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MEN'S HEALTH (R CARRION, SECTION EDITOR)

Alternative Treatment for Erectile Dysfunction: a Growing Arsenal in Men's Health

Wade Muncey[1,2] · Nicholas Sellke[1,2] · Tyler Kim[1] · Kirtishri Mishra[1,2] · Nannan Thirumavalavan[1,2] · Aram Loeb[1,2]

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Abstract

Purpose of Review To highlight and review encouraging preliminary studies behind several alternative products and interventions for erectile dysfunction (ED).

Recent Findings Alternative treatments for ED are becoming more prevalent with increased consumer interest. "Natural" products are sold online, and numerous clinics offer various off-label and investigational interventions. These alternative treatments have demonstrated varying degrees of efficacy in randomized trials and meta-analyses, but none of these interventions has robust enough evidence to be considered first-line therapy. These treatments may find a role in combination with guideline treatments or may be used in novel penile rehabilitation research protocols.

Summary With growing interest in alternative treatment for men's health, an awareness of the literature is imperative for patient counsel. Alternative treatments, like L-arginine, have a growing body of evidence for efficacy in combination with PDE5i, and low-intensity shock wave therapy and stem cell therapy continue to demonstrate encouraging outcomes in ED trials.

Keywords Erectile dysfunction · Alternative treatment · Extracorporeal shockwave therapy · Herbal supplements · Stem cell injections · Men's health

Introduction

Erectile dysfunction (ED) is one of the most prevalent sexual health conditions, with an estimated 18 million men affected in the USA alone [1]. ED is defined as the "consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity" [2]. It has been shown to significantly affect the quality of life of many afflicted men [3].

The current standard treatments, according to the 2018 American Urology Association (AUA) guidelines include the following: oral phosphodiesterase type 5 inhibitors (PDE5i), vacuum erection devices (VEDs), penile implants, intraurethral (IU) alprostadil suppositories, and intracavernosal injections (ICI) [4]. Oral PDE5i are the most common initial treatment of ED, but medical contraindications and decreased efficacy in advanced erectile dysfunction may prohibit this option [4]. While VEDs, penile implants, IU suppositories, and ICI are all viable therapies for ED, patients may not elect to undergo these treatments due to their varying levels of commitment and invasiveness. In addition, all currently recommended treatments treat the ED without causing a reversal of the pathophysiology. As such, patients may prefer

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✉ Wade Muncey
Wade.Muncey@uhhospitals.org

Nicholas Sellke
Nicholas.Sellke@uhhospitals.org

Tyler Kim
tjk148@case.edu

Kirtishri Mishra
kirtishri.mishra2@uhhospitals.org

Nannan Thirumavalavan
Nannan.Thirumavalavan@UHhospitals.org

Aram Loeb
Aram.Loeb@UHhospitals.org

[1] Case Western Reserve University School of Medicine, Cleveland, OH, USA

[2] University Hospitals Cleveland Medical Center, Urology Institute, Mailstop LKS 5046, 11100 Euclid Ave, Cleveland, OH 44106, USA

to try "natural solutions" and interventions that are available on the market but not necessarily FDA approved or recommended by the AUA or Sexual Medicine Society (SMS). In this review, we discuss the possible clinical uses, efficacy, and support for alternative therapies with existing and emerging literature in ED treatment.

Therapies Using Physical Energy

Low-Intensity Extracorporeal Shockwave Therapy

Low-intensity extracorporeal shockwave therapy (Li-ESWT) has received increased attention over the last decade with numerous studies attempting to demonstrate its effectiveness as a non-invasive treatment for ED. This modality was first proposed by Vardi et al. in 2010 as a proof-of-concept study, extrapolating from cardiovascular literature that Li-ESWT has the ability to induce neovascularization [5]. While the mechanism is not completely understood, it has been shown that energy meeting a target tissue creates cellular microtrauma, inducing signaling of angiogenic factors, and upregulation of nitric oxide (NO) [6, 7].

The novel use of Li-ESWT for ED was met with excitement as a possible curative or rehabilitative therapy. To date there are 7 meta-analyses evaluating Li-ESWT on ED that substantiate its short-term efficacy [8–14]. The trials primarily used either an electrohydraulic or electromagnetic generator, producing focused shocks to multiple sites on the penis. 1500 shocks/treatment with an energy density of 0.09 mJ/mm^2 was the most common regimen. The treatment schedule most commonly followed was twice weekly shockwave sessions for 3 weeks, a 3-week break, and then a second 3-week course. Despite the unanimous agreement that Li-ESWT may be a beneficial treatment for ED, the available meta-analyses differ in their limitations and numeric conclusions. Some studies included patients not only with ED but also with Peyronie's disease (PD) and data from nonrandomized-controlled trials [8, 12]. Lu et al. reported that International Index of Erectile Function (IIEF) scores of patients with mild ED had significant improvements, but patients with ED and PD did not [8]. Two meta-analyses did not include all the available RCT data at the time of their publication [9, 11]. Clavijo et al. included seven trials in their analysis, but 2 of these were extrapolated from conference abstracts [10].

