Technological Advancements for Treating Erectile Dysfunction and Peyronie's Disease

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KEYWORDS

• Erectile dysfunction (ED) • Peyronie's disease (PD) • Vacuum erection devices (VED)
• Penile traction devices (PTD) • Low-intensity extracorporeal shockwave therapy (LiESWT)
• Penile prosthesis

KEY POINTS

- Penile traction should be considered part of the initial management of erectile dysfunction and Peyronie's disease.
- Further basic science and clinical evidence need to elucidate the underlying mechanism for low-intensity extracorporeal shockwave therapy for treating erectile dysfunction before this can become a mainstream option.
- New penile prosthetic options will become available soon to ease the use for patients and it is hoped further improve patient-reported outcomes.

INTRODUCTION

Erectile dysfunction (ED) affects 30% to 65% of men in the general population between the ages of 40 and 80 years.[1] Because of the rapidly aging population, United Nations data predict that greater than 320 million men worldwide will be diagnosed and require treatment for ED by 2025.[2] ED affects the quality of life of men and their partners worldwide and costs the United States approximately $330 million annually.[3] Advances in basic science research and medical understanding have allowed therapeutic technologies to advance substantially since the original options first implemented more than 50 years ago.

Peyronie's disease (PD) is a connective tissue disease situated on the tunica albuginea of the penis. Screening studies have shown that currently there might be an underestimation of PD prevalence and incidence. A questionnaire-based survey in the United States revealed a definitive PD diagnosis in 0.7%, with an additional 11% having probable PD.[4] There is an increasing prevalence with age, diabetes, and preexisting ED, up to 9% to 13%.[4,5] Men between 50 and 60 years old seem to be most commonly affected, with a devastating impact on mental health; nearly half of all men with PD develop depressive symptoms.[6]

Restorative therapies, such as stem cell therapy and platelet-rich plasma, are being evaluated for their putative role in treating ED and PD; however, these are likely years away before mainstream acceptance and Food and Drug Administration (FDA) approval for routine use.[7] In contrast, technological advancements in the past decade have really improved the way ED can be treated, and

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the future holds many prospects for further advancement. Next, the authors discuss the advancements that have occurred in how men's health is treated over the past decade and explore the rapid expansion of this subspecialty field of medicine.

Vacuum Erection Devices

Vacuum erection devices (VED) have been used as a therapeutic option for ED since 1982 and have generally occupied a role as second-line therapy in the case of pharmacologic failure or intolerance.[8] The devices typically consist of a cylinder that encompasses the penis, a vacuum (manual or electric), and a constriction ring. Negative pressure is used to draw blood into the penile sinusoids and achieve rigidity, which is then maintained by the constriction ring at the penile base. Several recent studies highlight new insights into VED therapy.

Recognizing that VED usage is often limited by technical difficulty and patient discontinuation, Beaudreau and colleagues[9] reviewed patient outcomes at their andrology clinic. Notably, their patients were provided with in-person device training (Osbon Erecaid, Osbon Medical Systems, Augusta, GA, USA), videotaped and live demonstrations, written instructions, and discussions with psychologists about realistic expectations and the importance of practice. Satisfaction interviews were performed at follow-up. In their sample of 57 patients (mean age 64 years), 93% were able to obtain an erection with the device, and 91% were able to have intercourse. Of the patients, 100% would recommend VED therapy. These results demonstrate the strength of a multidisciplinary approach to patient education. The investigators concluded that evaluating the device in nonvaginal intercourse was a future area of study.[9]

ED after treatments for prostate cancer, such as radical prostatectomy or external beam radiation therapy (EBRT), is a common complication that affects up to 75% of men in contemporary series.[10] Jones and colleagues[11] sought to evaluate the real-world performance of VEDs in men who had exclusively undergone robot-assisted radical prostatectomy (RARP). They performed a follow-up survey of 137 patients (mean age 65 years) who attended a VED clinic an average of 462 days before. Patients had used the SOMA-erect response II device (Augusta Medical Systems LLC, Augusta, GA, USA) with a training session performed by the company. At follow-up, 71% of patients were still using the VED, with 56% reporting the therapy successful. Further studies should assess whether VEDs preserve penile size or hasten the recovery of erectile function in an RARP cohort.[11]

