Expert Opinion

Ashley Publications
www.ashley-pub.com

Transdermal and topical pharmacotherapy for male sexual dysfunction

Michael Ohebshalom & John P Mulhall†
†*Weill Medical College of Cornell University, New York Presbyterian Hospital, USA*

Transdermal and topical pharmacotherapies have been used for the treatment of male sexual dysfunctions for some time and are well-accepted treatment modalities for these conditions. A Medline search was conducted for transdermal and topical medications, examining published literature over the past two decades. From this search a comprehensive review has been compiled of the available transdermal and topical treatment options for the treatment of male sexual dysfunctions, particularly erectile dysfunction, Peyronie's disease and hypogonadism. It is likely that the transdermal and topical drug armamentarium for sexual dysfunction, male and female, will grow over the next decade.

Keywords: erectile dysfunction, hypogonadism, iontophoresis, Peyronie's disease, testosterone, transdermal

Expert Opin. Drug Deliv. (2005) 2(1):115-120

1. Transdermal delivery of drugs

The skin is the body's largest organ, weighing ~ 3 kg. It performs major functions including protection from external microorganisms and infection, body temperature regulation, excretion of waste products, sensation to the outside environment, and vitamin D production [1]. The skin has two main layers: the epidermis and the dermis. The epidermis is the outer layer of cells that serve as a protective shield for the body. It consists of five sublayers: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The dermis lies below these sublayers, and is richly supplied with blood vessels, lymph vessels, nerves and specialised glands [2]. It is held together by a collagen matrix produced by fibroblast, and consists of the papillary layer and the reticular layer: both integral to the absorption of drugs transdermally. The main barrier of the skin is located in the stratum corneum: the outermost layer of the skin. In fact, the major obstacle for topical drug delivery is the low diffusion rate across the stratum corneum. The lipid region in this stratum forms the only continuous structure, and substances applied to the skin must pass through these regions; therefore, lipophilic molecules are absorbed more readily [3].

Transdermal therapy is an accepted form of delivery for several drugs including nitroglycerine, lidocaine, nicotine, testosterone, opiates and clonidine among others [4]. There have historically been a handful of transdermal therapies for male sexual dysfunction. These involve gels for erectile dysfunction (ED), verapamil preparations for the treatment of Peyronie's disease and testosterone preparations for the treatment of hypogonadism [5]. The use of gels and creams applied to the skin has immediate acceptability and palatability for patients, and is one of the safest modalities of drug delivery; with adverse effects being limited to skin irritation.

2. Erectile dysfunction

ED is defined as the consistent inability to obtain and/or maintain an erection sufficient for satisfactory sexual performance [6]. The prevalence of ED of any degree is

in the range of 39 – 67% depending on the population, and increases in prevalence with age. It is estimated that > 20 million men in the US alone have ED.

The penis is a highly vascular organ made up of multiple layers [7]. The outside layer comprises the skin and peripheral blood vessels. Below that are the superficial (Dartos) fascia, and the deep (Buck's) fascia. Below these are the dorsal arteries and vein of the penis, and the tunica albuginea. The tunica consists of two fibro-elastic connective tissue layers, which are composed of predominantly collagen, specifically inner circular and outer longitudinal layers [8]. The inner circular layer serves to contain the erectile tissue's diameter during erection, whereas the outer longitudinal layer is present to regulate the length of the expanding penis during erection. The corpora cavernosa, which are paired cylinders that run on the dorsum of the penis, are composed of a latticework of spongy tissue known as the corporal sinusoids (lacunae). The sinusoids are composed of a combination of smooth muscle, endothelium and inter-digitating nerve fibres. A venous drainage system is situated between the tunica and corporal muscle, known as the subtunical venules. The corpus spongiosum is located ventrally between the two cavernosa, and is responsible for maintaining a lower pressure in order to allow semen to pass through the urethra during ejaculation.

2.1 Physiology of erection

Erection is a hydraulic event, which involves the inflow followed by the entrapment of pressurised arterial blood. The key event in the development of an erection is relaxation of the smooth muscle–sinusoidal complex, and the arteries and arterioles that feed it, primarily mediated by the molecule nitric oxide [9]. Arterial blood flows in to fill the relaxing sinusoids and the sinusoidal mass expands. In this phase of erection, arterial inflow exceeds venous outflow. While the central sinusoidal mass expands, the subtunical venules are compressed against the tunica. As the venous outlet is compressed, outflow decreases, thus causing an erection (tumescence and subsequently rigidity).

