Male Clinical

**Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia.** A Casabé, CG Roehrborn, LF Da Pozzo, S Zepeda, RJ Henderson, S Sorsaburu, C Henneges, DG Wong, L Viktrup. J Urol 2014;191:727–33.

**Editorial Comment:** Since the launch of the 5-alpha reductase inhibitor finasteride in 1992, medical management of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) has continued to evolve. Today, in addition to 5-alpha reductase inhibitors, both alpha-blockers and phosphodiesterase type-5 inhibitors are approved for the treatment of men with BPH/LUTS. Recently, various guidelines have recommended combination of a 5-alpha reductase inhibitor with an alpha-blocker to achieve earlier and greater LUTS improvement when compared with monotherapy of either group of drug alone. However, there is an increased risk of sexual dysfunction related to this combination of therapies that constructs the major concern related to this treatment option.

Tadalafil is a long-acting phosphodiesterase type-5 inhibitor that has recently been approved for the treatment BPH/LUTS. Clinical studies have demonstrated that tadalafil 5 mg once daily results in clinically significant improvements in BPH/LUTS with the additional benefit of restoring erectile function in patients with concomitant erectile dysfunction. In order to assess whether the combination of a 5-alpha reductase inhibitor with tadalafil may result in early LUTS improvement with fewer sexual side effects, Casabé et al. conducted a randomized, double-blind, placebo-controlled, multicenter study. The authors randomized 695 men to receive either tadalafil 5 mg or placebo once daily co-administered with finasteride 5 mg once daily over the course of 26 weeks. The results of this study demonstrated that tadalafil 5 mg coadministered with finasteride resulted in more rapid and more significant LUTS improvement when compared with finasteride coadministered with placebo. Moreover, the finasteride/tadalafil combination significantly improved erectile function in men who had erectile dysfunction prior to initiation of treatment. These results support that once daily coadministration of tadalafil with finasteride can be the treatment of choice for men with LUTS and erectile dysfunction symptoms.

_Ege Can Serefoglu, MD, FECSM_

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**Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: The Radiation Therapy Oncology Group [0831] randomized clinical trial.** TM Pisansky, SL Pugh, RE Greenberg, N Pervez, DR Reed, SA Rosenthal, RB Mowat, A Raben, MK Buuyounouski, LA Kachnic, DW Bruner. JAMA 2014;311:1300–7.

**Editorial Comment:** All currently available prostate cancer treatment modalities include the risk of erectile dysfunction (ED), and a significant amount of prostate cancer patients experiences ED after radiotherapy. In this multicenter, stratified, placebo-controlled, double-blind, parallel-group study, Pisansky et al. aimed to determine whether tadalafil 5 mg once daily maintains spontaneous erection.
erectile function in men treated with radiotherapy for prostate cancer. The authors randomized 242 men whose prostate cancer was treated with radiation to receive either daily tadalafil 5 mg treatment or placebo for 24 weeks. The International Index of Erectile Function (IIEF) was administered before radiotherapy, at week 2, week 4, between weeks 20 and 24, between weeks 28 and 30, and 1 year thereafter. IIEF did not demonstrate any statistically significant difference between the two groups. The authors concluded that daily use of tadalafil 5 mg compared with placebo did not result in improved erectile function, and they did not recommend this treatment modality to prevent ED in these patients.

Ege Can Serefoglu, MD, FECSM

Sildenafil citrate improves erectile function after castration in a rat model. JP Mulhall, N Verma, S Deveci, R Tál, K Kobylarz, A Müller. BJU Int 2014;113:656–61.

