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## *Current literature review*

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## Current Literature Review

Towards preparedness for PrEP: PrEP awareness and acceptability among MSM at high risk of HIV transmission who use sociosexual media in four Celtic nations: Scotland, Wales, Northern Ireland and The Republic of Ireland: an online survey

Frankis JS, Young I, Lorimer K, Davis M, Flowers P. *Sex Transm Infect* 2016. Epub ahead of print. doi:[10.1136/sextrans-2015-052101](https://doi.org/10.1136/sextrans-2015-052101).

**Editorial Comment:** In many parts of the world, particularly the western world, HIV infection continues to disproportionately impact gay and bisexual men, commonly referred to in the literature as MSM (men who have sex with men). Solid evidence now exists to support the high efficacy rates (73%–86%) of Pre-Exposure Prophylaxis (PrEP) in the prevention of HIV transmission in gay and bisexual men. Researchers continue working to identify barriers to widespread implementation and uptake of PrEP as a biomedical treatment as prevention strategy.

Key to the uptake of any new intervention, biomedical, behavioural or otherwise, is awareness and acceptability of the treatment by the target population. Frankis and colleagues address these possible barriers head on in a well-designed and straightforward research study in Celtic nations in the UK. Awareness of PrEP in their study of MSM with multiple condomless anal intercourse (CAI) partners was moderate at about one-third of participants. Those already engaged in sexual health care (eg, HIV/STI testing) were more likely to be aware of PrEP. Men with more CAI partners reported higher acceptability (considering taking PrEP), with acceptability at about half across the sample.

The article, in line with similar studies, provides an excellent and recent research snapshot of PrEP as an acceptable and even desired strategy for gay and bisexual men. As noted by the authors, additional work through a variety of mediums needs to occur to raise the level of awareness of PrEP as a prevention method for gay and bisexual men. Policymakers need to address other barriers such as availability and costs. Sexual medicine and public health practitioners can play a role in advancing PrEP as a tool to combat perhaps the most important health issue among gay and bisexual men—by helping to raise awareness in the patients and populations they serve and advocating for access and affordability. As this research indicates, we already know most gay and bisexual men would accept PrEP as another tool in the fight to eradicate HIV.

Christopher M. Fisher, PhD

Sonic hedgehog delivery from self-assembled nanofiber hydrogels reduces the fibrotic response in models of erectile dysfunction

Choe S, Veliceasa D, Bond CW, Harrington DA, Stupp SI, McVary KT, Podlasek CA. *Acta Biomaterialia* 2016;32:89.

**Editorial Comment:** The numerous causes of erectile dysfunction (ED) range from psychosocial stress to disruption of the anatomic or physiologic mechanisms responsible for erection. How each of these various etiologies results in ED on a molecular level, however, is far less appreciated. Also less appreciated is the more recent observation that symptomatic ED is associated with corporal cavernosal fibrosis, which can be particularly pronounced after cavernous nerve (CN) injury. While CN injury can result in decreased corporal cavernosal smooth muscle and elastic fiber content, with concomitant increases in collagen content, how this occurs remains an open question.<sup>1</sup> Until recently, the transforming growth factor- $\beta$  (TGF- $\beta$ ) pathway was considered to be the major driver of corporal fibrosis, with increased signaling in both humans and animal models of ED.<sup>2,3</sup> More recent work, however, suggests that crosstalk occurs between the TGF- $\beta$  and sonic hedgehog (SHH) pathways in fibrotic conditions, and that SHH may mediate epithelial-mesenchymal crosstalk contributing to the pathogenesis of fibrosis.<sup>4,5</sup> Furthermore, the SHH pathway has recently been shown to regulate penile and CN architecture and smooth muscle apoptosis.<sup>6–8</sup> In this study, Choe et al examine the collagen response to SHH signaling in the penis and CN of rats, and the importance of CN signaling in mediating this response, finding that SHH signaling results in relative inhibition of corporal collagen production, and that this is dependent on neural input. The authors also utilize a novel peptide amphiphile (PA)—mediated approach to delivering SHH to tissues of interest, highlighting a potential mode of delivery that may be effective in future clinical applications. These peptide amphiphiles represent programmable hydrogels that can deliver their payload either via an injectable solution, which assembles into a soft hydrogel, or using highly aligned monodomain nanofiber bundles. Thus, in this innovative study, the authors implicate a novel neural component in collagen regulation, further define the role of the SHH pathway in the penile fibrotic response to CN injury, and offer a potential treatment approach.