Penile Traction Devices

Penile traction therapy (PTT) for PD is based on the premise of using mechanical force to achieve a molecular signal, resulting in a gradual curvature reduction by a process known as mechanotransduction.[12] The first published report of this therapy in 2008 demonstrated a modest mean curvature reduction and improvement in stretched penile length (SPL)[13] in PD patients, and these results were corroborated with follow-up studies.[14–16] A major limitation of PTT is the prohibitive length of time the device had to be worn, historically greater than 4 hours per day to achieve benefit. Discomfort with the glans fixation mechanism was another barrier to utilization. Until now, the data have been immature, but this therapy maintains a weak recommendation in both the Canadian[17] and the European Association of Urology PD guidelines.[18] Currently, there is no recommendation for traction use in the American Urological Association PD guideline.[19] After further study and device refinement, PTT will certainly occupy an increasingly prominent role in PD treatment.

Modern penile traction therapy

The first prospective randomized clinical trial of PTT monotherapy for PD used the PeniMaster PRO device (MSP Concept, Berlin, Germany).[20] This device is characterized by its unique vacuum-based glans fixation mechanism (**Fig. 1**). The study enrolled 93 patients with chronic phase PD and randomized them to PTT 3 to 8 hours per day for 3 months versus no intervention. PTT with the PeniMaster PRO resulted in a mean reduction of curvature of 31.2° (41.1%) versus baseline. This result was statistically significant when compared with the no-intervention group in whom there was no change observed in the curvature. There was also a statistically significant improvement in mean SPL of 1.8 cm in the PTT group. There are some notable limitations to the results. The study used a per-protocol analysis and excluded 6 patients in the PTT arm with protocol violations or adverse events. Furthermore, the study excluded men with ED, multidirectional curvature, or hourglass/indentation deformities. The investigators speculated that the PeniMaster PRO glans fixation mechanism may be better tolerated than that of competitors, but the study did not assess for this.[20]

Recognizing the limitations of previous devices, the RestoreX (PathRight Medical, Plymouth, MN, USA) was developed featuring several of the

Fig. 1. PeniMaster PRO device characterized by its unique vacuum-based glans fixation mechanism.[20] (*From* Moncada I, Krishnappa P, Romero J, et al. Penile traction therapy with the new device 'Penimaster PRO' is effective and safe in the stable phase of Peyronie's disease: a controlled multicentre study. BJU Int. 04 2019;123(4):694-702. https://doi.org/10.1111/bju.14602.)

following innovations: (i) a wide penile clamp design, (ii) counter-bending, (iii) dynamic adjustment (**Fig. 2**). The device was evaluated in a pragmatic clinical trial, including a "true to life" PD population and an intention-to-treat analysis.[21] Men with PD were randomized 1:3 to no therapy or RestoreX for 30 minutes 1 to 3 times per day for 3 months. Adult men with curvature greater than 30° were included, and only those with an SPL <7 cm or severe diabetes were excluded. The primary study outcome was safety. Penile curvature, SPL, and IIEF scores were assessed as secondary outcomes.[21] At the study conclusion, data were available for 63 men in the PTT arm and 27 men in the control arm. No moderate to severe adverse events were reported. Mean primary curvature decreased 18%, and SPL increased a mean of 1.5 cm in the traction arm, both statistically significant compared with placebo. In men with baseline ED (defined as international index of erectile function [IIEF-EF] $\leq$25), RestoreX improved erectile function (mean 4-point improvement in the IIEF-EF).[21]

Open-label follow-up data have recently been published that provides insight into the utility of using the RestoreX device beyond 3 months.[22] At 6 months, patients that were originally randomized to the RestoreX device reported a further mean increase of 0.8 cm in SPL; however, no further curvature improvements were observed. These results likely underestimate the potential benefit of further RestoreX therapy given that not all participants reported using it during the open-label phase, and device usage was just 31 minutes per day.

