Current Urology Reports (2019) 20:44
https://doi.org/10.1007/s11934-019-0908-2

MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Emerging Treatments for Erectile Dysfunction: a Review of Novel, Non-surgical Options

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Abstract

Purpose of Review To review novel, non-surgical therapies for erectile dysfunction (ED).

Recent Findings Recently, a landmark study identified the *SIM1* locus, involved in the leptin-melanocortin pathway, as an independent risk factor for ED and a potential target for novel therapies. The recent literature otherwise has focused on low-intensity shock wave therapy (LiSWT), with several randomized trials and meta-analyses suggesting therapeutic efficacy.

Summary There are few novel oral agents for ED. There is growing evidence suggesting efficacy of intracavernosal stem cells therapy and low-intensity shock wave therapy (LiSWT), although these therapies are still investigational. A better understanding of the pathophysiologic spectrum of ED will offer new opportunities for novel, non-surgical therapies for ED.

Keywords Erectile dysfunction · Sexual dysfunction · Physiological · Dietary supplement · Platelet-rich plasma · Genetic therapy · Extracorporeal shockwave therapy

Introduction

Erectile dysfunction (ED), the inability to get or maintain a penile erection sufficient for sexual intercourse, is a common concern among men. It affects nearly 31–51% of men over the age of 50 years and nearly 500,000 men, 50–69 years old will develop ED in the USA every year [1–3]. Not only does ED affect quality of life, but also associated with cardiovascular disease, coronary artery disease, stroke, hypertension, diabetes, and all-cause mortality [4–8]. Diagnosis and appropriate treatment of ED offers an opportunity to improve a man's health in multiple ways.

Improvement in erectile function may be achieved through various lifestyle changes including weight loss, exercise, and smoking cessation [9]. Hypoandrogenism or low serum testosterone levels may cause symptoms of poor erections along with decreased libido and stamina. Current guidelines recommend screening patients with ED for low testosterone and offering testosterone replacement when appropriate, although testosterone replacement alone is usually not as effective ED treatment [10••]. Despite these interventions, many men with bothersome symptoms go on to additional treatments. Currently, there are several broad categories of ED treatment. Oral medications including PDE5 inhibitors (sildenafil, vardenafil, tadalafil, and avanafil) are an attractive option for most patients given the ease of administration. Since the approval of sildenafil in 1998, subsequent prescription oral medications that have come to market have a similar mechanism of action and comparable efficacy [11••]. Vacuum erection devices with a construction ring use negative pressure to increase arterial flow to the penis and decrease venous outflow to induce erection. Intracavernosal injections (alprostadil, phentolamine, papaverine, and/or atropine) or intraurethral suppositories (alprostadil) are alternatives in patients who are non-responders to oral medications, have adverse effects, or have contraindications to PDE5 inhibitors [11••]. Penile implants are the most invasive treatment, but provide durable results and have the highest satisfaction rates of all of treatments [11••].

Given the prevalence and impact of ED, diagnosis and treatment has a considerable burden on the healthcare system, with conservative estimates placing the cost of ED treatment

This article is part of the Topical Collection on *Men's Health*

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Published online: 18 June 2019

nationwide at $15 billion annually [12]. There is significant financial incentive to find more effective and less invasive ED treatments. However, relatively few groundbreaking treatments have been identified in the last decade. While there are some promising pathways for novel therapies, significant challenges remain. We review emerging, non-surgical treatment options for ED, focusing on future oral agents, nutraceuticals, topical agents, gene therapy, platelet-rich plasma (PRP), and extracorporeal low-intensity shockwave therapy (LiSWT).

Novel Oral Agents and Pathways

Since their introduction, PDE5 inhibitors remain the cornerstone of oral therapies for ED. Researchers have explored alternative pathways involved in erectile function for novel therapies, but there have been many challenges. Currently, there are no novel oral medications in clinical development. Prior targets have focused on central pathways (dopaminergic and melanocortin) and peripheral pathways (guanylyl cyclase and Rho-A/Rho kinase), although efficacy and tolerability of novel oral therapies directed at these pathways have been limited. An overview of the cellular pathways is shown in Fig. 1.