2.2 Transdermal drugs in erectile dysfunction

There have historically been a number of topical agents for the treatment of ED, and there are currently a number of topical drugs undergoing evaluation in trials for the treatment of ED. Nitroglycerine is a nitric oxide donor and in the form of a 2% paste is a well-recognised coronary vasodilator, which has been shown to induce penile arterial vasodilatation when applied directly to the penile shaft [10]. It has been found to result in tumescence, but rarely in penile rigidity of adequate quality for intercourse. Furthermore, unless applied beneath a condom, the medication is absorbed through the vulvar mucosa, resulting in adverse events for the female partner: especially headache. Such a headache may occur in men also. As a result, it has been abandoned in clinical practice.

Papaverine is a nonspecific phosphodiesterase inhibitor that has gained widespread acceptance as an effective intracavernosal (penile injection) medication for ED. It has also been formulated as a gel for application to the penile area. Unfortunately, studies have illustrated that the relatively large molecule (molecular weight 376 Da) does not readily cross the dermal barrier for adequate absorption. Results were disappointing for topical use and its development has been halted [11].

Alprostadil 1%+SEPA® gel (Topiglan®; Macrochem, Lexington, MA), is a topical agent applied to the glans penis. SEPA (soft enhancer of percutaneous absorption) is a transdermal enhancer that alters the fluidity of lipids in the stratum corneum and increases the penetration of alprostadil. In a Phase II, double-blind, placebo-controlled study involving 60 patients with moderate-to-severe ED, Topiglan produced a greater angle of erection and maximum rigidity compared with the placebo gel; 39% of patients reported an erection sufficient for vaginal penetration [12]. Side effects including site reactions (burning or warmth) were described as minor or mild and were not significantly different from placebo. Alprox-TD® (NexMed, Inc., Robbinsville, NJ) is a topical gel that combines alprostadil with the transdermal delivery enhancer: NexACT®. This gel is dripped onto the urethral meatus and, therefore, could be considered a transurethral agent. In a randomised, double-blind, placebo-controlled study involving > 1700 patients in 85 US clinics, Alprox-TD achieved a significant improvement in erectile function as measured by the validated Erectile Function Domain of the International Index of Erectile Function questionnaire [13]. Side effects were localised to local application sites, and the discontinuance rate due to this was 3%.

The mechanism of delivery of these agents is through the corpus spongiosum to the corpora cavernosa, a mechanism identical to that of transurethral agents (MUSE®, Vivus, Menlo Park, CA). The transfer of medication from the spongiosum to cavernosum is predicated based on the presence and patency of vascular channels between these two corporal bodies. Thus, in men with poorly developed vascular channels, or when these channels are not fully dilated (in the supine as opposed to the upright position for example), medication will fail to be delivered to the corpora cavernosa. It is unlikely that transdermal agents for ED will ever have efficacy greater than that of transurethral alprostadil as monotherapy. It is conceivable, however, that if combination agents were applied, or iontophoresis was utilised, the efficacy rates might be improved.

3. Peyronie's disease

Peyronie's disease is a fibromatosis of the penis, which affects up to 3% of men [14]. The initial presenting symptom is most often penile curvature, which results from scar (plaque) formation in the tunica albuginea of the penis. The plaque results in restricted expansion of the tunica during erection, which results in curvature. This may lead to an inability to participate in sexual intercourse, as well as a painful erection.

The aetiology of Peyronie's remains unknown, although it is thought that trauma is the most likely inciting event. Other proposed contributors include autoimmune factors, fibrogenic cytokine overexpression and cytogenic abnormalities. Current therapies for Peyronie's disease focus on reducing or reversing the fibrosis that occurs in this disease process, thereby decreasing the penile deformity and pain that are associated with it.

A number of oral agents have been used in the treatment of Peyronie's disease, including potassium para-aminobenzoate, vitamin E, colchicine and tamoxifen [14]. However, there are no randomised, placebo-controlled studies that demonstrate that any of these agents are effective in resolution of penile deformity. Likewise, there are a number of intralesional injection agents including verapamil, collagenase, interferon and corticosteroids. As with oral agents there is an absence of randomised, placebo-controlled trials demonstrating efficacy. However, uncontrolled studies have found improvements in curvature and hour-glass deformity; therefore, the drug continues to be used by some urologists.