The most recent meta-analyses have been more rigorous in their methods and have attempted to evaluate patients with vasculogenic ED only [13•, 14]. Campbell et al. found a statistically significant improvement in IIEF between treatment and sham at 1 month compared to baseline, with an increase of 4.23 ($p = 0.012$). Similarly, they found patients were six times more likely to have an erectile hardness score (EHS) ≥ 3 ($p = 0.0095$) [13•]. Sokolakis et al. included 10 RCTs in their analysis and found that the IIEF-EF score at final follow-up was significantly higher in the LI-ESWT group compared to sham, with a mean difference of 3.71 ($p = 0.03$). They also found more Li-ESWT patients achieved EHS ≥ 3 at follow-up when compared to the control group (OR 4.35 $p = 0.0009$) [14].

Despite these encouraging outcomes, there are still many unanswered questions for this treatment modality. Namely, the treatment protocol has not yet been standardized and validated, though several studies have attempted to establish this [15, 16]. Most trials followed the treatment regimen introduced by Vardi et al. which was modeled after the protocols performed in patients with cardiovascular disease [17]. Furthermore, identifying patients clinically who would maximally benefit from Li-ESWT is not well established at this time. One study suggested that younger patients (55.9 vs. 66.1 years) with a stronger response to PDE5i might have the greatest benefit [15]. At this time, the AUA defines Li-ESWT as investigational in their guidelines and it is considered experimental by the SMS, citing a lack of robust clinical evidence and regulatory approval.

Low-Intensity Pulsed Ultrasound

Over the last century, there has been growing interest surrounding therapeutic ultrasound as a modality to promote healing [18]. While the biological mechanism of low-intensity pulsed ultrasound (LIPUS) is unknown, recent studies have demonstrated its potential to induce angiogenesis, and investigators are evaluating it as a possible new non-invasive treatment for ED [19, 20]. The first LIPUS study for ED was performed by Lei et al. using a rodent model. Streptozotocin-induced diabetic rats were allocated into groups undergoing LIPUS with intensities at 100, 200, and 300 mW/cm^2 vs. Li-ESWT, and all interventions were compared to a non-diabetic rat control group. Therapy was completed 3 times per week for 2 weeks. Following a 2-week washout period, intracavernous pressure was measured by electrostimulation and found to be significantly improved for all interventions ($p \leq 0.05$). The greatest improvement was noted in LIPUS 300 mW/cm^2 and Li-ESWT groups [20].

The first clinical study was performed in 2019. Cui and colleagues conducted a blinded sham-controlled clinical trial in men with mild to moderate ED. LIPUS or sham treatment was applied to both sides of the penile shaft and crus, 2 times a week for 4 weeks. At 12 weeks, 54/80 (67.5%) of men in the treatment group scored significantly higher on the IIEF-EF compared to only 8/40 (20%) in the control group ($p \leq 0.05$). At 12 weeks, 73.08% had successful vaginal intercourse compared to 28.95% in the control group [21•]. There were no adverse events recorded. With favorable results in the animal model and first human trials, LIPUS has the potential to be a non-invasive and a safe option for mild to moderate ED that

could be offered as a clinic procedure. Further investigation with high-quality clinical evidence and discussion of technique, and treatment protocols are needed before widespread adoption. Neither the AUA nor SMS has issued statements regarding LIPUS.