Clostridium collagenase histolyticum and penile traction therapy

Clostridium collagenase histolyticum (CCH) is currently endorsed as the first-line therapy for PD.[17–19,23] One study has investigated the combination of CCH and PTT in a retrospective comparison of 3 cohorts of patients treated with CCH between March 2014 and January 2019.[24] The cohorts were as follows: (i) CCH alone, (ii) CCH with PTT with any device other than the RestoreX, and (iii) CCH + PTT with the RestoreX device. Patients in the second cohort used a PTT device of their choosing with the Andropenis, X4 labs extender (X4 labs, Vaudreuil-Dorion, Canada) and PeniMaster (MSP Concept) the most represented. This cohort was instructed to perform PTT greater than 3 hours per day, whereas those in the RestoreX were instructed to use it greater than 30 minutes per day. The primary outcomes were change in penile curvature and SPL. Data were available for 113 patients, including 56 CCH alone, 59 for CCH + PTT, and 57 for CCH + RestoreX. The groups were balanced at baseline in magnitude of curvature. Improvement in penile curvature was statistically superior in the CCH + RestoreX group with a mean 49.4% improvement compared with a CCH + PTT (30.2%) and CCH alone (31.2%). Penile length increased on average 1.9 cm in the RestoreX group compared with CCH (0.7 cm loss) and CCH + PTT (0.4 cm loss) groups. In the CCH + PTT cohort, only 7 (16%) of the men were able to wear the device the recommended more than 3 hours per day, which may explain the lack of observed efficacy in this group. Although the registry included patients from 2014 to 2019, the RestoreX device was first offered in 2017, and therefore, this cohort represents more recent patients. Therefore, the improvement in this group may be a reflection of improved provider experience with CCH. Nonetheless, this study provides the first evidence of an advantage to the addition of PTT to CCH, provided PTT is performed with the RestoreX device.[24]

Shockwave Therapy

Over the past decade, basic science and clinical studies have suggested that low-intensity extracorporeal shockwave therapy (LiESWT) may offer benefit for patients with ED,[25–29] chronic pelvic pain, and/or PD. Shockwave therapy (SWT) relies on an external energy source that applies pulses of energy into a fluid environment and then

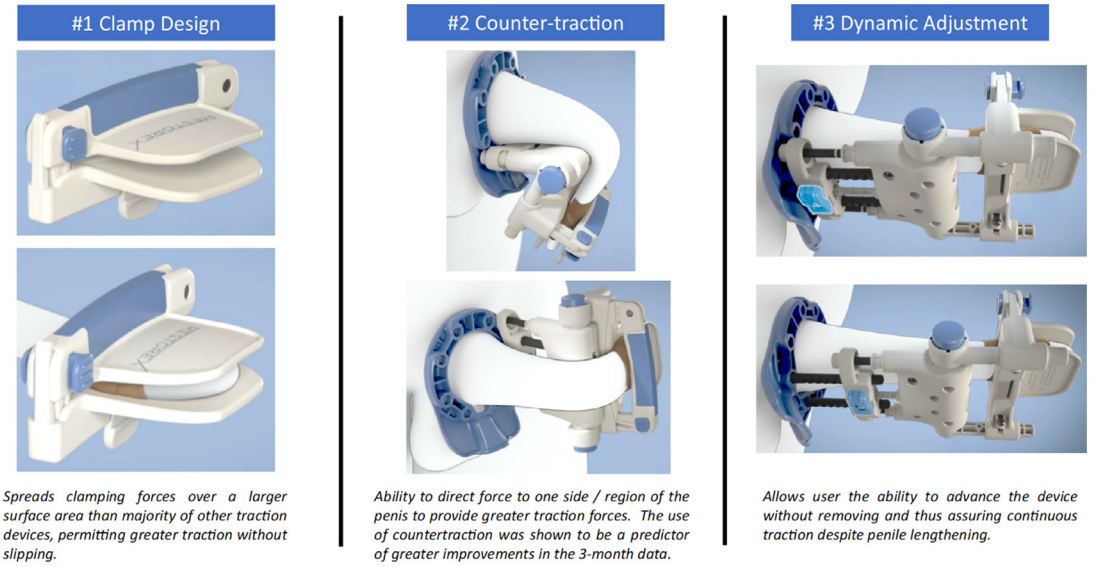

Fig. 2. RestoreX device featuring improvements in (1) clamp design, (2) counter-traction, and (3) dynamic adjustment.[21] (*From* Ziegelmann M, Savage J, Toussi A, et al. Outcomes of a Novel Penile Traction Device in Men with Peyronie's Disease: A Randomized, Single-Blind, Controlled Trial. J Urol. 09 2019;202(3):599-610. https://doi.org/10.1097/JU.0000000000000245.)

propagates the harnessed energy until it meets the target tissue where the energy is used.[30] In a low-intensity state, SWT has been shown to induce angiogenesis,[31] regenerate nerve fibers, recruit progenitor cells, vasodilate penile microcirculation,[32] and improve endothelial function.[33,34] LiESWT has been suggested to induce long-term structural changes that may augment erectile function.[35–37]