3.1 Transdermal drugs in Peyronie's disease

The drug most-studied as a transdermal agent for Peyronie's disease is verapamil. Verapamil is a calcium channel blocker, which under adequate concentrations has been demonstrated to change fibroblast behaviour and encourage scar remodelling [15]. Verapamil also increases levels of collagenase, which may increase scar matrix degradation. Transdermal verapamil gel was introduced to the market in the mid-1990s as a less invasive option as compared with the more invasive injectable (intralesional) form [16]. Verapamil gel is applied to the penile shaft overlying the location of the tunical scar. In a double-blind, randomised analysis of 50 patients treated for 3 months, verapamil gel was shown to be statistically better than placebo with regard to curvature correction, decrease in plaque size, and improvement in erection quality, with 91% of men reporting improvement in penile curvature and 71% of men reporting better erection quality. These data have not been replicated by other centres. Indeed, Martin *et al.* demonstrated that the application of verapamil gel to the penile skin failed to result in measurable levels of verapamil within the tunica albuginea [17]. In these patients verapamil was detected in the urine, indicating systemic absorption of the medication. Transdermal delivery of verapamil by iontophoresis is an alternative mode of administration.

Iontophoresis is an effective and painless method of delivering medication to a localised tissue area by applying electrical current to a solution of the medication. Depending on the positive or negative current of a specific medication, an oppositely charged current will drive the medication into the target tissue. Constant current iontophoresis involves the application of a small electrical potential to maintain, as its name suggests, a constant current. The amount of compound delivered is directly proportional to the quantity of charge passed. It depends on the applied current, the duration of current application, and the area of the skin surface in contact with the active electrode compartment. Advantages of this technique include an improved onset time and a more rapid offset time; that is, once the current is switched off, there is no further drug transport. Moreover, the current profile can be customised to achieve the desired drug input kinetics depending on whether continuous or pulsatile delivery in required.

Using an electromotive drug administration (EMDA) device, verapamil with dexamethasone has been administered to the penile shaft. In a prospective, uncontrolled study of 100 patients treated with dexamethasone and verapamil, it was found that 96% of men reported a reduction in pain, 37% reported a decrease in penile curvature, 39% had restitution of erectile function, and 44% reported an improvement in sexual activity. The only reported treatment-associated side effects were transient erythema and oedema at the electrode site in ~ 1% of patients [18].

EMDA is now FDA approved in the US for the treatment of Peyronie's disease and can be performed at home allowing convenient, undisturbed therapy. Additional studies are needed to investigate this modality. EMDA is a treatment that offers a new intermediate level option for the man who is distressed by his Peyronie's disease but does not want or need to undergo surgical correction and prefers to avoid intralesional injection therapy. At this time there is no convincing evidence that the simple application of any gel without iontophoresis has any role in the treatment of Peyronie's disease.

4. Hypogonadism

Hypogonadism is a condition in which there is a deficiency of testosterone. It may be caused secondarily by pituitary or hypothalamic defect, or by primary failure of the testes to function normally. Hypogonadism is associated with a number of abnormalities, including sexual dysfunction [19]. It has been reported to reduce the frequency of sexual thought and intercourse, as well as the quality of sexual performance [20]. In experimental models, administration of testosterone has been found to re-establish sexual behaviour, as well as contributing a role in maintaining nitric oxide synthase (NOS) activity necessary for erections [21].

4.1 Physiology of testosterone production

In males, most testosterone is produced in the Leydig cells of the testes. Its production and release is regulated by luteinizing hormone (LH) from the anterior pituitary, which converts cholesterol into testosterone [22]. Testosterone also suppresses the release of gonadotropin-releasing hormone in the hypothalamus, and follicle-stimulating hormone and LH in the pituitary by means of a negative-feedback mechanism [23]. In the blood, only 1 – 2% of total testosterone is unbound to proteins; only this free portion has endocrine effects on the target cells. About a half of the circulating testosterone is bound to sex hormone binding globulin, whereas the remaining half is bound to albumin. Testosterone secretion is circadian in

nature but highly variable. It is secreted in pulses 8 – 14 times a day; highest levels are present in the morning on waking.

4.2 Testosterone and sexual function

A number of researchers have demonstrated that castrating animals (rats, dogs, cats) results in decreased response of the erectile tissue to chemical and electrical stimulation, and that the castrated animals demonstrate greater amounts of collagen on histopathology [24]. Others have demonstrated that low testosterone states in animal models result in a decrease in the density of NOS staining nerve fibres within the corpus cavernosum [25]. These findings were confirmed by other workers assessing NOS nerve fibre density and NOS mRNA levels [21].

