endothelial cells of primary arteries, and, subsequently, this NO binds to guanylate cyclase in vascular smooth muscle cells to generate cyclic guanosine monophosphate (cGMP).[11] CGMP then serves as a second messenger inside muscle cells and causes relaxation and vasodilation, resulting in penile erection. The erection ultimately subsides when cGMP is degraded by phosphodiesterase (PDE) type 5 enzymes.[12]

Oral PDE type 5 inhibitor (PDEi) is currently the first-line treatment for ED.[13] PDEi increases penile smooth muscle relaxation by preventing cGMP degradation, thus helping maintain the erection.[14] Although previous studies have shown the strong efficacy of PDEi regardless of the cause of ED,[15] several factors have limited their use. First, a subpopulation of patients remains refractory to PDEi drugs.[16] Second, headache, flushing, and dyspepsia are common adverse effects of these drugs.[11] Third, their cost and contraindications, as well as concerns about adverse effects have restricted their use.[17]

Because of the above-mentioned reasons and the bias that "natural solutions" are safer and less invasive than pharmaceutical solutions, there seems to be a group of patients who prefer nutraceuticals. As the only physiological substrate for NOS, arginine has been recognized as a potential alternative for ED. The aim of this review was to evaluate the potential role of arginine/citrulline alone or arginine combined with other supplements (yohimbine, pycnogenol, ornithine, or adenosine monophosphate [AMP]) in ED of mild to moderate severity. To the best of our knowledge, this is the first meta-analysis to elucidate the efficacy and safety of arginine and its combination with other supplements as a remedy for ED.

METHODS

Literature Search

A systematic search was conducted using different electronic bibliographic databases (Google Scholar, PubMed, Medline, Embase, Kiss, DBpia, and Cochrane databases) to identify articles published up to April 2018 that evaluated the efficacy of arginine for ED. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] The search terms used were as follows: ("erectile dysfunction" [Medical Subject Headings {MeSH}] and "oral supplement" [MeSH]) and ("arginine" [MeSH] or "citrulline" [MeSH]). Free-text and MeSH search terms were used as keywords in searching, and references of the identified articles were also reviewed for additional articles. Articles with suitable data presented in English were included.

Study Selection Criteria

Studies that met the following criteria were included: (i) comparing arginine supplement with placebo or no treatment; (ii) focusing only on patients with mild to moderate severity of ED; (iii) presenting outcomes such as improvement rate and International Index of Erectile Function (IIEF) score; and (iv) designed as a randomized placebo-controlled trial. When 2 eligible studies were from identical cohorts, the study with the higher Jadad score[19] was selected. The following studies were excluded: (i) studies on patients with severe ED; (ii) studies lacking the necessary statistical data such as variance; (iii) studies with treatment (medication) using PDEi; (iv) studies that did not identify the information and daily dosage of the supplement; (v) non-randomized controlled trial; (vi) posters, review papers, comments, and abstract-only papers; and (vii) studies written in a language other than English.

Data Extraction and Quality Assessment

2 independent reviewers (M.S. and H.C.) evaluated the original studies, and the following details were extracted: (i) characteristics of the study (authors, year of publication, study design, ED type and severity, number of patients in each arm, and definition of improvement) and (ii) outcomes (improvement rate and IIEF subdomain score). The definition of improvement for each study is summarized in the last column of Table 1. The severity of ED was identified either according to IIEF (score of 11−≥17) or based on the description of the study methodology. 10 RCTs were included for analysis (Table 1) and qualitatively assessed using the Jadad score[19] (Table 2). Studies were evaluated on the basis of 5 factors: (i) described as a randomization study; (ii) the randomization method was described and appropriate; (iii) description of withdrawals was provided; (iv) described as a double-blinded study; and (v) the double-blinding method was described and appropriate.

Subgroup Analysis

Subgroup analysis was conducted to minimize the effect of supplement combination on outcomes. Hence, arginine alone and arginine combined with other supplements were separately analyzed for better interpretability. Any studies that examined arginine with other supplements such as pycnogenol or yohimbine were included in the arginine combination subgroup. These subgroup analyses were planned a priori.

Statistical Analysis

10 studies (10 RCTs) with a total of 540 patients with mild to moderate ED were included for meta-analysis. There were 274 patients in the treated group and 266 patients in the placebo or untreated group. Analysis was conducted using the statistical software Review Manager (RevMan version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous variables were analyzed using odds ratios (ORs), and continuous variables were analyzed using weighted mean differences

Table 1. Summary of included studies

Study	Design	Intervention (treated/ untreated)	Age	ED etiology	ED severity	Daily dose/ treatment duration	Definition of improvement
Mozaffari-Khosravi et al[20]	RCT, double blinded study	Arginine (34/35)	Treated 51.58 ± 2.67 Untreated 51.31 ± 2.65	—	Mild to moderate	5,000 mg/4 wk	Increase of IIEF erectile domain score by 2 or greater
Klotz et al[21]	RCT, cross- over study	Arginine (30/30)	Mean 51.6	Mixed type	Have difficulty in normal sexual life	1,500 mg/17 d	"Significantly improved" and "little improved" in validated questionnaire (Kolner Erfassungsbogen fur Erektile dysfunktion) were considered improved
Chen et al[22]	RCT, double blinded study	Arginine (29/17)	Range 55-75	Organic type	—	5,000 mg/6 wk	Subjective: O'Leary questionnaire/sexual function questionnaire (addressed the number of erection, the quality of erections, libido and sexual performance)/ sexual diary Objective: PSV, EDV, RI
Najima et al[23]	RCT, double blinded study	Arginine + Citrulline (22/ 22)	Treated 44.5 ± 9.1 Untreated 44.5 ± 9.1	—	—	3,960 mg/12 wk	—
Ledda et al[24]	RCT, double blinded, parallel arm study	Arg + Pycnogenol (54/57)	44 ± 5	—	Mild to moderate	80 mg pycnogenol + 2,800 mg L-Arg & Asp/6 mo	—
Stanislavov et al[25]	RCT, double-blinded, cross-over study	Arg + Pycnogenol (25/25)	30-50	—	Mild to moderate	80 mg pycnogenol + 3,000 mg L-Arg & Asp /1 mo	Self-reported questionnaire: "YES" for "has it been easier to initiate erection?" "has it been easier to sustain erection?"
Neuzillet et al[26]	RCT, double-blinded study, cross-over study	Arg + AMP (26/26)	56.46 ± 9.26	—	Mild to moderate	8,000 mg Arg + 200 mg AMP before intercourse/2 wk	—