Intracavernosal Injection Therapies

Stem Cell Therapy

Stem cells have the ability to differentiate into various cell types and repair damaged tissues [22, 23]. Their use for ED has been studied over the last decade, but the majority of research has been in animal models [24]. The most common delivery of stem cells is by cavernosal injection, with early animal studies demonstrating restoration of erectile function in cavernosal-injured mice [25, 26]. The mechanism by which stem cells lead to this benefit has not yet been fully elucidated. Key clinical trials to date are listed in Table 1. Bahk et al. published the first study in 2010 that described injection of umbilical cord cells into the corpora of 7 men with ED and diabetes. They found that 3 men regained morning erections by 1 month, and 2 men were able to achieve penetration, maintenance, and orgasm with the addition of a PDE5i [27]. In 2015, Yiou et al. administered bone marrow stem cells in 12 men following radical prostatectomy. The men were evenly split into 4 groups, each participant received one injection, and each group had increasing doses of stem cells (2×10^7, 2×10^8, 1×10^9, and 2×10^9 cells). At 6 months, 9 out of 12 patients were able to achieve successful penetration with PDE5i, and significant improvement in spontaneous erections was seen with the two highest dose groups ($p = 0.012$) [28]. After a mean follow-up of 62 months, the 12 patients demonstrated a nonsignificant decline in the IIEF-scores, suggesting a possible need for repeat injections with a longer follow-up [29]. The first autologous bone marrow–derived stem cell injections in 4 diabetic patients with ED was performed in 2018; the results demonstrated both significant improvement in IIEF scores at 1 year ($p = 0.04$) as well good tolerability and safety of the stem cell harvest procedure [30]. Another recent study evaluated a single injection of adipose-derived stem cells into the corpora of men with ED following radical prostatectomy. They found that 8 out of the 17 men regained erectile function without the use of medications, but this effect was only demonstrated in men who also regained urinary continence and had a normal preoperative erectile function. Potency was absent in those who remained incontinent at 6 months [31]. A follow-up survey at 1 year found that erectile function was sustained for those who regained function initially [32]. Finally, a recent study by Protogerou et al. evaluated the efficacy of adipose-derived stem cells combined with platelet lysate injection for organic erectile dysfunction and found that at 1- and 3-month follow-up, there was a significant improvement in IIEF-5 scores ($p \leq 0.05$) [33].

There is mounting evidence suggesting the benefit of stem cells for management of organic erectile dysfunction, but patients willing to undergo ICI should be counseled that currently available vasoactive agents have demonstrated superior efficacy. At this time, it is unclear if alterations in the source, dose, or repeat injections would be beneficial to improve durability, and current studies are mixed regarding a role following radical prostatectomy. The AUA and SMS consider stem cell injection therapy to be experimental.

Platelet-Rich Plasma

Intracavernosal injection of platelet-rich plasma (PRP) is an emerging therapy for men with ED. Despite there being little data supporting its efficacy, it is quickly becoming commercial with marketing directed at patients through the internet and social media platforms [34]. PRP is harvested from the patient's own blood and centrifuged to remove all RBCs. A platelet count > 1,000,000 U/mL is the concentration goal, and numerous growth factors that promote angiogenesis and wound healing are found in the supernatant [35–37]. The exact mechanism by which PRP works is not yet clear, but its potential to improve ED has been demonstrated in several animal studies [38–40]. There are only two human studies published to date, and only one in English [41, 42]. The most recent study in 2018 was a small-cohort retrospective review involving 16 male patients with ED and/or PD who had received PRP injections. Of these, only 4 men had organic ED. The patients were followed for an average of 15.5 months, and over that time received an average of 2.1 injections. The injections resulted in no major complications and IIEF-5 scores improved by an average of 4.14 points at the conclusion of the trial amongst all men [41]. To date, PRP injections for the treatment of ED lack robust clinical data to support its efficacy. Practitioners and patients should be abundantly aware that PRP for ED is an off-label use and regarded by both the SMS and AUA as an experimental therapy.

Amino Acids

L-Arginine

L-Arginine is a semi-essential amino acid and serves as a precursor of NO. Nitric oxide synthase (NOS) catalyzes the oxidation of L-arginine, produces NO, and begins an enzymatic cascade that results in penile tumescence [43, 44]. There has been continued interest in L-arginine for treatment of ED. Of note, it is the most studied ingredient found in online ED supplements and the most common amino acid included in men's health supplements [45, 46].

Table 1 Summary of key studies on alternative therapies for ED in the last decade (2010–2020)