Reduced androgens in the rat model have also been shown to lead to smooth muscle apoptosis within 7 days of castration [26]. Furthermore, significant work has been conducted on the ability of castration to induce veno-occlusive dysfunction in the rat model [27]. Thus, it can be seen that the complete absence of testosterone impacts negatively on erectile tissue structure and function. Whether these data can be readily extrapolated to the human penis is unknown, as the agonadal state induced in animals may not be representative of the hypogonadal male [28]. Likewise, studies of androgen supplementation in eugonadal males are difficult to extrapolate to clinical practice for the physician who is faced with a patient with low (but not castrate level) serum testosterone.

4.3 Transdermal and topical testosterone preparations

There have been six topical testosterone preparations developed for the treatment of hypogonadism, which involve testosterone application to -the skin or buccal mucosa. Testoderm® (AlzaCorp, Palo Alto, CA) is a transdermal patch placed on the scrotum once daily. It is applied in the morning, thereby mimicking the physiological diurnal pattern of morning peaks. 5α-Reductase in the scrotal skin then converts the testosterone to dihydrotestosterone (DHT). Ahmed *et al.* reported five men with mean pretreatment testosterone levels of 45 ± 12 ng/dl. Their testosterone increased to 436 ± ng/dl at 9 – 12 months [29]. McClure *et al.* reported normalisation of serum testosterone, mood, energy and sexual function, and no skin reactions in four men followed up to 26 months [30]. Androderm® (Watson Pharmaceuticals, Corona, CA) is a 2.5 mg nonscrotal permeation-enhanced testosterone transdermal system. Patches are applied to the arm, back or upper buttocks daily. Peak testosterone levels are achieved by morning time. Thirty-two to sixty per cent of patients have experienced skin irritation from this patch, and 9% have discontinued its use for skin reactions [31]. In a 4-week trial, pretreatment testosterone levels increased from 167 ± 27 ng/dl to 1273 ± 138 ng/dl [31]. Testoderm TTS (AlzaCorp, Palo Alto, CA) is a 5 mg patch that is applied to the skin in the morning, reaching peak levels in 2 – 4 h. Skin irritation has been observed in 12% of patients, with only 1% of patients discontinuing use [32]. Androgel® (Solvay Pharmaceuticals, Brussels, Belgium) is a 1% hydroalcoholic gel that is applied to the skin. It dries in < 5 min, and is slowly absorbed into the skin, releasing testosterone incrementally. It has been found to have substantially less skin irritation compared with the testosterone patches. The possibility of interpersonal transfer of testosterone gel has been shown to be very low. In the pivitol 6-month trial of testosterone gel, 227 hypogonadal men received daily testosterone gel 50 or 100 mg/dl or testosterone patch (nonscrotal 5 mg). Testosterone gel replacement improved sexual function and mood, increased lean mass and muscle strength, decreased fat mass and had substantially less skin irritation and study discontinuation compared with testosterone patch. Dose adjustment from 50 to 75 mg/dl was required in 27% of subjects and by study end, in 64.8% of subjects [33]. Testim® (Auxilium Pharmaceuticals, Norristown, PA) is another testosterone gel product, which is also applied in identical doses to Androgel. It has been found to produce higher serum levels of total and free testosterone and DHT than all other transdermal testosterone preparations [34].

Striant® (Columbia Laboratories, Livingston, NJ) is the first ever buccal system for testosterone delivery [35]. The drug is delivered via a tablet-like product that adheres to the gum surface of the mouth, above the upper teeth. As it is given twice daily, the buccal system softens and moulds to the shape of the gum, producing a gel-like form that remains in place over each 12-h dosing period. It is absorbed into the bloodstream directly, bypassing intestinal absorption, thus avoiding liver toxicity. In a Phase III trial involving 82 men, 86% of patients had an average testosterone concentration within the normal range at the end of the 12-week trial [33]. The most frequent adverse events were gum or mouth irritation, bitter taste, gum pain/tenderness and headache. Of note, most of the gum-related adverse events resolved within 14 days of use.

Clinical experience has shown us that using gels or patches translates into physiological serum testosterone levels in the vast majority of patients. The use of gels has significantly reduced the skin irritation rates; thus, in the authors' practice gels are first-line agents. Both have reduced the use of intramuscular testosterone administration dramatically. Finally, there is limited, but growing, experience with the buccal system, and its exact remains to be defined, but some transdermal agent failures with Striant have been salvaged, and have, thus, averted the need for intramuscular testosterone administration.