Dopaminergic Agents

An increased libido and improved erectile function have been noted as effects of dopamine agonists commonly used for Parkinson's disease. Agents in this category act on the central nervous system. An early study by Lai et al., demonstrated an erectile response with penile tumescence studies in eight impotent men after administration of apomorphine, a dopamine D1 and D2 receptor agonists [13]. In 2001, apomorphine was then approved for ED in Europe [14]. In a phase III double-blind parallel arm cross-over study of nearly 900 men with ED, over 50% of men using 4 mg of oral apomorphine were able to obtain an erection sufficient for intercourse compared with 33% of men using placebo, ($p < 0.001$) [15]. However, the FDA did not approve the drug in the USA given concerns about hypotension and syncope [14]. The most common adverse effect was nausea and vomiting. Similar medications targeted to the dopamine D4 receptor (ABT-724 and ABT-670) have also been studied, showing promise in early rat models [16]. However, development was stopped after phase II studies for undisclosed reasons.

Melanocortin Receptor Agonists

Melanocortin receptor agonists are central acting agents that have also been studied for ED. These medications include melanotan II (subcutaneous administration) and bremelanotide (intranasal or subcutaneous administration). Early studies by Wessells et al., demonstrated increased penile rigidity in 17 out of 20 men given subcutaneous injections of melanotan II, although the onset of action was approximately 2 h [17]. An intranasal form of bremelanotide was developed to provide a faster onset of action but caused considerable nausea and hypertension. Further development of melanocortin agonists has been abandoned to our knowledge within the published literature. However, a recent landmark study may spark additional interest in this medication class and pathway for novel therapies

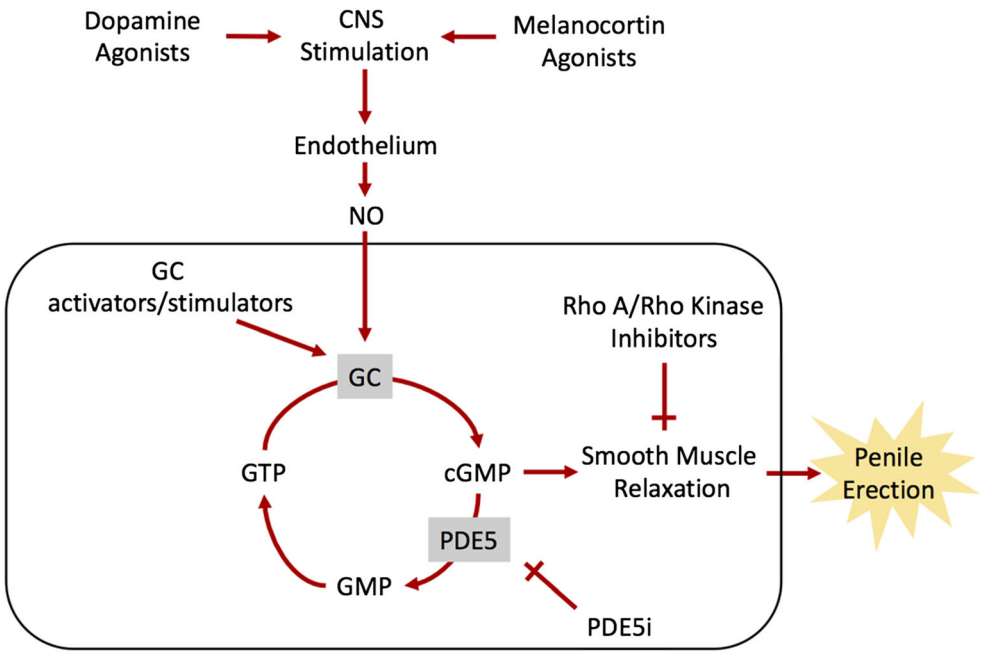

Fig. 1 Cellular pathways in erectile function. CNS, central nervous system; NO, nitric oxide; GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase-5; PDE5i, phosphodiesterase-5 inhibitor