Author	Study type	Proposed mechanism of action	Key findings	Limitations	Conclusions
Li-ESWT					
Campbell et al. [13•] (2019)	Meta-analysis (7 RCT)	Angiogenesis by release of growth factors ·Neuronal regeneration	·Increased IIEF-EF: + 4.23; ($p = 0.012$) ·EHS improvement RR = 6.63 (95% CI: 1.59, 27.71), $p = 0.0095$	·Inconsistent reporting and methodology ·Small trial sizes ·Limited follow-up data	·Potential restorative therapy for vasculogenic ED with two recent meta-analysis finding improvement in erectile function. ·AUA: Investigational
Sokolakis et al. [14] (2019)	Meta-analysis (10 RCT)		·Increased IIEF-EF: +3.97; ($p < 0.0001$) ·EHS improvement ≥ 3: OR = 4.35; (95% CI: 1.82–10.37); $p = 0.0009$	·Inconsistent reporting and methodology ·Small trial sizes ·Limited follow-up data	·SMS: Experimental
LIPUS					
Lei et al. [20] (2015)	Randomized, controlled study in diabetic rat model	·Alleviate fibrotic changes induced by diabetes	·Increased SM content, collagen I/collagen III ratio and NOS expression ·ICP improvement using intensity levels 100 to 300 mW/cm^2; $p < 0.05$	·Results may not correlate with chronic diabetes in humans ·Optimal intensity levels not demonstrated	·Potential non-invasive, portable or office-based, restorative treatment for ED ·Initial studies are encouraging ·Additional RCTs will be needed prior to recommending ·No statement from AUA/SMS
Cui et al. [21•] (2019)	Randomized, double blind, sham-controlled clinical study	·Local tissue regeneration, and anti-inflammatory effect	·IIEF response ≥ 2 points at 12 weeks = 54/80 (67.50%); $p < 0.001$ ·IIEF average score increase at 12 weeks = +4.29; $p < 0.05$	·Only 10 patients in treatment arm ·Length of follow-up only 12 weeks	·Potential non-invasive, portable or office-based, restorative treatment for ED ·Initial studies are encouraging ·Additional RCTs will be needed prior to recommending ·No statement from AUA/SMS
Stem cell injections					
Bahk et al. [27] (2010)	Prospective, single-blind study	·Unknown, possible tissue healing and regeneration	·Morning erections at 1 month in 1 man ·Erection and orgasm with PDE5i at 6 months in 2 men	·Findings not significant ·No placebo control ·Small study size (7 patients)	·Potential restorative therapy for treatment of ED with generally positive findings ·Small body of evidence, with limited sample sizes ·Most studies lacking placebo control ·Significant variation in treatment protocols, hindering adoption in clinical practice ·Invasive without demonstrable long-term safety ·AUA: Investigational ·SMS: Experimental
Yiou et al. [28, 29] (2016, 2017)	Prospective, nonrandomized, dose-escalation, phase 1 and 2 pilot clinical trial		·Improved IIEF- EF with PDE5i compared to baseline erectile function (17.4 vs. 7.3 $p = 0.006$) ·Higher doses of SCI demonstrated improved EHS at 6 months compared to low doses, $p = 0.012$ ·Nonsignificant decline in the IIEF-scores seen in phase 2 follow-up study (2017)	·Small sample size makes it difficult to assess true dose effects ·No placebo control	
Haahr et al. [31, 32] (2016, 2018)	Prospective, single-arm, phase 1 and 2 clinical study.		·Erectile function and intercourse accomplished in 8/17 men without PDE5i ·IIEF-5 scores in continent men increased from a median of 7 to 17 after 6 months; $p = 0.0069$· No improvement at 12 months in men who remained incontinent in phase 2 follow-up study (2018)	·Only men who regained continence following prostatectomy regained erections ·No placebo control group, ·Unclear if stem cells helped regenerate erectile function vs. natural course following prostatectomy	
	Prospective, phase 1 clinical trial			·Only 4 patients included	

Table 1 (continued)