**Editorial Comment:** Surgical or chemical castration is used as a standard therapy for metastatic cancer, and it is associated with impaired erectile function due to the imbalance between smooth muscle and collagen in the corpora cavernosa. Taking the beneficial effect of sildenafil citrate on penile tissue after cavernous nerve injury into consideration, Mulhall et al. assessed whether this molecule would result in preservation of erectile function and tissue structure in the rat penis after castration. They used 60 male Sprague-Dawley rats divided into three groups (sham, bilateral orchidectomy, and bilateral orchidectomy + sildenafil). The authors measured maximum intracavernosal pressure–mean arterial blood pressure (ICP/MAP) ratio, evaluated smooth muscle–collagen (SM–C) ratio, and defined apoptotic indices (AIs) on 7th and 28th postoperative days. The authors demonstrated that the ICP/MAP ratio was highest in the sham group, whereas it was lowest in the orchidectomy group. Rats treated with sildenafil after orchidectomy showed statistically significant improvements in their ICP/MAP ratio over the corresponding control groups; however, their ICP/MAP ratio was lower than that of rats in the sham group. On the other hand, the authors could not detect any significant differences in either SM–C ratio or AIs between the orchidectomy and orchidectomy + sildenafil groups. Considering the increased ICP/MAP ratios in the treatment group, the authors concluded that daily treatment with sildenafil may prevent or reduce the damage to penile tissue after castration.

Ege Can Serefoglu, MD, FECSM

**Lingual mucosal graft in treatment of Peyronie disease.** EA Salem, EH Elkady, A Sakr, AM Maarouf, L Bendary, S Khalil, A Shabin, H Kamel. Urology 2014;84:1374–7.

**Editorial Comment:** The optimal graft material to be used in the penile incision and grafting surgery for the treatment of Peyronie Disease (PD) continues to be a matter of debate. Although various materials have been used for grafting procedures (i.e., dermis, vein, cadaveric and bovine pericardium, dura mater, synthetic materials, and porcine small intestine submucosal extracellular matrix), there is no consensus about the ideal graft in patients with PD. Synthetic grafts are associated with inflammatory and infectious complications, whereas tissue-engineered grafts are costly. In spite of their favorable outcomes low cost, the high incidence of harvest site side effects of autologous grafts limit their wide spread use.

In this study, Salem et al. evaluated the use of lingual mucosa graft (LMG) in 17 patients with PD. The angle of deformity ranged from 45 to 70 degrees with a mean angle of 60 degrees. All patients were assessed with the International Index of Erectile Function-5 (IIEF-5) preoperatively. Postoperative evaluation included IIEF-5 score and the assessment of penile deformity after 1 month, and then every 3 months until 18 months. Donor site complications were also reported. The authors found only mild and transient donor site complications such as pain and numbness. Fifteen of the 17 patients (88.2%) had straightening of the penis at follow-up. Two patients had mild residual curvature of the penis (20 degrees) which was treated conservatively. Erectile function was maintained in 16 patients; 94% of patients reported satisfaction with the procedure. This report is the first study to analyze the use of LMG for PD, and excellent results were obtained. The advantages of this technique include easy accessibility of the tongue mucosa compared with the deeply seated buccal mucosa, lower costs compared with “off the shelf” graft materials, and lower donor site morbidity. These results must be analyzed with caution because of the short follow-up period, small sample size, and single institution nature of the study. As all patients in this series had curvature less than 70 degrees, the applicability of this tech-
technique to more severe curvature is unclear. Further studies on lingual grafts for PD are warranted.  

David Jacques Cohen, MD

**The relationship between total testosterone levels and prostate cancer: A review of the continuing controversy.** J Klap, M Schmid, KR Loughlin. J Urol 2015;193:403–14.

**Editorial Comment:** For many years, testosterone was believed to play a major role in the development of prostate cancer (PCa). In the last decades, serious controversies have emerged about the true relationship between testosterone and PCa. In this review article, the authors looked for the answers to the two main questions: (i) Is there any link between serum testosterone and incidence, grade, and aggressiveness of PCa? (ii) What is the true risk of testosterone replacement therapy (TRT) in patients with primary hypogonadism that already treated PCa or are in active surveillance program?