Three different generates for LiESWT are currently available using different forms of energy: electromagnetic, electrohydraulic, and piezoelectric. All 3 energy forms produce acoustic waves that transfer energy directly to the tissue to which it is applied, resulting in mechanical stress.[36,38]

Shockwave Therapy for Erectile Dysfunction

To date, there have been several human, prospective randomized controlled clinical trials[39–49] and meta-analyses[25–29,50,51] exploring the use of LiESWT for ED. The role of LiESWT in treating ED is to reestablish natural erections without the need for additional medical treatment. LiESWT may convert a phosphodiesterase type 5 inhibitor partial responder to a complete responder, thus avoiding the need for more aggressive interventions.[35]

Based on the currently available randomized controlled trials, there is an approximate improvement of 4 points in the IIEF.[29] A 4-point short-term improvement in IIEF would be considered a clinically significant improvement, but the studies included in such meta-analyses have significant bias, and the interpretation of these results is limited.

There does remain an uncertainty regarding the duration of effect with LiESWT when treating ED, and this appears to be one of the most important clinical considerations, especially when it comes to patient counseling. The longest follow-up results to date is 2 years, but of the near 100 patients with initial improvement at 1 month, only approximately 50% had continued improvement after 24 months.[52] Clinically, if 50% have continued benefit, this may be a tolerable sustainability, and perhaps maintenance treatments would be required similar to other disease processes. Further work and longer outcomes are needed to help evaluate this effect and inform practitioners on how to properly counsel patients.

Shockwave Therapy for Peyronie's Disease

Although prospective, single-center studies have recently evaluated the utility of LiESWT for PD, there is limited basic science or good-quality clinical data to support the use for this indication.[43,53–55] Di Mauro and colleagues[54] assessed more than 300 PD patients, and although they measured a slight change in plaque size, debatably the most important finding is the reduction of pain with LiESWT in acute phase PD. This study does not have a control group, and therefore, it is

unclear if this reduction in pain is due to just progression of disease from acute to chronic, or truly a reduction in inflammation secondary to the use of LiESWT.

Radial Wave Shock Wave Therapy

Radial wave therapy has been marketed as a treatment for ED; however, there is a paucity of adequate clinical research available to support its use. It is important for both patients and providers to realize that this technology is not the same as LiESWT. In contrast to LiESWT, radial wave generators produce dispersive waves away from the probe, and these waves have low tissue penetrance.[37,56] In comparison, LiESWT focuses more energy with a deeper tissue penetration over a shorter time, which is implicated as a regenerative technology.

Current Clinical Applications

Despite the breadth of exploration in the past decade, there are several limitations to LiESWT studies. First, there is a significant heterogeneity in shockwave generator and treatment protocols used for study, and the dosing, frequency of shocks, and location of probe are still not standardized. The diversity in therapeutic application makes this technology difficult to accurately study. Although many private men's health clinics currently use this technology, there is no agreed upon algorithm, and therefore, treatment remains up to the clinician. Next, although there is an abundance of randomized trials, many have different inclusion criteria and small sample sizes. This makes even meta-analysis of the data difficult, and there are many associated biases.[29] Different studies explore vascular versus aged-related or neurogenic causes of ED, and these heterogenous populations cannot be fairly compared.

The Sexual Medicine Society of North America (SMSNA) has published an updated position statement about the use of all regenerative therapies, including LiESWT.[37] In summary, the SMSNA recommends further exploration of the basic science behind shock wave technology and randomized placebo-controlled trials to determine appropriate patient populations, shock wave protocols, device choices, and long-term efficacy.[37] Similarly, the European Society of Sexual Medicine agrees that LiESWT has some significant support with clinical evidence; however, further work is required before it becomes an accepted form of treatment for male health conditions.[57]

The increased use in LiESWT by private clinics worldwide is controversial, and interpretation of the current data is contrasted by various guideline committees. The European Association of Urology states that LiESWT can be used to treat mild, organic ED, but has weak strength of recommendation.[35] In comparison, the updated American Urological Association guideline on ED has a conditional, grade C recommendation that LiESWT should be considered investigational and not yet ready for mainstream use.[58] The unpublished Canadian Urology Association guidelines have a weak recommendation against the use of LiESWT for treating ED.[59] None of the current guidelines support the use of LiESWT for chronic pelvic pain or PD.[19,35] As further evidence is elucidated, these guidelines will likely evolve, such that this may become a treatment option in select patient populations.

