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# Role of Nanotechnology in Erectile Dysfunction Treatment

Alice Y. Wang, BS,[1] and Carol A. Podlasek, PhD[2]

## ABSTRACT

**Introduction:** The biological importance of nanotechnology-based delivery vehicles for in vivo tissue regeneration is gaining acceptance by the medical community; however, its relevance and incorporation into the treatment of sexual dysfunction are evolving and have not been well evaluated.

**Aim:** To provide scientific evidence examining the use of state-of-the-art nanotechnology-based delivery methodology in the treatment of erectile dysfunction (ED) in animal models and in patients.

**Methods:** This review assessed the current basic science literature examining the role of nanotechnology-based delivery vehicles in the development of potential ED therapies.

**Results:** There are four primary areas where nanotechnology has been applied for ED treatment: (i) topical delivery of drugs for on-demand erectile function, (ii) injectable gels into the penis to prevent morphologic changes after prostatectomy, (iii) hydrogels to promote cavernous nerve regeneration or neuroprotection, and (iv) encapsulation of drugs to increase erectile function (primarily of phosphodiesterase type 5 inhibitors).

**Conclusion:** Basic science studies provide evidence for a significant and evolving role for nanotechnology in the development of therapies for ED and suggest that properly administered nano-based therapies might be advantageous for treating male sexual dysfunction.

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**Key Words:** Nanotechnology; Hydrogel; Cavernous Nerve; Penis; Erectile Dysfunction

## INTRODUCTION

Nanoparticle-based drug delivery is a popular topic for the development of translational therapy for many diseases, including erectile dysfunction (ED). ED is a common debilitating condition in aging men, affecting 52% of men 40 to 69 years old (Massachusetts Male Aging Study)[1] and 22% of men younger than 40 years.[2] Risk factors for developing ED are age, coronary artery disease, peripheral vascular disease, smoking, dyslipidemia, diabetes mellitus, and treatment for prostate cancer (including prostatectomy and radiation treatment).[1,3] A significant underlying cause of ED development is damage to the cavernous nerve (CN), a parasympathetic peripheral nerve that provides innervation to the penis. CN injury, which occurs with prostatectomy, diabetes, and aging, results in downstream morphologic remodeling of the penile corpora cavernosa, including smooth muscle apoptosis and ensuing fibrosis, which make the erectile tissue less able to respond to normal signaling mechanisms and standard-of-care treatments such as oral therapy with phosphodiesterase type 5 inhibitors (PDE5is). State-of-the-art therapies, thus far limited primarily to animal models, are designed to target CN regeneration and prevention of penile morphologic changes. This includes targeted and extended delivery of growth factors (involved in maintaining nerve architecture and penile smooth muscle) to the penis and CN and transdermal delivery of PDE5i for "on-demand" erectile function through increasing nitric oxide (NO) and temporarily increasing PDE5i.

The requirements of penile and CN delivery have some similarities and distinct challenges and requirements. For penile and CN delivery, extended release of growth factors with a biodegradable delivery vehicle that does not cause an immune response is needed. For the CN, vehicles that provide a surface for regenerating axons to grow against, acting as guidance factors, are desirable to promote regeneration of axons. In animal models, flexible linear hydrogels are ideal for this purpose. Although the anatomy of the CN in humans differs somewhat from that of rodent models, forming more of a neural net than one simple linear nerve structure (rat), the same principle applies for regenerating neurons. For corpora cavernosal delivery, an additional shear stress is encountered with blood flow through the sinusoidal spaces and a delivery vehicle cannot impede blood

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[1]Department of Urology, University of Illinois at Chicago, Chicago, IL, USA;
[2]Departments of Urology, Physiology, and Bioengineering, University of Illinois at Chicago, Chicago, IL, USA

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flow or it will impair function. Self-assembling hydrogels, which can form in vivo as a coating lining the sinusoidal spaces, is optimal. These potential therapies target long-term ED development by suppressing architectural changes in the CN and penis. Another option is transdermal delivery of NO or PDE5i, which can be useful for on-demand erectile function. This type of topical delivery to the penis would avoid systemic side effects, which result from oral PDE5i use, and could avoid pain and anxiety of injection of other vasoactive drugs. Barriers to this type of delivery are the permeability of skin and tunica, prevention of skin changes in response to the delivery vehicle and drug delivered, and potential toxicity to partners. In addition, similar target delivery vehicle requirements are needed as in CN and corpora cavernosal delivery (biodegradable, somewhat extended release, and no immune response).