The authors reviewed the literature from 1994 to 2014 and analyzed the results of 45 articles were selected and analyzed, of which 18 and 17 showed a relationship between PCa and low and high total testosterone, respectively. On the other hand, 10 studies showed no relationship between testosterone and PCa.

The discrepancy in these results may be attributable to biological and/or methodological factors. The first biological explanation is the Saturation Model, which states PCa cells are sensitive to fluctuations from very low doses of testosterone. As levels increase, the androgen receptors become saturated, and additional testosterone does not influence androgen-driven changes in prostate tissue growth. Additional biological factors that must be considered include the functional activity of androgen receptors in prostate tissue and the theoretical role of intraprostatic testosterone and dihydrotestosterone. Finally, the effects of estrogens on carcinogenesis of PCa are incompletely elucidated; some of the biological effects of testosterone on the prostate may be mediated by aromatization of testosterone to estradiol.

The main methodological failure of this analysis is that only three of the 45 studies collected blood for testosterone assay in the morning and only one study collected two or more samples. Thus, testosterone identified as low in some studies may have been normal on another day or at another hour during the day. No definitive conclusions can be made about the relationship about testosterone and PCa from these trials. Additional trials must be done to overcome the methodological obstacles and clarify biological hypothesis.

There are relatively few papers on TRT in patients previously treated for PCa. It is advisable that patients considering TRT after treatment for PCa be extensively counseled on the controversies surrounding TRT in this situation; patients who wish to proceed should sign informed consent forms and be followed very closely with serial digital rectal examination and PSAs. There are only two studies of TRT in patients in active surveillance for PCa with contradictory results. TRT may be considered in such cases, but it must be made clear that the long-term risks are unknown, and there exists the possibility of PCa progression from this treatment.

David Jacques Cohen, MD

**Male Basic Science**

**Oxidative stress associated with middle aging leads to sympathetic hyperactivity and downregulation of soluble guanylyl cyclase in corpus cavernosum.** FH Silva, C Lanaro, LO Leiria, RL Rodrigues, AP Davel, MA Claudino, HA Toque, E Antunes. Am J Physiol Heart Circ Physiol 2014;307:H1393–400.

**Editorial Comment:** The role of sympathetic neurotransmission in erectile dysfunction (ED) is increasingly becoming a hot topic in sexual medicine, particularly in the field of penile rehabilitation program after radical prostatectomy. The leading theory dictates that nitric oxide (NO) is a negative modulator of sympathetic neurotransmission. Vasoconstriction and increased corporal smooth muscle tone produced by sympathetic signals are enhanced by impaired NO bioavailability. This enhancement of hypercontractility in cavernosal tissues and their supplying arteries promotes the development of ED.

In the present article, the authors investigated the role of oxidative stress in the pathogenesis of ED focusing on its link with the development of an aberrant sympathetic neurotransmission in the erectile tissue. The authors report that ED in middle-aged rats (10 months old) is associated with up-regulation of mRNA coding for tyrosine hydroxylase (a specific marker for sympathetic nerve), and increased phenylephrine-induced contractions in organ bath studies, along with alpha1-adrenoceptor-mediated cavernosal vasoconstriction. Furthermore, decreased expres-
sion of soluble guanylyl cyclic in cavernosal smooth muscle was also reported.

NADPH oxidase is localized in sympathetic nerve fiber endings, which indicates a superoxide-mediated mechanism in neurovascular control. Interestingly, the present study reported that the treatment with the NADPH oxidase inhibitor “apocynin” normalized the reactive oxygen species (ROS) levels and restored the tyrosine hydroxylase mRNA expression and hence the sympathetic cavernosal contractions. These results demonstrate a role for the elevated oxidative stress contributing to ED in middle-aged rats. Excess of superoxide could promote a higher tyrosine hydroxylase expression, whereas in the latter, it reduces NO bioavailability and sGC expression, which in turn causes ED by mechanisms involving impairment of relaxations and facilitation of contraction. Based on these data, the authors concluded that antioxidant therapies might represent an interesting approach to manage ED in aging population.