for ED. Jorgenson et al. identified a single locus near the *SIM1* gene that was associated with risk of ED, independent of known risk factors in a large cohort [18••]. *SIM1* encodes transcription factors involved in the leptin-melanocortin pathway. The authors performed a large genome wide association study of 36,000 men in the Kaiser Permanente Northern California Genetic Epidemiology Research in Adult Health and Aging cohort which was then replicated in nearly 225,000 men in the United Kingdom (UK) Biobank. The authors found that the rs17185536-T locus on chromosome 6 located adjacent to the *SIM1* gene was significantly associated with ED risk when controlling for known risk factors with an odds ratio of 1.26 in the Kaiser Permanente cohort and 1.25 in the UK Biobank [18••]. This association is one of the first established genetic links with ED development and may represent an exciting target for patient risk stratification and/or future novel therapies.

Guanylyl Cyclase Activators

Soluble guanylyl cyclase is a key component of the nitric oxide (NO) pathway and when stimulated results in increased NO levels and enhanced erections (Fig. 1). Direct activation of guanylyl cyclase is an alternative mechanism for increasing NO levels independently or in combination with PDE5 inhibitors. Agents in this category are peripherally acting. Albersen et al. studied human cavernosal tissue incubated with BAY 60-4552 (a guanylyl cyclase activator) and vardenafil. Corporal tissue was obtained from patients during penile prosthesis implantation (patients with ED deemed PDE5i non-responders), compared with patients undergoing transurethral surgery (healthy controls) [19]. Prior to incubation, mRNA expression profiles showed downregulation of the entire NO/GMP/soluble guanylyl cyclase pathway. After incubation with BAY 60-4552 and vardenafil, there was a significant upregulation in the NO/GMP/soluble guanylyl cyclase pathway, which was more pronounced when compared with healthy control tissue. The authors were able to demonstrate an improved response in terms of mRNA expression to vardenafil when given with a guanylyl cyclase activator. This combination therapy may prove promising for post-prostatectomy ED and diabetes-induced ED where there are lower rates of success with oral PDE5i alone. Unfortunately, this medication has not progressed past phase II studies for unknown reasons.

Rho Kinase Pathway

The RhoA/Rho kinase pathway causes cavernosal smooth muscle contraction, independent of the NO pathway. When the RhoA/Rho kinase pathway is activated, inhibition of myosin light chain (MLC) phosphatase allows phosphorylation of the smooth muscle MLC. This causes calcium sensitization and eventually smooth muscle contraction. Animal models of hypertension and diabetes suggest an upregulation in this pathway and pronounced erectile dysfunction. Novel agents in this category are peripherally acting. SAR407899 is a specific RhoA/Rho kinase inhibitor studied by Guagnini et al. [20]. The ability of SAR407899 to relax corpus cavernosum muscle strips obtained from rats and human tissue has been investigated. SAR407899 caused dose-dependent relaxation of the muscle strips in both models. This result was unaffected after administration of a NO inhibitor, suggesting that a NO-independent pathway was resulting in cavernosal smooth muscle contraction/relaxation. Development of SAR407899 has ceased after completion of Phase II clinical trials, without formal reporting of the results.

Nutraceuticals

Nutraceuticals are alternative, natural, or herbal additives with claims of health benefits. In the last decade, the nutraceutical market has experienced significant growth secondary to consumer marketing and loose federal regulation. These supplements are regulated as foods rather than medications as outlined by the Dietary Supplement Health Act of 1994, creating a more favorable environment for commercial development [21]. The presumed negative stigma associated with ED diagnosis and aversion to seeking appropriate medical care for this condition is also an important component for market growth. Many nutraceuticals are commercially available without prescription and may include a combination of different ingredients, including yohimbine, L-arginine, red ginseng, and *Epimedium* spp. (or horny goat weed) (Table 1). There is considerable variability in the ingredients and formulations that impacts bioavailability and presumed efficacy. Therefore, use of nutraceuticals for ED should be approached with caution, especially when combined with other herbal or prescription medications.