Author	Study type	Proposed mechanism of action	Key findings	Limitations	Conclusions
Demour et al. [30] (2018)			·Demonstrated safety and tolerability of autologous bone-marrow SCI ·Improved IIEF-EF; $p = 0.03$	·No placebo control	
Protogerou et al. [33] (2019)	Prospective phase 1, single-center pilot study		·Improved IIEF scores at 3 months in both groups of patients, (stem cells + platelet lysate[PL] vs. PL only); $p < 0.05$	·Small sample size ·PL alone resulted in significant improvement in IIEF ·Without placebo control or SCI alone comparison	
Platelet-rich plasma					
Matz et al. [41] (2018)	Retrospective review	·Growth factors found in PRP promote recovery of erectile function	Average IIEF improvement of 4.14 after 2 injections	·Retrospective ·Only 4 subjects with isolated ED	·No prospective RCTs demonstrating efficacy, safety, or risks. ·AUA/SMS: experimental
L-Arginine					
Rhim et al. [49] (2019)	Meta-analysis (10 RCT)	·Oxidation of L-arginine produces NO, relaxing corporal smooth muscle	·Improvement in ED compared to placebo: OR = 3.37 (95% CI: 1.29–8.7); $p = 0.01$ ·Increased IIEF + 4.39 (mean difference); $p = 0.02$	·Included RCT had varying doses and durations of treatment ·Patients with severe ED were excluded ·Did not include studies combining PDE5is	·Plausible mechanism of action ·It appears superior to placebo for mild to moderate ED ·The optimum dose or treatment protocol is not defined
Taeib et al. [50•] (2019)	Double-blind, randomized, controlled clinical trial	·L-Arginine increases NO and cGMP, and PDE5is allow higher levels to accumulate	·Increased IIEF-5 in combination vs. placebo: 23.52 vs 13.28; $p < 0.001$ ·Combination improved IIEF vs. either monotherapy; $p < 0.001$	·Only men with DM2 included, excluded patients with HTN and smoking history ·Only 8 week follow-up ·Did not include men with severe ED	·Emerging studies have demonstrated superior efficacy when combined with PDE5i ·Can be offered to men with unsatisfactory or failed response with PDE5i ·AUA: lacking enough evidence to make generalizations
Gallo et al. [51] (2020)	Prospective, randomized, multicenter study		·Combination therapy was superior in improving IIEF vs. either monotherapy ·Mean increase in IIEF-EF score after combination therapy was 7.1; $p < 0.0001$	·No placebo group ·Excluded men with diabetes	·SMS: no position statement
El-Wakeel et al. [53] (2020)	Randomized controlled study		·Improvement in ED grade based on IIEF-5 with combination therapy; $p < 0.0001$ ·IIEF improvement in combination vs. sildenafil alone (19.8 vs.18.5); $p = 0.05$)	·Short follow-up (8 weeks) and small sample size ·No placebo-control group	
L-Citrulline					
Cormio et al. [60] (2011)	Single-blind, placebo-controlled, prospective pilot study.	·L-Citrulline is converted to L-arginine in the kidney, thereby producing NO	·12 out of 24 men taking L-citrulline had improvement in EHS > 3; $p < 0.01$ ·Mean intercourse episodes increased 2.3 per month; $p < 0.01$	·Did not report IIEF scores ·No comparison to PDE5i	·Plausible mechanism of action ·Appears safe from limited studies ·No publication to date reporting a significant improvement in IIEF scores
Shirai et al. [63] (2018)	Randomized, double-blind, placebo-controlled crossover pilot study	·Transresveratrol upregulates NOS and the combination with L-citrulline may be synergistic	·SHIM score improved with combination compared to placebo; $p < 0.05$ ·No statistical significant improvement in EHS	·Only 1-month follow-up ·No L-citrulline monotherapy ·Allowed on-demand PDE5i, but no comparison with PDE5i monotherapy	·AUA/SMS: No position statement
Ginseng					
Borrelli et al. [70] (2018)	Meta-analysis (5 RCT)	·Increasing NOS activity and relaxing corporal smooth muscle	·Effective in treating ED in all included trials ·Increased IIEF-EF: standard mean difference 0.43 (95% CI: 0.15–0.7); $p = 0.012$	·Small number of trials included in meta-analysis ·Inconsistent methodology in RCTs ·Inconsistent scoring systems in RCTs	·Limited, heterogeneous trials preclude recommendation ·AUA: Lacking enough evidence to make generalizations ·SMS: No position statement

Table 1 (continued)

Author	Study type	Proposed mechanism of action	Key findings	Limitations	Conclusions
Hyperbaric oxygen therapy					
Yuan et al. [85] (2011)	Prospective, randomized, placebo-controlled study	·Increased O2 delivery to tissues leading to angiogenesis and healing	·Following urethroplasty: IIEF-5 scores significantly higher in HBOT group compared to control (19.17 vs. 15.67); $p < 0.05$	·Only 3-month follow-up, small study size, younger population (< 45 years old)	·Potential restorative therapy for treatment of ED with generally positive findings ·Small body of evidence, with limited sample sizes and placebo-control
Hadanny et al. [86•] (2018)	Prospective, uncontrolled clinical study		·Increased IIEF-EF: 21.9 post-HBOT vs. 11.4 pre-HBOT; $p < 0.0001$ ·Increased penile perfusion on MRI: 153.3 43.2% of Ktrans values; $p < 0.0001$.	·Only 3-month follow-up ·Small study size, no control group	·No defined treatment protocol ·Potentially cost prohibitive ·AUA/SMS: No position statement
Sahin et al. [87] (2018)	Prospective, uncontrolled clinical study		·Increased IIEF-EF: 19.5 post-HBOT vs. 15.74 pre-HBOT; $p < 0.001$	·No control group ·Heterogeneous patient sample with various HBOT indications.	
Chiles et al. [89] (2018)	Prospective, double-blind, placebo-controlled, randomized study		·No difference in IIEF score in sildenafil daily + HBOT vs. sildenafil + room air	·Men in the placebo "room air" group actually received air with a partial pressure two times higher than oxygen at standard atmospheric conditions.	
Sen et al. [88] (2020)	Prospective, uncontrolled clinical study		·Increased IIEF-EF: 25.4 post-HBOT vs. 20.6 pre-HBOT; $p < 0.001$	·No control group ·Heterogeneous patient sample with various HBOT indications.	
Penile vibratory stimulation					
Fode et al. [92] (2014)	Prospective, randomized, control study	·Restoration of erectile function by stimulation and activation of pelvic nerves	·Non-significant increase IIEF-5 score in PVS vs. control group: 18 vs. 7.5 at 12 months; $p = 0.09$	·Small study population ·No placebo-control treatment ·Treatment arm had significantly more LUTS preoperatively compared to control	·No publication to date reporting a significant improvement in IIEF scores ·AUA/SMS: No position statement