While the results presented provide a clear message on the role of oxidative stress in sympathetic hyperactivity in aging induced ED, this study is not devoid of limitations. The major study limitations include the lack of an in vivo evaluation of erectile function and the “age” of the rat selected for mimicking the middle age human condition. Without an in vivo evaluation, it not possible to evaluate the degree of erectile function impairment in the rats. Moreover, a 10-month-old rat is equivalent to a 28-year-old man, and older animals (20–22 months) should have been selected to study the age-dependent effects on erectile function.

**Fabio Castiglione, MD**

Inhibition of ninjurin 1 restores erectile function through dual angiogenic and neurotrophic effects in the diabetic mouse. GN Yin, MJ Choi, WJ Kim, MH Kwon, KM Song, JM Park, ND Das, KD Kwon, D Batbold, GT Oh, GY Koh, KW Kim, JK Ryu, JK Suh. Proc Natl Acad Sci U S A 2014;111:E2731–40.

**Editorial Comment:** Much progress over the past two decades has improved our understanding of the molecular pathophysiology of erectile dysfunction (ED). However, few medical therapies have been developed since the introduction of phosphodiesterase inhibitors in 1998. Nonetheless, our improved understanding of erectile function and dysfunction has yielded new drug targets over the past several years, including extracellular-related kinase, guanylate cyclase, the RhoA/Rho-kinase pathway, and the endothelin and angiotensin receptors. In 1996, nerve injury-induced protein 1 (Ninjurin 1, Ninj1) was identified as an induced factor after axotomy in neurons and Schwann cells that promote neurite extension [1]. Ninj1 is a cell surface molecule that has roles in regulating nervous and vascular systems. In 2013, Yin et al. examined the role of Ninj1 in the penis and found that Ninj1 levels are upregulated after murine penile cavernous nerve injury, and that Ninj1 inhibition results in increased neurofilament and endothelial cell proliferation [2]. These findings established a foundation for Ninj1 as a novel therapeutic target for cavernous nerve injury-induced ED.

Rather than merely focusing on surgical nerve injury, the same group more recently evaluated the role of Ninj1 in mice with diabetes-induced ED, finding that Ninj1 inhibition facilitates erectile function in this setting as well [3]. In this study, Yin et al. evaluated the efficacy of Ninj1-neutralizing antibody and knockout of Ninj1 in preserving erectile function in streptozotocin (STZ)-treated mice. STZ results in a diabetic condition via pancreatic beta cell toxicity. First, the authors demonstrated increased expression of Ninj1 in the penis of diabetic mice and in mouse cavernous endothelial cells (MCECs) exposed to high glucose conditions mimicking diabetes mellitus. They then evaluated erectile function after intracavernosal injection of Ninj1-blocking antibody in the STZ mice, observing restoration of erectile function to baseline in these mice. However, this positive effect on erectile function was short-lived, indicating that optimization of Ninj1 inhibition is necessary. Ninj1 inhibition also resulted in proliferation of cavernous endothelial cells, and decreased apoptosis in these cells, supporting an angiogenic effect. The authors demonstrated that Ninj1-mediated angiogenic effects arise from signaling via the angiopoietin 1 (Ang1)-tyrosine kinase with Ig and epidermal growth factor homology domain-2 (Tie2) pathway by blocking this pathway. The Ang1–Tie2 pathway is essential in generating functional, nonleaky blood vessels. Ninj1 inhibition was also found to lower levels of reactive oxygen species (ROS), a further positive finding given that high levels of ROS induce apoptosis.

When evaluating the effects of Ninj1 inhibition on nerve content, the authors found not only more
neurofilaments in mouse penis undergoing Ninj1 inhibition but higher levels of neuronal nitric oxide synthase (nNOS) in Ninj1-inhibited penis. Preservation of nNOS is significant given that nNOS release from nerve terminals initiates penile erection. These effects on nerve preservation were mediated by secretion of nerve growth factors (NGFs) including brain-derived neurotrophic factor, NGF, and neurotrophin 3, which were markedly upregulated during Ninj1 inhibition.