PENILE PROSTHETICS

The Evolution of Penile Prosthesis Surgery

The first penile prosthetic was devised by Dr Ambroise Pare and dates to the sixteenth century. Dr Pare inserted a wooden pipe to facilitate micturition for a patient who required a penile amputation as a result of trauma. Although this prosthesis was initially described as successful, the wooden pipe was later resorbed by the body.[60] In 1936, Dr Nikolaj Bogoraz, a pioneer in phalloplasty, used rib cartilage to provide rigidity.[61] The first use of synthetic material for penile prosthesis was developed by Dr Scardino in 1950, but the data went unpublished. In 1952, Drs Goodwin and Scott performed 5 acrylic penile transplants and provided the first descriptions of alloplastic penile implants. Unfortunately, only 2 of the 5 remained successful at 5 years postimplant because of infection or patient intolerance. The first large study of penile prosthesis was Dr Beheri in 1966, who described the intracavernosal placement of polyethylene rods. His proposed technique is still followed to this day, with the use of Hegar dilators for cavernosal dilation and the formation of a tunnel for the prostheses. Dr Beheri's placement of the prosthesis within the tunica albuginea has since become the prominent method.[62] In 1967, Dr Pearman described placement of a silicone rod between Buck fascia and the tunica albuginea.[63] This caused patients significant pain, and Pearman subsequently changed his technique to be similar to that of Dr Beheri, with placement of the silicone rod within the tunica albuginea.[64] During the 1970s, there was a significant upswing in the surgical management of ED because of novel surgical options. It was at this time that research and design likely reached the critical point, which led to novel designs in penile prosthesis.

Malleable Penile Prosthesis

The semirigid prosthesis was introduced in 1975 by Small and colleagues and was designed to fill both corporal bodies.[65] This was upended in 1977 by Dr Finney, who introduced the Flexi-Rod prosthesis, a paired semirigid implant with a softer proximal compartment below the pubis.[63] The silicone core was later reinforced with Dacron fabric to create a firmer prosthesis, becoming the Flexi-Rod II.[66] In 1983, American Medical Systems (AMS) designed the AMS Malleable 600 prosthesis, a silicone device containing a stainless wire core wrapped in fabric. This design included the addition of rear tip extenders and allowed for 3 length adjustments.[67] In contrast, Mentor (now known as Coloplast) designed the Mentor Malleable, also available with multiple rear tip extenders and in 3 size lengths.[68] Also, during the 1980s, Omniphase and Duraphase malleable implants were introduced and advertised to have the twisting of a "gooseneck lamp." Both were pulled from the market in 1986 because of technical failures.[69] In 1992, the Dura-II malleable penis prosthesis was introduced, which contained a series of polyethylene disks connected by a metal cable running down the middle.[70] Drs Ferguson and Cespedes[71] went on to present data in 2003 that supported long-term quality-of-life improvements in patients who had undergone Dura-II implantation. Many of these options remain on the market to this day.

One-Piece Inflatable Penile Prosthesis

In 1986, 2 different one-piece inflatable penile prostheses (IPP) were introduced to the market: AMS' Hydroflex and Surgitek's Flex. These devices included a rigid core, where fluid was transferred into the core by a pump at the distal end. However, Surgitek is no longer manufacturing penile prosthetics, and the AMS Hydroflex was replaced by the Dynaflex prosthesis in the 1990s. The Dynaflex, although similar to the AMS Hydroflex, included multiple channels connecting the pump and reservoir, which provided a more rigid erection in comparison to other malleable prosthesis at the time.

Two-Piece Inflatable Penile Prosthesis

The first two-piece IPP was designed by Mentor (Coloplast) and was dubbed the "GFS prosthesis." The novel design had 2 cylinders attached to a single reservoir unit, located in the scrotum, that was made up of both the reservoir and the pump, called the "resipump."[72] Around the same time, Surgitek introduced the Uniflate 1000. The Uniflate 1000 is filled through a self-sealing penetrable port on the bottom of the resipump; however, the cylinders have 2 layers: an outer silicone layer and an inner Dacron fabric layer, with the outer chamber functioning to add extra girth. This did not receive FDA approval, as studies done in Spain showed high rates of mechanical failure.[73] AMS introduced Ambicor in the 1990s, which consists of a pair of cylinders and a pump of silicone elastomers. The Ambicor remains on the market to this day.[74]