(continued)

Table 1. Continued

Study	Design	Intervention (treated/ untreated)	Age	ED etiology	ED severity	Daily dose/ treatment duration	Definition of improvement
Najima et al[27]	RCT, double-blinded study	Arg + Ornithine (12/12)	Treated 48.4 ± 11.3 Untreated 48.8 ± 11.4	—	—	3,600 mg/12 wk	—
Akhondzade et al[28]	RCT, double- blinded study	Arg + Yohimbine (20/20)	Treated 38.16 ± 6.12 Untreated 38.45 ± 5.65	—	Mild to moderate	Nature's Gifts SX 2,800 mg/4 wk	Respond "yes" for Global Assessment Question: "Have the treatment you have taken over the past 4 weeks improved your sexual function?"
Lebret et al[29]	RCT, double- blinded study, cross-over study	Arg + Yohimbine (22/22)	—	—	Mild to moderate	6,000 mg Arg + 6 mg yohimbine/2 wk	Used IIEF erectile domain score for assessing success rate

AMP = adenosine monophosphate; Arg = arginine; Asp = aspartate; Cit = citrulline; EDV = end-diastolic velocity; IIEF = International Index of Erectile Function; PSV = peak systolic velocity; RCT = randomized placebo-controlled trial; RI = resistance index.

(WMDs), presented with 95% CIs. Statistical heterogeneity was estimated using Higgins I^2 statistics[30] and Cochran Q test. I^2 values were estimated as follows: <25% as low, 25%−50% as moderate, and >50% as high heterogeneity.[31] A random-effect model was used for analysis when the heterogeneity was high ($I^2 > 50\%$ or $P < .100$); otherwise, a fixed-effect model was selected. If data are given as median and range or interquartile range, they were converted to derive the mean and standard deviation according to the Cochrane handbook[32] and other reference formulas.[33,34]

RESULTS

Study Characteristics

The combined searches identified 545 abstracts, as demonstrated in Figure 1. After eliminating 99 duplicates and excluding irrelevant articles, 92 articles were considered for peer review. Among these, 3 were superseded by other articles with overlapping data sets, and 4 were available only in abstract form. Among the remaining 60 articles, 50 articles were excluded because 17 articles showed no robust statistical data, 28 articles used treatments with unknown mechanisms, and 5 articles were non-randomized controlled trials (RCTs). In total, 10 articles (10 RCTs)[20−29] with a total of 540 patients with ED met the inclusion criteria. Data were analyzed as reported by the authors.

The included studies are summarized in Table 1. All studies reported the treatment daily dose and duration. 4 studies involving 219 subjects investigated the effect of arginine/citrulline alone. The treatment duration was at least 2 weeks or longer. 6 studies used yohimbine, pycnogenol, ornithine, or AMP combined with arginine. The treatment duration of these studies was at ≥2 weeks.

Primary Outcome: Improvement of ED

Figure 2 shows the forest plot comparing the improvement of ED after treatment vs placebo or no treatment. 6 studies including 309 patients were identified. Arginine supplement caused more improvement of ED than placebo or no treatment (OR 5.73 [2.02, 16.23], $P = .0001$, $I^2 = 67\%$). Subgroup analysis was performed to examine the effect of arginine alone and supplements combined with arginine on ED. 3 studies including 175 subjects were identified as investigating arginine alone. Arginine alone induced significant improvement of ED (OR 3.37 [1.29, 8.77], $P = .01$, $I^2 = 44\%$). 3 studies including 134 subjects were identified as examining supplements combined with arginine. Supplements combined with arginine induced a significant improvement of ED (OR 18.93 [1.69, 212.21], $P = .02$, $I^2 = 80\%$). Supplements combined with arginine demonstrated higher ORs than arginine alone, implying that arginine used as a combination remedy has better efficacy. The study heterogeneity was probably due to the different durations of supplement intake.

Table 2. Jadad score of the studies included

Study	Randomization		Description of withdrawals	Blinding		Total score
	Described as randomized	Randomization method described and appropriate		Described as double-blinded	Double-blinding method described and appropriate	
Mozaffari-Khosravi et al[20]	*	*	*	*	—	4
Klotz et al[21]	*	*	*	—	—	3
Chen et al[22]	*	*	*	*	—	4
Najima et al[23]	*	*	*	*	*	5
Ledda et al[24]	*	*	*	*	—	4
Stanislavov et al[25]	*	*	*	*	*	5
Neuzillet et al[26]	*	—	*	*	—	3
Najima et al[27]	*	*	*	*	*	5
Akhondzadeh et al[28]	*	*	*	*	*	5
Lebret et al[29]	*	—	*	*	—	3

*Indicates "fulfilled" or "yes."

Secondary Outcomes

Figure 3 shows the forest plot comparing each IIEF subdomain score after treatment vs placebo with subgroup analysis (alone vs combination) for ED.

IIEF Overall Satisfaction Score

The IIEF overall satisfaction score (Figure 3a) was evaluated in 5 studies including 233 subjects. The IIEF overall satisfaction score significantly improved with arginine supplements (WMD 0.57 [0.30, 0.84], $P < .0001$, $I^2 = 42\%$). Significant improvement in the IIEF overall satisfaction score was observed both with arginine alone and with supplements combined with arginine, and the difference in score was more apparent with the combination remedy than with arginine alone (WMD 0.37 [0.07, 0.68], $P = .02$, $I^2 = 0\%$ in arginine alone vs WMD 1.22 [0.65, 1.79], $P < .0001$, $I^2 = 0\%$ in the combination remedy).