The authors then expanded their investigations to Ninj1 knockout mice, which had preserved erectile function even in the setting of STZ treatment, further confirming a role for Ninj1 in ED pathogenesis. Finally, while the presence of Ninj1 and Ang1-Tie2 are important in regulation of diabetes-induced ED, the entire pathway has not yet been described. To identify Ninj1 target genes, the authors used gene expression microarray technologies in MCECs exposed to high and normal glucose conditions, and with and without knockdown of Ninj1 using siRNA, finding numerous genes that may play a role in the pathway.

This study is significant in that it describes a novel pathway regulating both angiogenesis as well as neurogenesis in the penis and suggests a novel therapeutic target in the setting of ED. The detailed mechanisms by which Ninj1 is induced, the components of the Ninj1 pathway, and the mechanisms of angiogenesis and neurogenesis mediated by this pathway remain to be defined. In addition, the role of the Ninj1 pathway in humans is currently unknown. It will indeed be interesting to see what future investigations yield in determining whether Ninj1 is a bona fide regulator of human erectile function, and therefore a target for future therapies.

Alexander W. Pastuszak, MD, PhD

References
1 Araki T, Milbrandt J. Ninjurin, a novel adhesion molecule, is induced by nerve injury and promotes axonal growth. Neuron 1996;17:353–61.
2 Yin GN, Kim WJ, Jin HR, Kwon MH, Song KM, Choi MJ, Park JM, Das ND, Kwon KD, Batbold D, Kim KW, Ryu JK, Suh JK. Nerve injury-induced protein 1 (Ninjurin-1) is a novel therapeutic target for cavernous nerve injury-induced erectile dysfunction in mice. J Sex Med 2013;10:1488–501.
3 Yin GN, Choi MJ, Kim WJ, Kwon MH, Song KM, Park JM, Das ND, Kwon KD, Batbold D, Oh GT, Koh GY, Kim KW, Ryu JK, Suh JK. Inhibition of Ninjurin 1 restores erectile function through dual angiogenic and neurotrophic effects in the diabetic mouse. Proc Natl Acad Sci USA 2014;111:E2731–40.

Male Mental Health

Relations between trait impulsivity, behavioral impulsivity, physiological arousal, and risky sexual behavior among young men. KJ Dereffinko, JR Peters, TA Eisenlohr-Moul, EC Walsh, ZW Adams, DR Lynam. Arch Sex Behav 2014;43:1149–58.

Editorial Comment: The outcomes of risky sexual behavior have a long-term negative impact on individuals’ private and public lives. Young adults are at particular risk for these outcomes. A sample of 135 undergraduate men (Mage = 19.5) participated in an experimental study aimed at assessing the unique predictive value of impulsivity-related traits, behavioral markers of risk taking, and physiological reactivity in three distinct indicators of risky sex: number of sexual partners, having sex with strangers, and irregular condom use. For the first time, three approaches, usually considered individually in the study of sexual risk taking, were incorporated in a single design: (i) trait markers of risky sex (evaluated by self-report), (ii) behavioral markers of risky decisions (measured by experimental means, usually involving some level of awareness), and (iii) physiological reactivity to emotional stimuli (measured experimentally, involving no awareness by the participant). In this study, participants answered to a set of self-report measures assessing impulsivity (negative urgency, positive urgency, and sensation seeking), participated in a behavioral risk taking task (the Balloon Analogue Risk Task [BART]) and in a reward-seeking Go/No-Go task, and underwent a psychophysiological evaluation (skin conductance reactivity) to pleasant vs. unpleasant stimulation. Scores on these markers were used as predictors of the mentioned indicators of risky sex. Sensation seeking (β = 0.19) and risk taking on the BART (β = 0.18) significantly predicted number of sexual partners (P < 0.05). Also, sensation seeking (β = 0.60), risk taking on the BART (β = 0.52), and skin conductance reactivity to both types of stimuli (β = 0.53) predicted the risk of ever having sex with a stranger (P < 0.05). Finally, negative urgency predicted irregular condom use (β = 0.14, P < 0.05). Prevention programs (e.g., HIV prevention) are expected to benefit from this kind of multimethod assessment. Sexual risk indicators are differently impacted by trait and physiological markers; preventive strategies should be designed accordingly.