L-Arginine has the ability to increase systemic concentrations of NO when taken in supraphysiologic doses [47]. The importance of dosing was first seen in the earliest trials evaluating its efficacy. In 1999, Klotz et al. found that 500 mg 3 times a day did not demonstrate significant benefits [48]. On the contrary, several studies showed that erectile function improved when taking larger doses: between 2.8 and 6 g/day [43, 44]. The first systematic review and meta-analysis was published in 2019 by Rhim et al. where they evaluated the efficacy of L-arginine on ED, both as monotherapy and in conjunction with other over the counter supplements. They concluded that for the treatment of mild to moderate ED, L-arginine was more beneficial than placebo at doses of 1500 to 5000 mg with a low adverse event rate. Concomitant dosing of other supplements involved in an NO-producing pathway (e.g., yohimbine, pycnogenol, ornithine, and AMP) leads to more pronounced improvement in ED than L-arginine alone [49]. This review did not include the most recent studies describing the efficacy of taking PDE5i in combination with L-arginine.

Several RCTs have evaluated tadalafil in combination with L-arginine. The first was conducted in 2019 which found that that L-arginine (5 g) taken in combination with tadalafil increased IIEF-5 scores significantly compared to either L-arginine or tadalafil separately ($p \leq 0.001$) [50•]. A second trial was published in 2020 which again found that combination therapy with both tadalafil and arginine (2.5 g) once a day was superior to either monotherapy for patients with mild and severe ED [51].

L-Arginine with sildenafil has also been evaluated. The first study in 2001 found the combination to be equally as effective as sildenafil alone. However, this study was performed on post-radical prostatectomy patients and, regrettably, improvement was measured by a buckling test, rather than IIEF-5 score [52]. In 2020, sildenafil was compared with sildenafil + L-arginine for patients with organic ED. They found that the combination resulted in a statistically significant improvement of ED grades based on IIEF-5 scores compared to sildenafil alone ($p \leq 0.0001$) [53]. It appears that L-arginine can be successful in improving erectile function and may be a good option for patients in combination with PDE5i before progressing to invasive options. It may also be beneficial for men seeking a more "natural" solution for their ED. A greater body of evidence will be necessary prior to adoption by the AUA guidelines as an adjunctive ED treatment.

L-Citrulline

L-Citrulline is a semi-essential amino acid that is found both in the diet (e.g., watermelon) and is synthesized in the intestinal tract from glutamine. L-Citrulline is involved in NO production after being converted to L-arginine in the kidney (Fig. 1). When taken orally, L-citrulline avoids both hepatic first-pass and intestinal bacteria metabolism [54–56]. In fact, L-citrulline has been shown to increase blood levels of L-arginine *better* than oral L-arginine with higher productions of NO [57, 58]. Men with severe ED have also been shown to have lower blood levels of citrulline and arginine, and oral supplementation could possibly represent a modifiable risk factor [59•]. Despite biologic plausibility, few experiments have been performed on humans. The first study was published in 2011 with a small cohort of 24 patients. Cormio et al. found that oral L-citrulline (1.5 g/day) resulted in significant improvement in EHS compared to placebo ($p \leq 0.01$). They did not evaluate IIEF-5 scores [60]. Following this study, several rodent experiments were published that demonstrated NO production increased and intracavernosal pressure improved after oral L-citrulline administration [61, 62]. A second human trial performed in 2018 combined oral L-citrulline and trans-resveratrol vs. placebo with outcomes measured by EHS and Sexual Health Inventory for Men (SHIM) scores. Thirteen men completed the study. They found a significant improvement in mean SHIM scores with treatment vs. placebo ($p \leq 0.05$), but no difference in EHS. IIEF-5 scores were not evaluated [63].

Most recently, a study was published evaluating pre- and post-op interventions for penile rehabilitation following nerve-sparing radical prostatectomy. One patient group began L-citrulline (3 g) and tadalafil daily for 2 weeks prior to surgery and a second group did not. Both groups then took citrulline and tadalafil postoperatively. They found that men who began tadalafil and citrulline prior to surgery were more likely to report return of erectile function at 12 months [64]. Overall, there are few studies on L-citrulline and those that are available generally have short follow-up, small sample sizes, and various reporting methodologies. A formal evaluation of PDE5i combination studies vs. placebo is warranted.