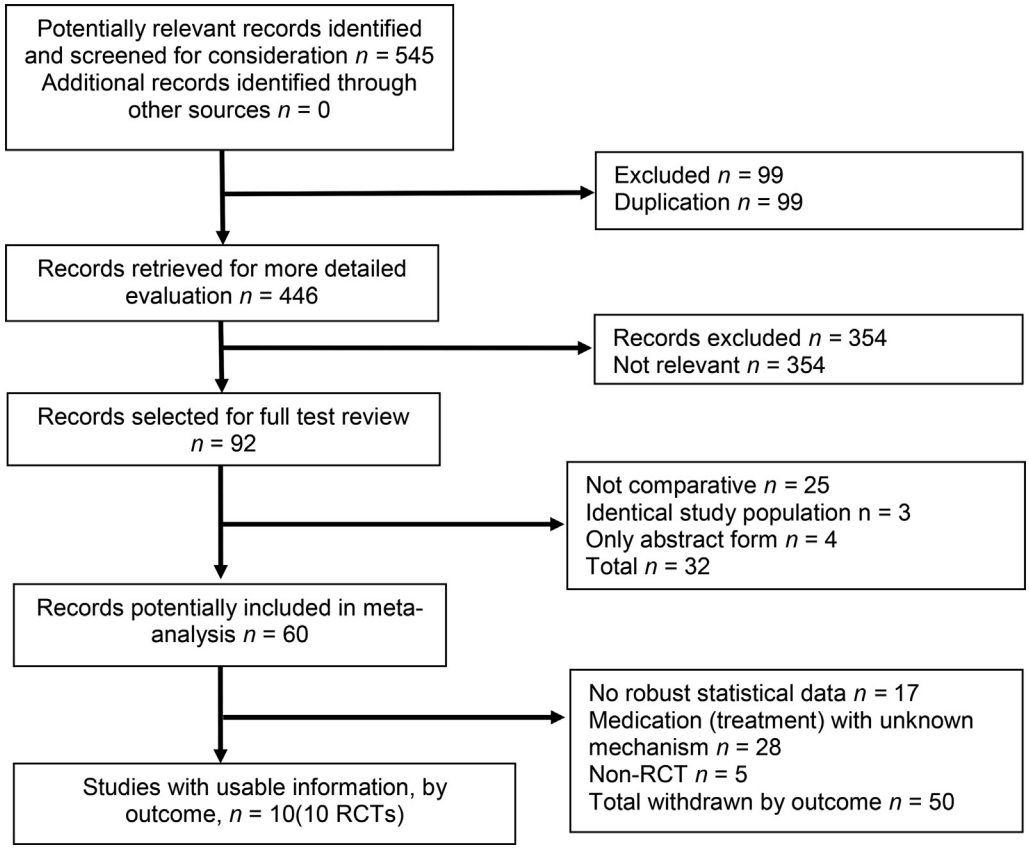

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram shows the selection of articles for analysis.

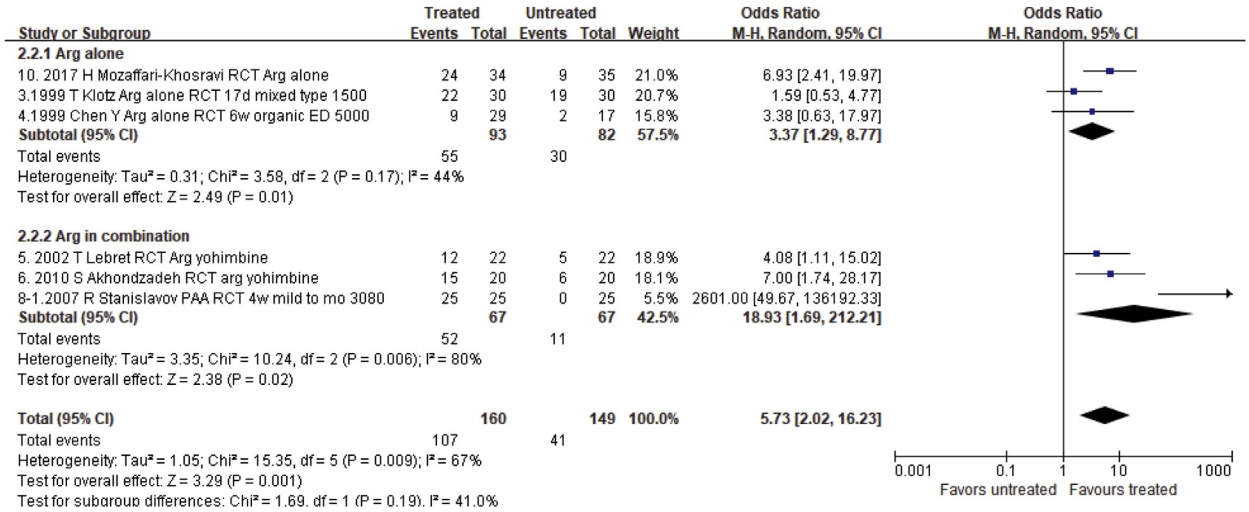

Figure 2. Improvement rate: subgroup analysis of improved erectile dysfunction (ED) with arginine alone and supplements combined with arginine. A random-effects model was used for meta-analysis. Figure 2 is available in color online at www.jsm.jsexmed.org.

IIEF Intercourse Satisfaction Score

The IIEF intercourse satisfaction score (Figure 3b) was assessed in 5 studies including 233 subjects. Arginine supplements caused a significant improvement in intercourse satisfaction (WMD 1.07 [0.32, 1.83], $P = .005$, $I^2 = 65\%$). There was no significant difference in the arginine-alone group (WMD 0.88 [−0.61, 2.36], $P = .25$, $I^2 = 86\%$); however, supplements combined with arginine demonstrated a meaningful difference (WMD 1.27 [0.56, 1.98], $P = .005$, $I^2 = 0\%$).

IIEF Sexual Desire Score

Sexual desire (Figure 3c) was evaluated in 5 studies including 233 subjects. Arginine supplements did not increase sexual desire (WMD 0.63 [−0.42, 1.68], $P = 0.24$, $I^2 = 92\%$). Both subgroups (alone vs combination) showed consistent results with no significant difference (WMD 0.13 [−0.41, 0.67], $P = .64$, $I^2 = 49\%$ and WMD 1.01 [−0.87, 2.88], $P = 0.29$, $I^2 = 94\%$, respectively).

IIEF Orgasmic Function Score

Orgasmic function (Figure 3d) was assessed in 5 studies including 233 subjects. Arginine supplements significantly improved orgasmic function (WMD 1.02 [0.29, 1.74], $P = .006$, $I^2 = 65\%$). In subgroup analysis, arginine alone significantly improved the orgasmic function score (WMD 0.73 [0.17, 1.30], $P = .01$, $I^2 = 0\%$). Although supplements combined with arginine did not show a statistically significant difference (WMD 1.23 [−0.20, 2.65], $P = .09$, $I^2 = 80\%$), it demonstrated meaningful trends on orgasmic function in favor of arginine ($P = .09$).