Joana Carvalho, PhD
Midlife menopause: Male partners talking. L Liao, S Lunn, M Baker. Sex Relation Ther 2015;30:167–80.

Editorial Comment: How do men appraise menopause? A lot has been written about women’s perceptions of menopause and so little about the male perspectives. In this qualitative study, eight heterosexual male partners ($M_{age} = 51.5$) described their perceptions about midlife menopause. Male partners’ views of menopause were analyzed through thematic analysis (TA); this method is particularly suitable when no structured empirical data exist. Participants were interviewed by a white female psychologist in her early thirties, either at the participant’s home or the interviewer’s workplace. The following general topics emerged:

**Female Transformation**
Menopause was seen as a process, something to be entered into and completed. During this process, women were described as emotionally charged. Simultaneously, some men appraised menopause as a chance of personal growth and a period in which women can expand into a more liberating life.

**A Shared Process**
Men recognized that menopause is a shared process implying a transition to a new dyadic stage. Yet men felt they were pulled unprepared into this process. They felt helplessness. They were expected to support their partners but were left unsupported by the system. Also, men alluded to some positive and negative outcomes in sex. Some expressed preoccupation about the partner’s loss of libido. But, on the other hand, menopause was also regarded as positive (e.g., liberation from the contraceptive constraints).

**A Sex Taboo**
Menopause was referred as a taboo topic possibly because of its overlap with sexual phenomena. Men do not talk about it because they feel embarrassed. Menopause was regarded as a sign of diminished female sexuality. Men felt they had to respect the partners’ privacy rather than discuss this topic. Finally, most interviewees agreed that there is a lack of general knowledge on this subject; menopause was defined as a nebulous area and not many options exist to clarify men’s doubts. Women seem to be the only target of information and support.

In all, men lack knowledge on menopause because of a social etiquette that defines who is expected to receive such information. Yet men want to know more about menopause as they too have to go through this process. Although this was a first attempt to understand men’s perspectives about menopause, findings support the role of professionals in assisting male partners of menopausal women.

Joana Carvalho, PhD

LGB/Transgender

Social connection, relationships, and older lesbian and gay people. Barrett C, Whyte C, Comfort J, Lyons A, Crameri, P. Sex Relation Ther 2015;30:131–42.

Editorial Comment: Many sexual medicine issues arise in older patients and clients. Yet the issues cannot be addressed successfully if the person experiencing them does not (i) present to the practitioner in the first place or (ii) is fearful of fully disclosing their specific situation. For older lesbian and gay people, both of these challenges to treatment and care present a larger barrier than for their heterosexual counterparts. Barrett et al. provide ground-breaking exploratory research into the issues which often prevent older lesbian and gay persons from seeking medical assistance or being forthcoming with their situation. The research appropriately uses qualitative methods to delve deep for a robust understanding of how these older lesbian and gay people have come to manage their lives in today’s world, one that is massively different from the one in which they grew up. In a word, discrimination is still very much a perceived reality for older lesbian and gay persons, perhaps more so than for younger generations. The person we are today is the sum of a lifetime of experiences. The sexual medicine practitioner would benefit from reading the article to gain a more robust and lived historical understanding of their older lesbian and gay patients or clients, leading to better treatment and care.

Christopher Fisher, PhD, MA, AA, BS