Yohimbine

Yohimbine is derived from the African yohimbe tree. It inhibits central alpha-2 adrenergic receptors to increase libido, although the true mechanism is unknown. It is also unclear how the derivative affects erectile function. An early meta-analysis of seven studies suggested therapeutic efficacy of yohimbine when compared with placebo [22]. They did not find many severe or irreversible adverse reactions as a result of taking this nutraceutical [22]. A more recent double-blind randomized cross-over study evaluated combination treatment of yohimbine and L-arginine glutamate for ED. Forty-five patients with ED as assessed by IIEF randomly received the combination therapy or placebo for 2 weeks in a cross-over design [23]. Those who received the combination treatment

Table 1 Common ingredients in nutraceutical supplement formulations (Cui et al.)

Ginseng
Tribulus spp.
Zinc
Epimedium spp. (Horny goat weed)
Vitamin B_6
Fenugreek
L-Arginine
Maca
Niacin (vitamin B_3)
Saw palmetto
Folate (vitamin B_9)
Dehydroepiandrosterone (DHEA)
Vitamin E
Ginkgo biloba
Magnesium
Yohimbine
Thiamin (vitamin B_1)
Riboflavin (vitamin B_2)
Selenium

had improved erectile function domain responses on the International Index of Erectile Function (IIEF) compared with placebo. The effect was more pronounced in patients with mild-moderate ED (> 14 on IIEF) [23]. In this series of small studies, yohimbine has shown therapeutic efficacy when compared with placebo, although it is uncertain how it compares with current oral ED medications.

L-Arginine

L-arginine is a naturally occurring amino acid found in many nutraceuticals. Supplementation with L-arginine can boost nitric oxide levels causing smooth muscle relaxation and increased cavernosal blood flow. However, the efficacy of L-arginine supplementation has not been rigorously evaluated. Klotz et al. were unable to show improvement in erectile function scores after 17 days of oral L-arginine treatment when compared with placebo in a randomized, cross-over trial of 30 men with impotence, after 7-day washout period [24].

Red Ginseng

Red ginseng affects the NO pathway, stimulating nitric oxide synthase (NOS). Many randomized studies evaluating the use of red ginseng for ED have been performed; however, quality of the literature is low [25, 26]. Although many of these studies have reported a positive effect of red ginseng on erectile function, these studies have methodologic flaws including selection bias, dosing, and follow-up. Adverse effects of red ginseng include gastrointestinal upset, skin irritation, and reports of symptomatic hypoglycemia specifically in diabetics. Currently, there is no strong evidence for therapeutic efficacy of this compound for ED.

Epimedium spp. (Horny Goat Weed)

Horny goat weed is popular since the name is marketable. It is derived from the *Epimedium* plant and it contains the flavonol, icariin. Icariin has a mild PDE5 inhibitor effect. Small animal studies have demonstrated an improvement in erectile function after administration of intravenous icariin for 4 weeks after cavernous nerve injury in rats [27]. Toxicity in animal studies has resulted in hypomania and tachyarrhythmia. There are currently no human studies with *Epimedium* spp. or icariin.

Topical Agents

Topical agents for ED are appealing to patients who experience adverse effects with systemic oral therapies and/or who do not desire more invasive local treatments. A topical formulation of alprostadil (typically found in urethral suppositories and intracavernosal injection therapies) has been studied. Several double-blind, placebo controlled trials have shown improvements in IIEF scores and few minor side effects such as erythema at the administration site [28]. Topical sildenafil is currently being studied for ED as well; a Phase I pharmacokinetic and safety trial has shown good penetration of topical sildenafil without significant side effects. A phase II proof of concept study has been completed, although results have not yet been reported in the published literature. Various formulations of both topical alprostadil and sildenafil are available through online outlets and compounding pharmacies, though tissue penetration and efficacy are variable. While promising, considerable investigation of topical agents is still needed. Currently, there are no approved topical agents for ED in the USA.