IIEF Score

Erectile function (Figure 3e) was evaluated in 4 studies including 276 subjects. Erectile function significantly improved with arginine supplements (WMD 4.39 [0.75, 8.02], $P = .02$, $I^2 = 96\%$). Both arginine alone and supplements combined with arginine caused improvement in the IIEF score (WMD 2.36 [1.15, 3.57], $P = .0001$, $I^2 =$ not applicable and WMD 5.11 [0.50, 9.71], $P = .03$, $I^2 = 95\%$, respectively).

Adverse Effect

Of 216 patients with arginine supplementation, including arginine alone and in combination, 16 patients experienced mild adverse effect (8.3%) compared with placebo (2.4%). The adverse effects included headache, itching, and insomnia, and no severe adverse effect was observed. The arginine-alone group presented even fewer complications, in that only 2 of 99 patients (2%) reported adverse effects. On the other hand, the placebo group showed no adverse effect.

Risk of Bias

The risk of bias graph and summary (Figure 4a) were constructed using RevMan software. 10 RCTs were evaluated on 6 categories including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Attribution bias (incomplete outcome data) was shown to have a relatively high risk in about 20% of the included studies because dropout was frequently observed in placebo groups owing to the ineffectiveness of placebo. Frequently, estimation of selective reporting was not possible because of lack of information. Publication bias was evaluated using a funnel plot, and no potential risk was detected (Figure 4b).

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis on the efficacy and safety of arginine or supplements combined with arginine for ED. The primary outcome measure was ED improvement, and the secondary outcome measures were IIEF-15 subdomain scores (overall satisfaction,

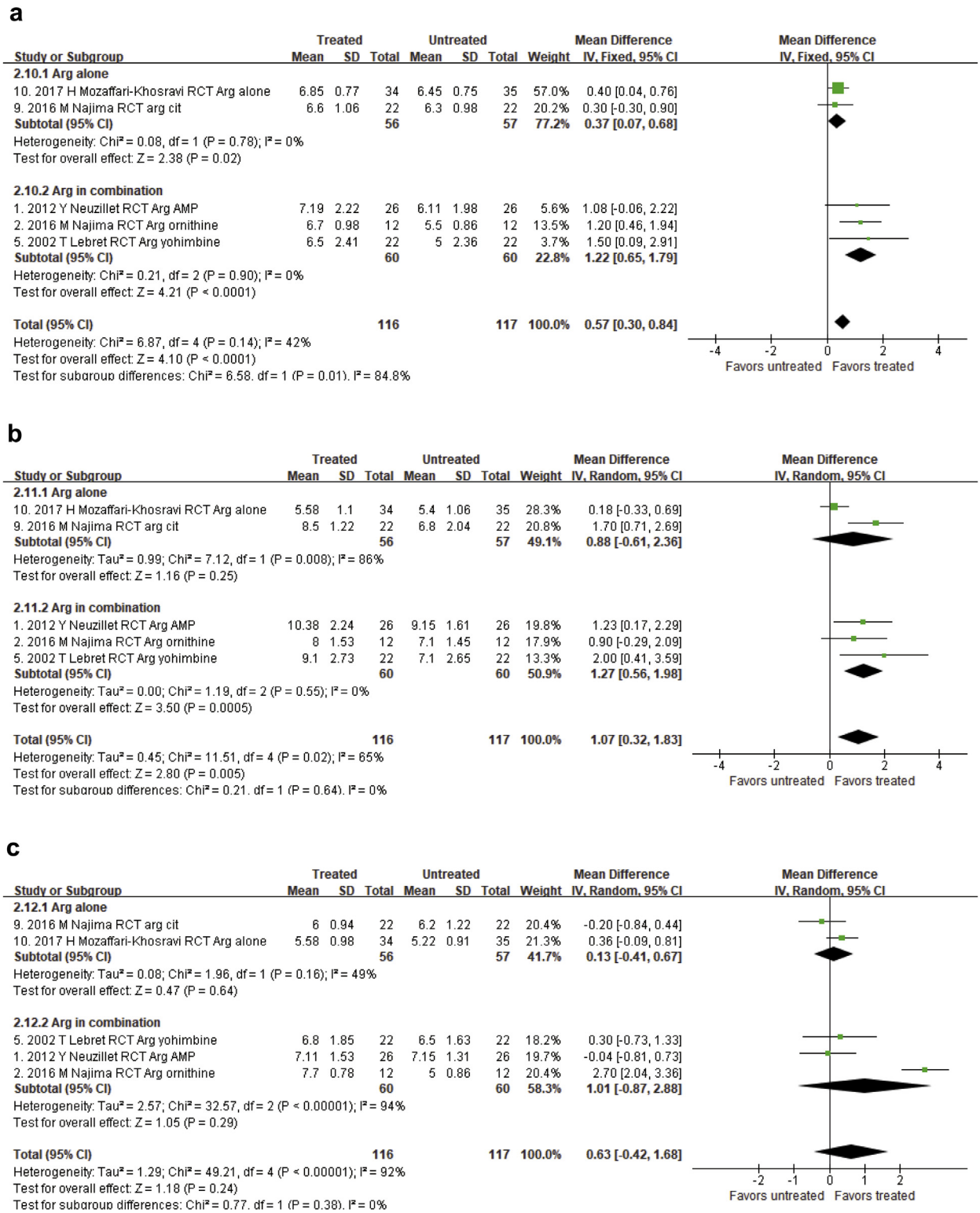

Figure 3. International Index of Erectile Function (IIEF) domain score: subgroup analysis for (Panel a) IIEF overall satisfaction score, (Panel b) IIEF intercourse satisfaction score, (Panel c) IIEF sexual desire score, (Panel d) IIEF orgasmic function score, and (Panel e) IIEF score. A random-effects model (Panels b, c, d, and e) and a Mantel-Haenszel fixed-effect model (Panel a) were used for meta-analysis. Figure 3 is available in color online at www.jsm.jsexmed.org.

intercourse satisfaction, sexual desire, orgasmic function, and erectile function). The results suggested that arginine, compared with placebo or no treatment, improves ED of mild to moderate severity.