## METHODS

In this review, state-of-the-art nanotechnology-based delivery vehicles designed for future translation to patients with ED, and which are useful for ED research in animal models, are discussed. Studies on nanotechnology are conducted at the nanoscale (1−100 nm) and involve the manipulation of matter on the atomic, molecular, and supramolecular scales. These potential therapies are divided into four methods of delivery: (i) topical delivery of drugs for on-demand erectile function, (ii) injectable self-assembling hydrogels for extended growth factor release to the corpora cavernosa of the penis, (iii) application of hydrogels for extended release of proteins to regenerate the CN, and (iv) encapsulation of drugs for oral delivery to increase erectile function. Recent publications in each area and their potential benefits and pitfalls are discussed (Table 1).

## RESULTS

### Topical Delivery of Drugs for On-Demand Erectile Function

Han et al[4] investigated whether nanoparticles that encapsulate known erectogenic agents, such as tadalafil, sialorphin, and NO, would improve erectile function with transdermal delivery, thus avoiding systemic side effects. Many currently used erectogenic agents such as PDE5is have significant adverse side effects, including headache, facial flushing, nasal congestion, and dyspepsia. The transdermal delivery system used a nanoparticle-based hybrid hydrogel-glass composed of polyethylene glycol (PEG), tetramethyl ortho silicate, chitosan, sodium nitrite, and glucose, which were delivered as a suspension in carboxymethylcellulose.[4] When hydrated, the suspension releases the encapsulated material and this material was applied as a gel to the glans and penile shaft of an aging Sprague-Dawley rat model of ED. Results showed that spontaneous erections were visible 4.5 minutes after gel application of NO and after 9 minutes with sialorphin. The NO-generated erection lasted 1.42 minutes and the sialorphin-generated erection lasted 8 minutes. Tadalafil-releasing nanoparticles resulted in erection 1 hour after application.[4] The study concluded that nanoparticles encapsulating erectogenic agents resulted in spontaneous erection when applied to the penis and could be useful for drug delivery to promote erection. This type of on-demand erection can have potential application for aging patients with ED. Several interesting questions arose from this study, including the duration in which the drug delivery was effective in eliciting an erection, the in vivo penetration and release kinetics of the nanomaterials, and whether the nanomaterial would have an adverse effect on the sexual partner's physiology and function.

In this second topical drug delivery study, Tar et al[5] answered some of the questions that arose in their previous study on transdermal delivery of erectogenic agents in an aging rat ED model. In this work, they examined whether topically applied NO-releasing nanoparticles would induce erection in a CN resection model, which mimics post-prostatectomy erectile function. They hypothesized that the NO-releasing nanoparticles would be effective for on-demand erection by increasing penile blood flow. The nanoparticle used for this study included PEG and chitosan as additives to a basic tetramethyl ortho silicate recipe for sol-gel preparation, which is referred to as a hydrogel-glass composite.[6] NO is spontaneously generated through the reduction of nitrite to NO, which is facilitated by the hydrogen bonding network provided by the nanoparticle platform.[5] It was effective for NO formation, retention, and slow and sustained release and was applied with coconut oil or hyaluronic acid as a carrier 1 week after bilateral CN resection. Control rats received empty vehicle. In response to NO treatment, 6 of 10 rats exhibited spontaneous erections of approximately 1-minute duration. The onset of spontaneous erections was 5 to 37 minutes after application and occurred for at least 45 minutes.[5] Similar results were obtained for application of NO nanoparticles delivered in a coconut oil base rather than dimethyl sulfoxide gel. No spontaneous erections were observed after application with the empty nanoparticle vehicle. Release kinetics showed that the nanoparticles released NO within a few minutes and release occurred in a continuous manner for approximately 5 hours and was attenuated by 7 hours. Microcirculatory blood flow, measured in a hamster model, significantly increased with NO treatment and was sustained longer than 90 minutes.[5] This study concluded that NO delivered by the nanoparticle platform could be useful for penile rehabilitation to facilitate oxygenation after prostatectomy. Whether corpora cavernosal changes induced by nerve injury are suppressed and penile architecture is maintained or rescued in the post-prostatectomy model remain to be evaluated.

The next study that examined topical delivery of drugs for on-demand erectile function was by Park et al,[7] which aimed to determine whether alcoholic hydrogels containing prostaglandin $E_1$ (PGE1) ethyl ester (prodrug for PGE1) improve erectile

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