Herbal Supplements

Ginseng

Ginseng is one of the most extensively studied nutraceuticals in human sexual health and is the most common ingredient found in top-selling erectile dysfunction supplements [45, 47]. Physiologically, it has demonstrated an ability to increase penile blood flow by increasing activity of NOS, amplifying production of NO. Several rabbit models demonstrated this pathway, describing a dose-dependent relationship with ginseng and corpus cavernosum relaxation [65, 66]. The first meta-analysis was completed in 2008 by Jang et al., evaluating its efficacy in treating ED. The authors included 7 RCTs in their review and found that 6 studies demonstrated improvement in erectile function compared to placebo. Of note, the methodology between the reviewed studies was highly heterogeneous: dosing ranges from 600 mg TID to 1000 mg TID with mixed etiologies of ED. Despite the lack of generalizability in their conclusions, they were able to demonstrate that ginseng is more effective than placebo [67]. A decade later,

the findings from the previous study were confirmed in an updated meta-analysis that included more recent RCTs [68–70]. Despite the apparent benefit over placebo, the AUA states there is insufficient evidence to make recommendations. Standardized dosing protocols will be crucial in future studies prior to routine utilization in a clinical practice.

Yohimbine

Yohimbine is an alpha-2 antagonist that is extracted from central African yohimbine tree bark [71]. It is thought to work by increasing arousal, stimulating the sympathetic drive and consequently enhancing sexual function [72]. In 1998 the first and only systematic review and meta-analysis was performed by Ernst et al. Their review included 7 randomized, placebo-controlled, double-blind clinical trials, and they concluded that yohimbine is clinically more effective than placebo with rare adverse events [71]. Since this time, only one small monotherapy study has been performed, with only half of participants (9/18, no placebo arm) responding to supplementation [73]. More recent randomized control studies have evaluated yohimbine in combination with L-arginine and demonstrated a synergistic effect, significantly improving IIEF scores [74, 75]. Still, at present there is no study evaluating the efficacy of yohimbine vs. PDE5i, and similar to ginseng, the AUA does not believe there is enough evidence to recommend its use.

Topical Alprostadil

Interventions requiring cavernosal injection or intraurethral suppository have demonstrated to be effective, but the adverse experiences can be significant with a high dropout rate [76]. To address these shortcomings, a new delivery method was developed for alprostadil. As a prostaglandin E1 (PGE1) analogue, alprostadil activates an enzymatic cascade that results in an increase of cAMP and ultimately corporal smooth muscle relaxation [77]. The cream is applied onto the meatus of the penis with effects beginning as early as 30 min [78].

Topical alprostadil became available in Europe in 2014 based largely on the results from 2 phase III studies that evaluated its efficacy for ED [79]. Padma-Nathan et al. in 2006 published 2 randomized, double-blind, placebo-controlled trials, identical protocols, and reported an integrated analysis. The study included 1732 patients, who were given either 100, 200, or 300 μg of alprostadil for 24 single doses over a 12-week period. Compared to baseline, alprostadil cream at 200–300 μg showed a statistically significant increase in IIEF-EF (2.5 point) and improved Sexual Encounter Profile scores (vaginal penetration and maintenance to ejaculation) ($p \leq 0.001$). They reported the adverse events were mild and localized, with only 4% of participants discontinuing treatment during the trials [78].

A long-term study was performed in 2009 evaluating the safety, efficacy, and adjustable dosing of topical alprostadil. Of the 995 patients receiving treatment, 846 (72%) titrated to 300 μg and demonstrated significant improvement in EF at the time of study closure ($p \leq 0.001$). Similar to the previous studies, only 5% of patients discontinued treatment due to adverse events [80]. Despite these encouraging results, topical alprostadil has failed to receive FDA approval twice: first in 2008, and recently in 2018 due to concerns regarding the safety of the 2.5% concentration of the chemical DDAIP, which improves its absorption [81]. Topical alprostadil has the benefit of avoiding systemic side effects in patients on nitrate medications and could still be efficacious for men post-radical pelvic surgery. At this time, this product is currently only available in Europe and Canada.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) involves administration of 100% oxygen at a pressure greater than 1 standard atmosphere. The exact mechanism is not clear, but this therapy has been shown to increase blood perfusion and promote healing [82]. Creating a hyperbaric environment leads to increased dissolved oxygen levels in the blood and increased oxygen delivery to tissues, inducing angiogenesis [83]. The first study suggesting the possible therapeutic effect of HBOT on ED was proposed in 2008. Muller et al. evaluated the effects HBOT on the recovery of erectile function in rodents who had undergone cavernous nerve crush injury. They found that rodents who underwent HBOT had a significant improvement in erectile hemodynamics vs. rodents that did not [84].