As the only physiological substance for NOS, it was logical to try arginine as a treatment of ED,[35] and citrulline has the potential advantage over arginine because it escapes intestinal or

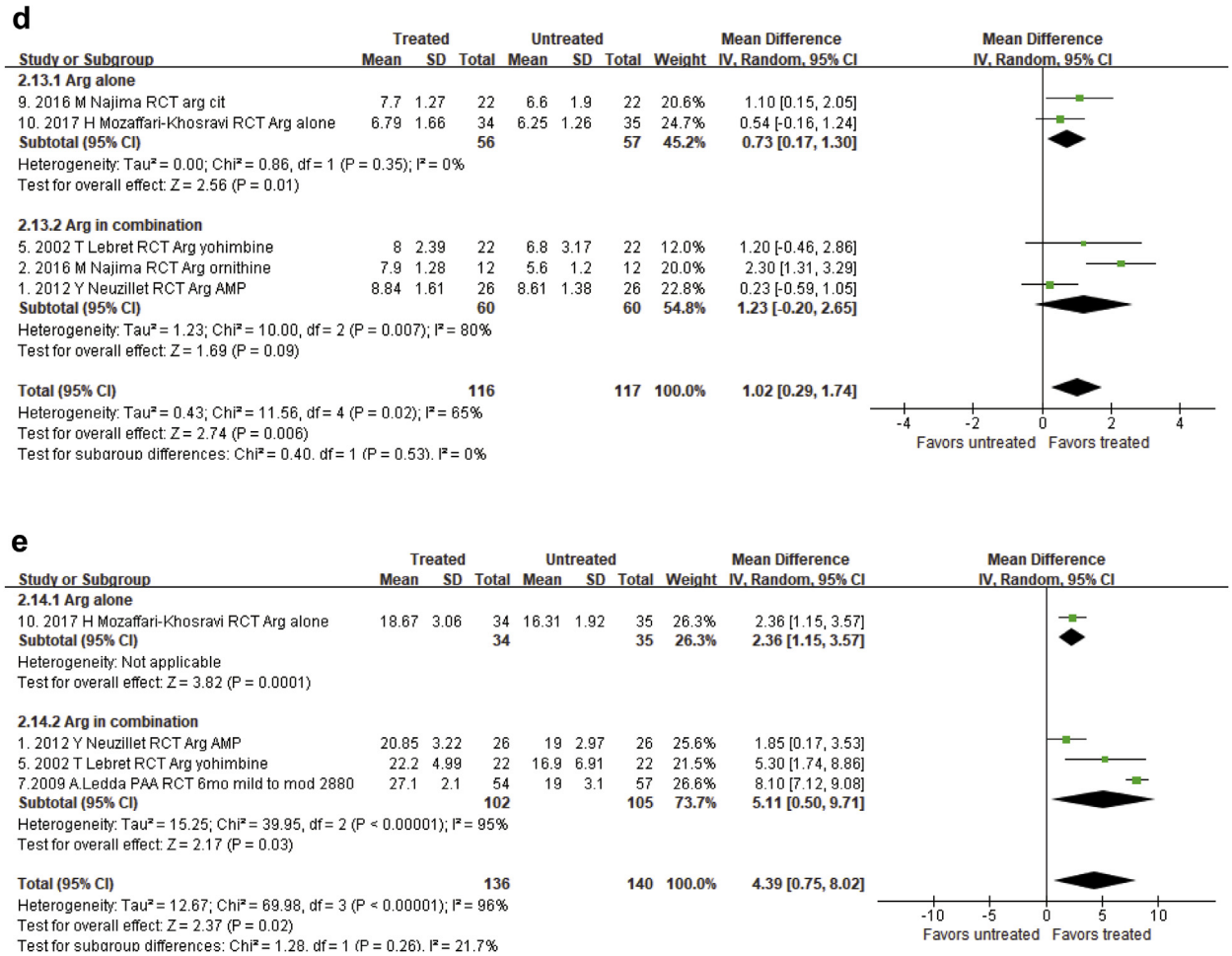

Figure 3. Continued.

hepatic metabolism and can be converted rapidly to arginine in the kidneys. Thus oral citrulline supplementation has been shown to increase the plasma arginine concentration and to amplify NO-dependent signaling in a dose-dependent manner.[36] We grouped citrulline and arginine in the same category because the rationale behind citrulline supplementation is to increase plasma arginine, the actual substrate for NOS. The overall results of our study suggested that arginine and citrulline may be beneficial in ED.

Several supplements have been combined with arginine to examine any synergistic effects. In this analysis, the combinations of arginine with yohimbine, pycnogenol, ornithine, or AMP were examined together because these supplements all involve an NO-producing pathway to some degree. Yohimbine is an alkaloid originating from the bark of the Central African yohimbine tree, which has α-adrenoreceptor—blocking activity.[37] Yohimbine blocks presynaptic α_2-adrenergic receptors, which, in turn, enhances the NO release from the nonadrenergic, non-cholinergic nerve.[29] In the United States, yohimbine exists as a Food and Drug Administration—approved medication called *yohimbine hydrochloride* and as a supplement form under 49 different brand names. The amount of yohimbine differs among various dietary supplements; however, most supplements contain lower quantities of yohimbine than the pharmaceutical drug.[38] In this discussion, the term "yohimbine" refers to the active ingredient of either the pharmaceutical drug or the supplement because a difference seems to exist in the quantity of yohimbine content. Although a meta-analysis and systemic review of yohimbine medication published in 1998 concluded that it is a reasonable therapeutic option for ED,[37] yohimbine medication alone may not be as effective because the predominant adrenoreceptors in the corpus cavernosum are α_1-adrenergic receptors.[39] Subsequently, later researchers conceived the idea of combining arginine with yohimbine.[29] The rationale behind this combination is that the substrate (ie, arginine) must be present before yohimbine can play a role in an NO-producing pathway. Indeed, Padma-Nathan et al[40] demonstrated that arginine with yohimbine significantly increases penile artery inflow measured with color-flow Doppler ultrasonography in men with ED. This result shows that the addition of arginine may overcome the disadvantage of less-dominant α_2-adrenergic receptors present in the corpus cavernosum and suggests that combining arginine with yohimbine may produce a synergistic effect.