In order to lay the foundation for their hypothesis in humans, the authors first examined collagen production in corporal tissue from men who had undergone prostatectomy and men with diabetes, as well as control men with Peyronie's disease, and found significantly greater collagen content in penile tissue from post-prostatectomy and diabetic men. Given that both

prostatectomy and diabetes can impact vascular and neural penile inputs, these findings provided initial support for a role of neural signaling in penile fibrosis. In rats, increasing amounts of collagen in penile tissue as a function of age were observed, even after adulthood was reached. Since CN degeneration occurs with age in rats, this finding further supported the hypothesis that CN signaling is important in maintaining normal penile architecture, as progressive fibrosis past adulthood was not previously thought to occur.

Next, the authors examined penile collagen content as a function of CN injury and time after injury. While mode of injury (crush vs cut) did not affect collagen content, time after injury did, with collagen content peaking 7–14 days after CN injury; qualitative increases in collagen type III were also observed, consistent with prior studies.<sup>2</sup> Once the relationship between CN input and collagen content had been established in their rat model, the authors examined the role of SHH signaling in modulating penile collagen content. First, SHH signaling was inhibited using the 5E1 antibody coupled to Affi-Gel beads injected directly into the corpora cavernosa, which resulted in increased penile collagen content relative to controls. Next, the CN was resected in male rats, followed by PA hydrogel and Affi-Gel-based treatment with SHH or bovine serum albumin (BSA, control) by direct injection into the corpora cavernosa. Compared with controls, lower collagen content was observed in SHH-treated rats than controls within 4 days of injury, with no significant differences 7 days after injury, consistent with the time needed to release all SHH from the PA. To more definitively demonstrate a role for neural signaling in penile collagen deposition, SHH signaling was inhibited at the level of the pelvic ganglion (PG) using the 5E1 antibody and cyclopamine, a chemical inhibitor of SHH signaling. Both treatments demonstrated significant reductions in penile collagen content 7 days after treatment. Finally, PA-based treatment with SHH or BSA using monodomain nanofiber bundles after CN crush injury also resulted in significantly lower collagen content after SHH treatment when compared with control.

Taken together, these findings are significant, as they further establish a role for SHH signaling in penile corporal fibrosis in the setting of ED, and demonstrate the importance of neural signaling in the regulation of penile collagen content. Furthermore, they establish a proof of principle for the use of PAs in the treatment of ED. While the relationship between the SHH and TGF- $\beta$  pathways in the setting of ED, and corporal fibrosis more generally, remains to be determined, this work supports a significant contribution for SHH in modulating this condition. Given the overall short duration of response to PA-based treatments, future work should aim to enhance the duration of action of this promising drug delivery system to minimize the need for repeated interventions in the clinical setting. Nevertheless, these findings speak to our growing understanding of the multiple molecular mechanisms that coalesce to drive ED in the setting of neural injury, and

highlight the likely need for a multipronged approach to treatment to maximize efficacy.

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Testosterone Trials Investigators. Effects of testosterone treatment in older men

Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, Gill TM, Barrett-Connor E, Swerdloff RS, Wang C, Ensrud KE, Lewis CE, Farrar JT, Cella D, Rosen RC, Pahor M, Crandall JP, Molitch ME, Cifelli D, Dougar D, Fluharty L, Resnick SM, Storer TW, Anton S, Basaria S, Diem SJ, Hou X, Mohler ER 3rd, Parsons JK, Wenger NK, Zeldow B, Landis JR, Ellenberg SS. *N Engl J Med* 374;7:611-624.

**Editorial Comment:** Testosterone concentrations decrease with aging and elderly men experience worsening in their sexual functions. The link between these two events is not well understood and the efficacy of testosterone replacement therapy (TRT) on these men is a controversial topic. In this prospective randomized, double blinded, multicenter study, Snyder et al evaluated 790 men older than 65 years of age, with a serum testosterone concentration lesser than 275 ng/dl and symptoms suggesting primary hypogonadism. The authors randomized

these men to receive either testosterone gel or placebo gel for 1 year. Afterwards, patients were separated into three different trials: i. Sexual Trial evaluated the change in the score for sexual activity (question 4) on the Psycho-sexual Daily Questionnaire; ii. Physical Function Trial evaluated the percentage of men who improved their walking distance in the 6-minute walk test and; iii. Vitality Trial evaluated the percentage of men whose score on the FACIT–Fatigue scale increased by at least 4 points.