Three-Piece Inflatable Penile Prosthesis

The original three-piece IPP was developed by Dr Scott and colleagues in the 1990s to prevent penile shortening and to increase penile girth and length. This IPP device, the AMS 700, consisted of 2 pumps (one in each hemi-scrotum), 2 cylinders, and a fluid reservoir.[75] The initial design included new rear tips, polytetrafluoroethylene (PTFE) sleeves for decreased wear, and a new connector system that did not require sutures. However, the PTFE sleeves did not permit adequate expansion and were prone to aneurysmal dilation.[76] In 1986, the kink-resistant tube was introduced, subsequently reducing complications and providing more forgiveness to length and width measurements.[77] In 1987, the PTFE sleeves were replaced by multilayer silicone material that better facilitated expansion. This material includes an inner layer of woven fabric resembling Dacron, and an outer layer made of silicon to allow for controlled expansion. This material remains the standard for use in penile expansion devices to this day.[66,76]

Since the early 2000s, there have been numerous modifications to the AMS 700 three-piece inflatable prosthesis. AMS added an additional parylene coating to the inner surface of the silicon to decrease wear and tear, which further reduces risk of aneurysmal dilation. Furthermore, AMS added a lockout valve to prevent autoinflation.[78] AMS also introduced the first permanent antibiotic-eluting implant, named the InhibiZone, which consisted of minocycline and rifampin. This was impregnated onto the outer surface of the device, resulting in the yellow-orange trace effect.[79] Currently, there are 3 variations in the AMS 700 series: the AMS 700 LGX, AMS 700 CX, and AMS 700 CXR, with LGX referring to length and girth expansion, whereas CX refers to controlled expansion.[70]

In a bid to compete with AMS, Mentor (Coloplast) patented the Bioflex material in the early 1980s. The Bioflex material provided advantages over the silicon material used by AMS, including an ~7 times higher tensile strength, while

maintaining biodegradability.[80] Furthermore, Mentor (Coloplast) later went on to patent their own reservoir, and in 1987, they improved the reservoir by adding nylon to the reservoir and caps on the rear tip extenders. In 2002, the addition of a hydrophilic coating allowed for the surgeon's choice of antibiotic use, which subsequently reduced infection rates by 50%. Other modifications over the years include changing the tubing connector from a crimp to slip-on design, developing a zero-degree junction between cylinders, and addition of new tubing to better facilitate intracorporeal cylinder placement. Recently, the Coloplast Cloverleaf was introduced for ectopic reservoir placement in anatomically compromised patients in order to reduce autoinflation.[81]

Surgical Innovation and Future Advances in Penile Prosthesis

Although we have come a long way since rib cartilage-enhanced erections, a new frontier of penile prostheses is constantly on the lookout. Futuristic advances in operative technique and inflation mechanics reinvigorate hope for continued safe and effective prosthetic aid in men's sexual health.

Over the past few decades, there have been many changes to the penile prosthesis to improve durability, improve comfort, and reduce rates of infection. Current prosthesis companies, such as Boston Scientific and Coloplast, aim to integrate software programming and shape memory alloys (SMA) into upcoming penile prosthesis for the treatment of ED. In 2019, Boston Scientific designed Tactra, a semirigid penile prosthesis made up of silicone cylinders with a core of Nitinol (nickel-titanium alloy), which provides increased rigidity and flexibility. The novel semirigid prosthesis is not coated with Inhibizone, which has been associated with lower rates of postoperative infections.[82] Second, a novel approach has been the integration of temperature into the SMA IPP, which "remembers" a predetermined shape. The mechanism of these involves setting a critical temperature point. Above the set temperature, the penis achieves a rigid state, whereas below the temperature point, the SMA achieves a flaccid state. At this time, the critical temperature point has been set at 42°C, which is above normal resting body temperature and below the threshold at which pain nociceptors activate. Furthermore, this allows transitions between flaccid and rigid states without the use of a reservoir or pump.[83] Last, a novel physiologic technique also using SMAs involves use of magnetic induction, instead of hydraulic pressure, to stimulate the transition to an erect penis. Done in animal models, an external inducer wand was used to successfully activate the SMA penile prosthesis with no direct contact in less than 45 seconds.[84]

SUMMARY

In summary, much progress has been made in technology that can improve male sexual health. Current limitations in advanced technology include a lack of multicenter clinical trials, studies evaluating complex patient populations, and well-established treatment protocols. As technology developments and artificial intelligence expand within the medical realm, one can only expect that treatments for men's health will continue to improve over the next decade and beyond.

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