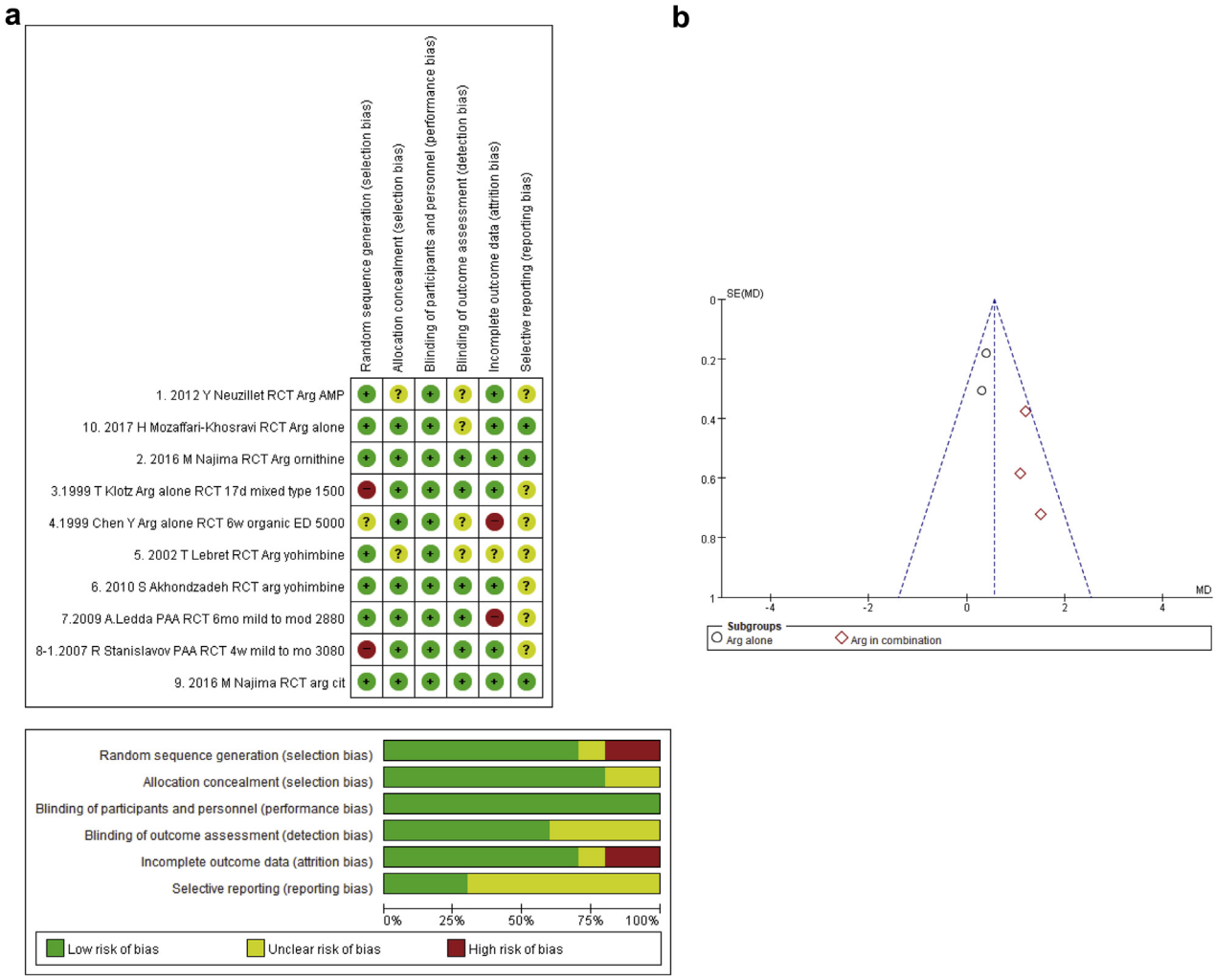

Figure 4. Bias evaluation. Panel a shows risk of bias in the included studies. Panel b shows the funnel plot for overall satisfaction. Figure 4 is available in color online at www.jsm.jsexmed.org.

Pycnogenol is an extract of French maritime pine bark (*Pinus pinaster*) that consists of a concentrate of polyphenols, mainly procyanidins.[41] Pycnogenol was proposed to improve ED by activating eNOS, which, in turn, increases NO production and promotes vasodilation.[42] In 2003, a group of researchers added arginine, a substrate of NOS, with pycnogenol, thereby not only stimulating the enzyme itself but also providing higher substrate quantities.[43] Although each formulation is mixed with different dosages, the results of this meta-analysis showed that arginine combined with pycnogenol can significantly improve ED. These supplements were not only effective, but they also have been shown to be safe.

Ornithine or AMP has also been combined with arginine to investigate any synergistic effects. Ornithine was reported to alleviate fatigue after working out[44] and may be converted into arginine through urea cycle,[45] thereby possibly increasing the serum arginine level. Ingestion of arginine combined with ornithine for 12 weeks induced improvement of male sexual function without adverse effects.[27] Oral AMP supplementation may increase the cyclic AMP level, which would then decrease the intracellular calcium concentration and consequently result in smooth muscle relaxation.[46] Increased cyclic AMP from AMP combined with increased cGMP from arginine may synergistically enhance smooth muscle vasodilation in penile arteries. Indeed, on-demand oral supplementation of such combination was shown to be effective in patients with mild to moderate ED, with minimal adverse effects.[26]

Although PDEi is currently the first-line treatment, arginine supplements can be attractive alternatives for patients with mild to moderate ED for several reasons. First, arginine supplements might be more psychologically accepted because they are perceived as nutrients rather than drugs. Cormio et al[17] demonstrated that all patients who reported improvement in the erection hardness score after citrulline administration continued with the same treatment rather than asking for a PDEi. The results of our analysis demonstrated that patients with ED may benefit from any arginine-containing supplements, whether it is arginine alone or in combination. It is interesting to note that, when arginine is combined with other substances, the combination may work synergistically and cause even greater

improvement (Figures 2 and 3). Second, the studies included in this review showed that arginine supplements have a relatively high safety profile. In this systematic review, 8.3% of patients treated with arginine supplements, both arginine alone and in combination, and only 2% of the arginine-alone group experienced adverse effects, none of them severe. This result implies the safety of arginine compared with PDEi. In a previous systematic review and meta-analysis on sildenafil, nearly half of the men (48%) randomized to sildenafil treatment reported at least 1 adverse event.[47] Moreover, McMahon et al[48] demonstrated that as much as 43.6% of patients treated with sildenafil may experience a moderate to severe adverse event. Sildenafil may be more effective in treating ED, but its stronger potency may be related to more adverse events. Therefore arginine supplements can be potential alternatives for patients who had already experienced adverse events with PDEi.