All men were evaluated at baseline and at 3, 6, 9 and 12 months of the treatment. There was a moderate improvement in sexual activity and desire in men who received TRT, compared with the placebo group. On the other hand, improvements in physical function and vitality domains were not significantly different. Moreover, there was not any difference between the groups in terms of prostate cancer incidence, lower urinary tract symptoms and cardiovascular events.

The findings of this study are important as it illustrates that TRT can ameliorate the sexual functions of elderly men without increasing the risk of adverse effects. However, further clinical studies must be conducted in order to elucidate the actual efficacy and safety of TRT in hypogonadal men.

David Cohen, MD

The malleable implant salvage technique: infection outcomes after mulcahy salvage procedure and replacement of infected inflatable penile prosthesis with malleable prosthesis

Gross MS, Phillips EA, Balen A, Eid JF, Yang C, Simon R, Martinez D, Carrion R, Perito P, Levine L, Greenfield J, Munarriz R. *J Urol* 2016;195:694-698.

**Editorial Comment:** The implant of penile prosthesis (PP), especially the inflatable penile prosthesis (IPP), is the gold standard procedure for erectile dysfunction when all other treatment options have failed. Infection of PP is the most concerning complication of this procedure, with rates ranging between 1–3% for newly implanted PP and 10%–18% in removal and replacement procedures secondary to malfunction or malpositioning. In these cases the classical and most conservative approach is to remove all the PP, wait for a few months and reimplant the PP after the infection is healed. However, the outcomes of replaced PP are compromised due to corporal fibrosis, penile shortening and technical difficulties.

In the middle of 90's, Mulcahy et al introduced a salvage technique consisting of complete explantation of infected PP, followed by irrigation of corporal bodies with several antibiotic and antiseptic solutions and an immediate reimplantation of a new IPP. This protocol resulted in a 82% infection-free rate during follow up of 65 patients. Nevertheless, recent study of Zargaroff et al showed that the salvage technique was used only 17.3% of the time to treat PP infection between 2000 and 2009. In this paper, Gross et al describes a new procedure called malleable implant salvage technique (MIST) that consist of the

removal of the infected prosthesis, irrigation of corporal bodies and immediate reimplantation of a malleable prosthesis, leaving the conversion to an IPP for a second surgery. The objective was to increase the infection-free rate by maintaining the corporal space and separating it from potentially infected sites. In their retrospective, multi-institutional study that evaluated 58 patients, Martin et al reported that 54 patients (94%) remained free of infection during a follow up that ranged between 1 to 84 months. Interestingly, 70% of the patients preferred to maintain with the malleable prosthesis. The patients that decided to undergo IPP replacement were 10 years younger than the ones that did not undergo the conversion surgery.

This paper supports the high safety profile of salvage techniques in managing infected PP and provides new insights into the patients' preferences related to the reimplantation procedure. Future studies must focus on patients' satisfaction after salvage procedure and replacement of infected PP.

David Cohen, MD

Sac-1004, a pseudo-sugar derivative of cholesterol, restores erectile function through reconstruction of non-leaky and functional cavernous angiogenesis in the streptozotocin-induced diabetic mouse

Batbold D, Song KM, Park JM, Park SH, Lee T, Ryu DS, Suh YG, Kwon YG, Ryu JK, Suh JK. *J Urol* 2016. Epub ahead of print.

**Editorial Comment:** Diabetes mellitus (DM) is one of the most common chronic diseases in nearly all countries<sup>1</sup>; DM is characterized with inappropriate hyperglycemia due to lack of (or resistance to) insulin, which facilitates the onset of erectile dysfunction (ED). The frequency of ED in diabetic men has been reported to be as high as 75%.<sup>1,2</sup> Finding new treatments for diabetic ED represents a major challenge in the field of andrology as diabetic patients have poor responses to the currently available ED medications.<sup>2</sup>

Impaired neural and penile endothelial functions are hypothesized to be the main reasons for the high incidence of ED in men with DM. The potential mechanisms involved in endothelial dysfunction include the accumulation of advanced glycation products; increased levels of oxygen free radicals that reduce the availability of Nitric oxide (NO); impaired endothelial and neuronal NO synthesis, expression, and activity; and increased endothelial barrier permeability.<sup>1</sup>