Gene Therapy

Gene therapy is a novel therapy that has been proposed for ED treatment. There are several advantages for the exploration of gene therapy for ED including the following: exogenous genetic material can be directly injected into the penis and the rate of smooth muscle turnover is relatively slow; therefore, a single treatment can theoretically have lasting effects. Gene therapy can be delivered using viral vectors or non-viral vectors such as stem cells. Viral vectors have been used for many clinical situations for gene therapy, but can induce a significant inflammatory reaction, and the effects of therapy can be short-lived.

Stem cells have become an attractive therapy for ED, particularly post-prostatectomy, where ED is secondary to

cavernosal nerve damage. Stem cells for the treatment of ED have been derived from a number of sources including adipose tissue, bone marrow, urine, placenta, umbilical vein endothelium, and amniotic fluid. Adipose-derived stem cells are the most studied in ED treatment in the rat model, with several studies showing an improvement in intracavernosal pressure in rats injected with viral vectors or stem cells directly into the corpus cavernosum. More recently, Gu et al. demonstrated a significantly increased intracavernosal pressures (ICP) to mean arterial pressure (MAP) ratio after 12 weeks in a cohort of 32 rats after bilateral cavernous nerve crush injury treated with penile injections of umbilical vein endothelial cells, adipose derive stem cells, and amniotic fluid stem cells when compared with injections with normal saline [29••]. Despite these results in animal models, data examining therapeutic efficacy and safety of gene therapy for treatment of ED is limited in humans. Currently, the American Urological Association (AUA) guidelines and the Sexual Medicine Society of North America (SMSNA) position statement on restorative therapies for ED consider intracavernosal stem cell therapies as investigational [11••].

Several targets for gene therapy have been identified. NOS has been previously explored as a potential target. Neuronal activation of NOS (nNOS) leads to increased cyclic guanosine monophosphate concentration and smooth muscle relaxation in the penis. This causes generation of endothelial NOS (eNOS) locally that further increases cavernosal blood flow, producing penile erections. Several studies by Bivalacqua and colleagues using adenovirus vectors and mesenchymal stem cells in rats to increase NOS activity in vivo have shown an improved erectile response and higher ICP [30–32]. More recently, there has been interest in pigment epithelium-derived factor (PEDF) as a potential target for gene therapy. This serpin protein has a role in the nuclear factor kappa B pathway and is an inhibitor of angiogenesis through the vascular endothelial growth factor (VEGF) pathway [33, 34]. In a study by Chen et al., the authors show higher ICP/MAP ratios in cavernous nerve injured rats after 4 weeks using PEDF-stem cells compared with control stem cells [35]. With the recent identification of *SIM1* and its association with risk of ED by Jorgenson et al., it is likely that this locus and the melanocortin pathway will also become a target of novel gene therapies [18••].