A recent study showed that a significant proportion of patients with ED have low arginine or citrulline level. Especially, this condition is more prevalent in patients with arteriogenic etiology.[49] Because our data suggest that arginine or other amino acids (citrulline, ornithine) that can increase serum arginine level can improve ED, these NOS substrates may be beneficial for the treatment of ED, particularly in patients with an arteriogenic cause.

Moreover, it was reported that higher levels of homocysteine are often observed in patients with ED.[50] In a rabbit model, hyperhomocysteinemia promoted a marked inhibitory effect on NO formation in isolated corpus cavernosum.[51] It was found that homocysteine directly inhibits the activity of dimethylarginine dimethylaminohydrolase, an enzyme that degrades asymmetric dimethylarginine. Asymmetric dimethylarginine is an endogenous inhibitor of NOS and can accumulate in the state of hyperhomocysteinemia.[52] On the basis of these results, it can be postulated that a high level of homocysteine may be an independent risk factor for ED by impairing the NO pathway. Interestingly, in other diseases associated with high levels of homocysteine, oral supplementation of arginine was shown to reduce its effect.[53–55] This result suggests that increased substrate levels of NOS may help overcome the inhibitory effect induced by homocysteine. Further studies should investigate the possible role of arginine in the presence of high levels of homocysteine.

Most important, a previous study demonstrated that arginine was effective as part of combined treatment with PDEi in patients with ED refractory to PDEi monotherapy.[56] This study implies that patients who were initially not responsive to PDEi possibly had low arginine to begin with, because PDEi can work only after sufficient cGMP is produced. If arginine is low, NO will not be sufficiently generated, and, if NO is insufficient, cGMP will not be produced subsequently. Therefore previous studies along with our result, which shows the additive effect of arginine, indicate the potential synergetic effect of arginine with the current first-line treatment (PDEi). A milestone might be reached if the addition of arginine to PDEi can increase the efficacy of treatment, thereby reducing the dosage of PDEi. Decreasing the dosage of PDEi is expected to partly overcome its adverse effects, which have been the primary disadvantage of this treatment. Measuring plasma arginine level may help identify the potential cause of refractory ED, and patients with low arginine would benefit the most from this synergistic combination. This idea should be confirmed in further studies.

Our meta-analysis has some limitations. First, the treatment dosage and duration varied among studies, which may have contributed to study heterogeneity. In addition, patients with severe ED were excluded from our analysis. Therefore our results cannot be applied to patients with severe ED. Moreover, the etiology of ED was not clearly identified. Thus it is difficult to interpret which type of ED would benefit the most from arginine or supplements combined with arginine. More high-quality studies distinguishing the severity and cause of ED and investigating the dose dependency of each supplement are necessary to establish which severity and type of ED would benefit the most from these supplements.

CONCLUSIONS

The results of our systematic review and meta-analysis provide evidence on the effectiveness and safety of arginine for mild to moderate ED. Arginine and supplements combined with arginine may play an important role in patients who are reluctant to take drugs or are experiencing adverse effects and economic burden.

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Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

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REFERENCES

1. Health NIo. Consensus Development Panel on Impotence. NIH Consensus Conference: Impotence. **JAMA 1993;270:83-90.**
2. Eardley I. The incidence, prevalence, and natural history of erectile dysfunction. **Sexual medicine reviews 2013;1:3-16.**
3. Vitezic D, Pelcic JM. Erectile dysfunction: Oral pharmacotherapy options. **Int J Clin Pharmacol Therap 2002;40:393-403.**
4. Aytac I, McKinlay J, Krane R. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. **BJU Int 1999;84:50-56.**
5. Chen D, Yan Y, Huang H, et al. The association between subclinical hypothyroidism and erectile dysfunction. **Pak J Med Sci 2018;34:621-625.**
6. Sansone A, Romanelli F, Sansone M, et al. Gynecomastia and hormones. **Endocrine 2017;55:37-44.**
7. Rastrelli G, Corona G, Maggi M. Testosterone and sexual function in men. **Maturitas 2018;112:46-52.**
8. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo-and hyperthyroid patients. **J Clin Endocrinol Metab 2005;90:6472-6479.**
9. Sansone A, Romanelli F, Gianfrilli D, et al. Endocrine evaluation of erectile dysfunction. **Endocrine 2014;46:423-430.**
10. Maggi M, Filippi S, Ledda F, et al. Erectile dysfunction: From biochemical pharmacology to advances in medical therapy. **Eur J Endocrinol 2000;143:143-154.**
11. Ückert S, Kuczyk MA, Oelke M. Phosphodiesterase inhibitors in clinical urology. **Expert Rev Clin Pharmacol 2013;6:323-332.**
12. Ückert S, Küthe A, Stief CG, et al. Phosphodiesterase isoenzymes as pharmacological targets in the treatment of male erectile dysfunction. **World J Urol 2001;19:14-22.**
13. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. **Eur Urol 2013;63:902-912.**
14. Boolell M, Gepi-Attee S, Gingell J, et al. Sildenafil, a novel effective oral therapy for male erectile dysfunction. **BJU Int 1996;78:257-261.**
15. Kim T-H, Jeon SH, Hahn E-J, et al. Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction. **Asian J Androl 2009;11:356-361.**
16. Davies KP. Development and therapeutic applications of nitric oxide releasing materials to treat erectile dysfunction. **Future science OA 2015;1(1).**
17. Cormio L, De Siati M, Lorusso F, et al. Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction. **Urology 2011;77:119-122.**
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **Int J Surg 2010;8:336-341.**
19. Jadad AR, Rennie D. The randomized controlled trial gets a middle-aged checkup. **JAMA 1998;279:319-320.**
20. Mozaffari-Khosravi H, Fallahi M, Afkhami-Ardekani M. Effect of oral supplementation of L-arginine on sexual function in men with type 2 diabetes: A double-blind clinical trial. **J Nutr Food Secur 2017;2:165-172.**
21. Klotz T, Mathers M, Braun M, et al. Effectiveness of oral L-arginine in first-line treatment of erectile dysfunction in a controlled crossover study. **Urol Int 1999;63:220-223.**
22. Chen J, Wollman Y, Chernichovsky T, et al. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. **BJU Int 1999;83:269-273.**
23. Najima M, Munekata M, Kohiyama R. Efficacy of supplement containing arginine and citrulline on male sexual function in healthy Japanese. **Healthcare and New Drugs 2016;12:50-62.**
24. Ledda A, Belcaro G, Cesarone MR, et al. Investigation of a complex plant extract for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study. **BJU Int 2010;106:1030-1033.**
25. Stanislavov R, Nikolova V, Rohdewald P. Improvement of erectile function with Prelox: A randomized, double-blind, placebo-controlled, crossover trial. **Int J Impot Res 2008;20:173-180.**
26. Neuzillet Y, Hupertan V, Cour F, et al. A randomized, double-blind, crossover, placebo-controlled comparative clinical trial of arginine aspartate plus adenosine monophosphate for the intermittent treatment of male erectile dysfunction. **Andrology 2013;1:223-228.**
27. Najima M, Munekata M, Kohiyama R. Efficacy of supplement containing arginine and ornithine on male sexual function in healthy Japanese. **Healthcare and New Drugs 2016;3:81-92.**
28. Akhondzadeh S, Amiri A, Bagheri AH. Efficacy and safety of oral combination of yohimbine and L-arginine (SX) for the treatment of erectile dysfunction: A multicenter, randomized, double blind, placebo-controlled clinical trial. **Iran J Psychiatr 2010;5:1-3.**
29. Lebret T, Herve JM, Gorny P, et al. Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: A new oral therapy for erectile dysfunction. **Eur Urol 2002;41:608-613; discussion 613.**
30. Borenstein M, Hedges LV, Higgins J, et al. References. Wiley Online Library; 2009.
31. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. **Stat Med 2002;21:1539-1558.**
32. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version; 2005.
33. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. **BMC Med Res Methodol 2014;14:135.**

34. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. **BMC Med Res Methodol 2005;5:13.**
35. Zorgniotti A, Lizza E. Effect of large doses of the nitric oxide precursor, L-arginine, on erectile dysfunction. **Int J Impotence Res 1994;6:33-35.**
36. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: Impact on nitric oxide metabolism. **Br J Clin Pharmacol 2008;65:51-59.**
37. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized clinical trials. **J Urol 1998;159:433-436.**
38. Cohen PA, Wang YH, Maller G, et al. Pharmaceutical quantities of yohimbine found in dietary supplements in the USA. **Drug Test Anal 2016;8:357-369.**
39. Andersson KE. Pharmacology of penile erection. **Pharmacol Rev 2001;53:417-450.**
40. Padma-Nathan H. Hemodynamic effects of the oral administration of a combination of arginine and yohimbine measured by color duplex ultrasonography in men with erectile dysfunction [poster]. 3rd Meeting of the European Society for Impotence Research (ESIR). January 30—February 2; 2000; Barcelona, Spain.
41. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. **Int J Clin Pharmacol Ther 2002;40:158-168.**
42. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. **Int J Clin Pharmacol Therap 2002;40:158-168.**
43. Ďuračková Z, Trebatický B, Novotný V, et al. Lipid metabolism and erectile function improvement by pycnogenol, extract from the bark of pinus pinaster in patients suffering from erectile dysfunction-a pilot study. **Nutr Res 2003;23:1189-1198.**
44. Sugino T, Shirai T, Kajimoto Y, et al. L-ornithine supplementation attenuates physical fatigue in healthy volunteers by modulating lipid and amino acid metabolism. **Nutr Res 2008;28:738-743.**
45. Shi HP, Fishel RS, Efron DT, et al. Effect of supplemental ornithine on wound healing. **J Surg Res 2002;106:299-302.**
46. Wyatt AW, Steinert JR, Wheeler-Jones CP, et al. Early activation of the p42/p44MAPK pathway mediates adenosine-induced nitric oxide production in human endothelial cells: A novel calcium-insensitive mechanism. **FASEB J 2002;16:1584-1594.**
47. Fink HA, Mac Donald R, Rutks IR, et al. Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. **Arch Intern Med 2002;162:1349-1360.**
48. McMahon CG, Samali R, Johnson H. Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. **J Urol 2000;164:1192-1196.**
49. Barassi A, Corsi Romanelli M, Pezzilli R, et al. Levels of l-arginine and l-citrulline in patients with erectile dysfunction of different etiology. **Andrology 2017;5:256-261.**
50. Sansone A, Cignarelli A, Sansone M, et al. Serum homocysteine levels in men with and without erectile dysfunction: A systematic review and meta-analysis. **Int J Endocrinol 2018;2018:7424792.**
51. Jones RW, Jeremy JY, Koupparis A, et al. Cavernosal dysfunction in a rabbit model of hyperhomocysteinaemia. **BJU Int 2005;95:125-130.**
52. Stuhlinger MC, Tsao PS, Her JH, et al. Homocysteine impairs the nitric oxide synthase pathway: Role of asymmetric dimethylarginine. **Circulation 2001;104:2569-2575.**
53. Rizzo A, Trisolini C, Spedicato M, et al. In vitro effects of L-arginine on spontaneous and homocysteine-induced contractility of pregnant canine uteri. **Theriogenology 2011;76:715-720.**
54. Rasic-Markovic A, Hrncic D, Krstic D, et al. The effect of subchronic supplementation with folic acid and l-arginine on homocysteine-induced seizures. **Can J Physiol Pharmacol 2016;94:1083-1089.**
55. West SG, Likos-Krick A, Brown P, Mariotti F. Oral L-arginine improves hemodynamic responses to stress and reduces plasma homocysteine in hypercholesterolemic men. **J Nutr 2005;135:212-217.**
56. Cumpanas A, Botoca M, Minciu R, et al. UP-3.114: Can L-arginine added to tadalafil improve the results on patients with erectile dysfunction non-responsive to tadalafil as monotherapy? **Urology 2009;74(Suppl):S330.**