The maintenance of the endothelial barrier is critical for vascular homeostasis and it is maintained by the interaction of junction proteins between adjacent cells. This interaction is stabilized by actin cytoskeleton forming cortical actin ring. Sac-1004, a pseudo-sugar derivative of cholesterol which was recently demonstrated to prevent vascular leakage, normalize tumor vessels and prevent metastasis in a sustained manner. Sac-1004 inhibited endothelial hyperpermeability induced by vascular endothelial growth factor, histamine and thrombin via

stabilization of cortical actin ring and adherens junction proteins at the cell-cell junction.<sup>3,4</sup>

In the present study, Batbold et al<sup>5</sup> evaluated the efficacy of Sac-1004 as a treatment for ED in streptozotocin (STZ) induced diabetic mice. At 8 weeks after induction of diabetes, the mice were treated with repeated penile injections of different dosage of Sac-1004 or vehicle. One week after the injections, the Sac-1004 treated mice showed a restored erectile function, increased cavernous endothelial and smooth muscle contents, induced eNOS phosphorylation and a restored endothelial cell-cell junction proteins. However, erectile function, cavernous endothelial and smooth muscle contents were returned to baseline level at 2 weeks after Sac-1004 administration, showing a lack of efficacy of the drug in a long term setting.

In addition, the authors evaluated the role of angiotensin-1 (Ang1) in Sac-1004-mediated enhancement in angiogenesis and an improvement in erectile function. For this purpose, a separate group of diabetic mice was treated, immediately before the injection of Sac-1004, with subcutaneously injection of soluble antibody to tyrosine kinase with immunoglobulin and epidermal growth factor homology domain-2, a receptor tyrosine kinase for Ang1. Interestingly, Sac-1004-mediated cavernous angiogenesis and erectile function recovery was abolished by inhibition of angiotensin-1-Tie2 signaling with soluble Tie2 antibody.

The results of this study suggested that Sac-1004 might be a highly promising treatment modality for diabetic ED; however, the lack of long term efficacy of this molecule represents a limitation of this study. Further studies are necessary to determine whether chronic administration of Sac-1004 induces long lasting recovery of erectile function.

Fabio Castiglione, MD

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How common is men's self-reported sexual interest in prepubescent children?

Dombert B, Schmidt AF, Banse R, Briken P, Hoyer J, Neutze J, Osterheider M. *J Sex Res* 2016;53: 214-223.

Many people—including *professionals*—hold the assumption that only clinical/forensic samples present a sexual interest in prepubescent children. However, statistics have shown otherwise; sexual interest in children is found among community male samples (ie, samples with no relationship to the criminal or clinical context), more often than one might think. Indeed, about 20% of community men report child pornography consumption<sup>1</sup> and 9% of men consider the possibility of having sex with children if they weren't caught.<sup>2</sup> These numbers have caught the attention of researchers, particularly because outside the forensic context it is not known if sexual interest in children is related to *actual* sexual offending against children. To overcome this gap, Dombert, Schmidt, Banse, Briken, Hoyer, and Osterheider (2016) conducted a study aimed at assessing men's self-reported sexual interest in children on the community level, and the link between sexual fantasies and sexual behaviors involving prepubescent children ( $\leq 12$  years of age). 8,718 German men responded to a web-survey; 4.1% reported sexual fantasies involving prepubescent children, 3.2% reported sexual offending against prepubescent children, and 0.1% reported a pedophilic sexual preference. Additionally, fantasizing with children was related to sexual offending against children. Furthermore, men presenting a sexual interest in children also reported the need of getting therapeutic help. While data seem to be showing that these men are conscious about their psychosexual condition, it is worth questioning whether the current health/social structures are ready for dealing with these individuals and their specific needs. As the authors suggest, the numbers revealed by the study—the current prevalence estimates are possibly the most accurate estimates of pedophilic sexual interest in a Western culture to date, along with the evidence showing that community men presenting sexual interest in children *actually* feel distressed and want to be helped, confirm the importance of implementing evidence-based prevention programs at the community level; these programs are ultimately aimed at preventing child sexual abuse, including child prostitution and child sex tourism.

Joana Carvalho, PhD

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