Extracorporeal Low-Intensity Shockwave Therapy

Extracorporeal low-intensity shockwave therapy (LiSWT) is an emerging treatment for ED. It has been studied previously for a number of other conditions including tissue ischemia, wound healing, and musculoskeletal disorders. LiSWT utilizes direct mechanical forces from a pulse energy source and indirect force through cavitation that is directed at the treatment target. For ED, LiSWT is thought to induce micro-trauma to the cavernosal tissue that upregulates angiogenesis and other factors that promote healing and tissue remodeling. Vardi et al. were the first to systematically report their experience with LiSWT for ED in 2010 [36]. The authors treated 20 men with ED using LiSWT (two sessions per week for 3 weeks, followed by second cycle after another 3 weeks, applied to the penile shaft and the crura at 5 total sites). There was a significant increase in the IIEF–ED domain scores at 1 and 6 months post-treatment. There were no adverse events reported. Since then, a number of other studies have been published suggesting some therapeutic efficacy, with minimal adverse effects. Prior studies have used electrohydraulic or electromagnetic units for delivery of LiSWT. The most common regimen includes 1500 shocks per session at an energy density 0.09 mJ/mm^2 and frequency 120/min applied to five areas of the penis (left and right crura as well as the distal, mid, and proximal penile shaft) [37••]. Recent meta-analyses of the available literature have suggested therapeutic efficacy of LiSWT for ED using the IIEF or the erectile hardness score (EHS) [37••, 38, 39]. However, the ability to draw conclusions from the current literature is limited due to difference in treatment protocols, follow-up time, and patient selection. There are several ongoing randomized clinical trials that will help understand the role of LiSWT in the treatment of ED and a standardized treatment protocol [40]. Currently, LiSWT is considered investigational per AUA guidelines and the SMSNA position statement on ED restorative therapies [11••].

Autologous Platelet-Rich Plasma

Platelets have a pivotal role in the inflammatory response, tissue remodeling, and angiogenesis. The use of autologous platelet-rich plasma (PRP) has been explored in the treatment of a number of medical conditions [41–44]. A blood sample is obtained through venipuncture and which is then centrifuged to remove inflammatory cells and red blood cells. The supernatant contains platelets and plasma proteins, including growth factors and other components that can aid healing. The supernatant is directly injected into the target area. For ED, injections are performed directly into the corpus cavernosum. Wu et al. published one of the first studies on PRP for ED in an animal model [45]. In this study, male rats were divided into three groups: (1) sham surgery, (2) bilateral cavernosal nerve crush injury and intracavernosal injection of normal saline, and (3) bilateral cavernosal nerve crush injury and

intracavernosal injection of PRP. Rats treated with saline or PRP were treated immediately after the nerve injury. When comparing the saline vs. the PRP cohorts, the authors were able to demonstrate a significant improvement in return of erectile function with higher intracavernosal pressures after electrical nerve stimulation and significant preservation of myelinated axons with the PRP cohort compared with the saline control. This study suggested PRP as a novel therapeutic for ED. [45] However, no studies evaluating efficacy of PRP for ED in humans are currently available. The safety of PRP has been suggested in a study by Matz et al. where PRP fibrin matrix was used in 16 patients for ED and/or Peyronie's disease, with no major complications and with minor complications such as mild pain or bruising at the injection site in approximately 20% of patients [46•]. Although PRP is an interesting potential therapy for ED, further studies are warranted to evaluate safety and efficacy. Although this therapy is advertised direct to consumers and readily available, the AUA guidelines and SMSNA position statement consider PRP an experimental therapy for ED. [11••] Patients should be appropriately counseled regarding the unproven efficacy of this therapy in the published literature despite common claims.

Conclusions

We have developed a better understanding of the pathophysiology of ED over the last decade. However, this has not translated to novel non-surgical therapies, especially novel oral therapies. Other innovative therapies including stem cell therapy and LiSWT are in early clinical stages show promise, but there remain unanswered questions about patient selection and efficacy. A better understanding of the pathophysiologic spectrum of ED and further technological advances will translate to novel therapies for ED in the future.

Compliance with Ethical Standards

Conflict of Interest Darshan P. Patel declares no potential conflicts of interest.

Alexander W. Pastuszak reports advisor, speaker, consultant, and research and fellowship support from Endo Pharmaceuticals; is an advisor for Boston Scientific and Antares Pharmaceuticals; and holds a leadership position with Woven Health.

James M. Hotaling reports a research and fellowship grant from Endo Pharmaceuticals and a fellowship grant from Boston Scientific; and holds leadership positions with Nanonc, SteamDx, and Andro360.

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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- •• Of major importance

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