Yuan et al. in 2010 published the first clinical study evaluating HBOT on erectile function recovery following posterior urethroplasty. There was a total of 24 men separated into 2 groups, with 12 assigned to HBOT postoperatively. The treatment group underwent 14 sessions of HBOT, and all patients were assessed at 3 months follow-up with IIEF scores. In both groups the IIEF scores statistically decreased, but the scores were statistically higher in the HBOT group compared to the control group ($p \leq 0.05$) [85]. Hadanny et al. were the first to suggest that HBOT may also improve chronic non-surgical ED. They accrued 30 patients who completed 40 hyperbaric sessions and found significant improvements in erectile function based on IIEF scores ($p = 0.0001$). Of these patients, 7 agreed to undergo a dynamic contrast-enhanced MRI pre- and post-HBOT. They found that HBOT resulted in significant improvements in penile perfusion ($p = 0.0001$) [86•]. Several recent studies have replicated these findings for non-surgical ED patients, concluding a therapeutic effect [87, 88].

To date, only one recent study has found HBOT to *not* be beneficial for ED. Chiles et al. randomized patients who had undergone nerve sparing radical prostatectomy to sildenafil

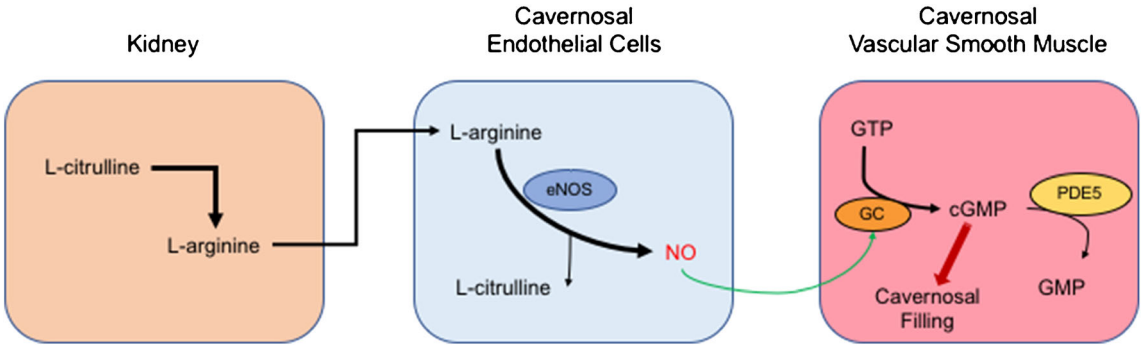

Fig. 1 Citrulline-NO cycle. eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase-5; GMP, guanosine monophosphate

50 mg with HBOT vs. sildenafil with room air. At 18 months, no significant difference was observed in IIEF scores [89]. At this time there is no set protocol regarding number of sessions, length of treatments, target pressures, or understanding of who would benefit most from this therapy. In comparison to other therapies, it requires greater patient commitment and cost, and unlike Li-ESWT, fewer human trials have been performed to demonstrate its success.

Penile Vibratory Stimulation

Penile vibratory stimulation (PVS) for the treatment of erectile and ejaculation dysfunction was first reported in 1965, but a consumer device was not approved by the FDA as a treatment for ED until 2011 [90]. The device is thought to stimulate erection through vibratory stimulation of the pudendal nerve, triggering a reflex parasympathetic response [90]. The first clinical proof-of-concept study was performed by Segal in 2013. His group tested the device on 5 men with normal erectile function and found that after PVS, 4 reported an IIEF-EF of 30/30 and the fifth had an IIEF-EF of 29/30, with no adverse effects [91]. The following year, Fode et al. conducted a RCT investigating the effect of PVS in preserving and regaining erectile function following nerve sparing radical prostatectomy. In total, 30 patients were randomized to use PVS daily, beginning 1 week prior to surgery and for 6 weeks postoperatively. At 12 months, patients in the control group had a mean IIEF-5 of 7.5 compared to 18.5 in the treatment group. Despite this encouraging trend, these results did not reach significance [92]. More recently, at the 2018 World Meeting on Sexual Medicine, a RCT on the efficacy of PVS for penile rehabilitation following nerve-sparing radical prostatectomy was presented. In this study, 31 men were randomized to PVS and followed for 1 year. They found a positive trend in IIEF scores was seen for PVS, but like the previous study, it did not reach statistical significance [93]. Given the body of literature, there can be no firm conclusions drawn regarding PVS and treatment of organic ED. It appears it could potentially become a component of penile rehabilitation used in a postoperative protocol alongside PDE5i, but this has not been formally evaluated. In both penile rehabilitation studies, stimulation was performed once daily, with vibration settings and total vibratory time being set arbitrarily. The optimal regimen for efficacy is currently unknown.

Conclusion

Alternative medicine is becoming more popular and accessible, with many patients seeking these treatments for ED. A variety of new and innovative modalities are emerging with promising preliminary results. Providers should have an understanding of the literature behind these investigational therapies in order to set appropriate expectations and give recommendations regarding off-label treatment. The writers of this review hope that readers may utilize the information presented here as a scaffold to initiate further investigation into the presented modalities, and for quick reference in clinical scenarios.

Compliance with Ethical Standards

Conflict of Interest None of the authors has any conflict to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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