5. Expert opinion

The role of transdermal gels in the management of hypogonadism is well established. This route offers the most physiological approach to testosterone supplementation with abrogation of the peaks and troughs that occur with intramuscular supplementation, and circumvents skin irritation issues that occur with transdermal patches. In the management of ED it is virtually certain that transdermal agents will be available in the not-too-distant future. However, it is also almost certain in our opinion that this route will have utility only in

men with mild ED. This route has all of the problems associated with transurethral delivery. The medication will be applied to the glans penis or dripped into the urethral meatus, will be absorbed into the corpus spongiosum and then will need to be transferred to the corpora cavernosa. This system, using a mechanism identical to the true transurethral route, will probably lack efficacy and consistency for men with moderate-to-severe ED, as has been seen with the currently available transurethral agent. Of note, this population of ED sufferers represents the majority of men seen in the authors' practices. Finally, in Peyronie's disease there is no data that transdermal application of drugs can permeate the tunica albuginea without the use of iontophoresis. The use of the latter technology can deliver medication to the tunica; however, there is a need for robust, randomised, placebo-controlled studies to document efficacy in the resolution or prevention of progression of the penile deformity associated with Peyronie's disease.

Bibliography

1. SALASHE SJ, BERNSTEIN G, SENKARIK MS: *Surgical anatomy of the skin.* McGraw Hill (1988):241.
2. FREINKEL R, WOODBY D: *The Biology of the skin.* Parthenon Publishing (2001):162.
3. BOUWSTRA JA, HONEYWELL-NGUYEN PL: Skin structure and mode of action of vesicles. *Adv. Drug Deliv. Rev.* (2002) **54**(Suppl. 1):S41-S55.
4. MORALES A: Developmental status of topical therapies for erectile and ejaculatory function. *Int. J. Imp. Res.* (2000) **12**(Suppl. 4):S80-S85.
5. PRYOR JL, REDMAN B: New therapies and delivery mechanisms for treatment of erectile dysfunction. *Int. J. Imp. Res.* (2000) **12**:S158.
6. NIH Consensus Developmental Panel on Impotence. *JAMA* (1993) **270:**83.
7. Gray's Anatomy of the Human Body, 30th edition ed.
8. ABOSEIF SR, LUE TF: Fundamentals and hemodynamics of penile erection. *Cardiovasc. Intervent. Radiol.* (1988) **11**(4):185-190.
9. RAJFER J, ARONSON WJ, BUSH PA, DOREY FJ, IGNARRO LJ: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to noradrenergic, noncholinergic transmission. *N. Engl. J. Med.* (1992) **326**(2):90-94.
10. OWEN JA SAUNDERS F, HARRIS C *et al.*: Topical nitroglycerin: a potential treatment for impotence. *J. Urol.* (1989) **141**(3):546-548.
11. KIM ED, ELRASHIDY R, MCVARY KT: Papaverine topical gel for treatment of erectile dysfunction. *J. Urol.* (1995) **153**(2):361-365.
12. GOLDSTEIN I, PAYTON TR, SCHECHTER PJ: A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the office treatment of erectile dysfunction. *Urology* (2001) **57**(2):301-305.
13. PADMA-NATHAN H, STEIDLE C, SALEM S, TAYSE N, YEAGER J, HARNING R: The efficacy and safety of a topical alprostadil cream, Alprox-TD, for the treatment of erectile dysfunction: two Phase II studies in mild-to-moderate and severe ED. *Int. J. Impot. Res.* (2003) **15**(1):10-17.
14. HELLSTROM WJ, BIVALACQUA TJ: Peyronie's disease: etiology, medical, and surgical therapy. *J. Androl.* (2000) **21**(3):347-354.
15. ANDERSON MS, SHANKEY TV, LUBRANO T, MULHALL JP: *In-vitro* inhibition of peyronie's plaque fibroblast proliferation by biologic agents. *Int. J. Impot. Res.* (2000) **12**(Suppl. 3):S25-S31.
16. FITCH W, EASTERLING WJ: Topical verapamil, trifluoroperazine, and magnesium sulafate for peyronie's disease. *Int. J. Impot. Res.* (2001)**13**:S62.
17. MARTIN DJ, BADWAN R, PARKER M, MULHALL J: Transdermal application of verapamil gel to penile shaft fails to infiltrate tunica albuginea. *J. Urol.* (2002) **168**(6):2483-2485.
18. RIEDL CR, PLAS E, ENGELHARDT P, DAHA K, PFLUGER H: Iontophoresis for treatment of Peyronie's disease. *J. Urol.* (2000) **163**(1):95-99.
19. MILLS TM, REILLY CM, LEWIS R.W: Androgens and penile erection: a review. *J. Androl.* (1996) **17**(6):633-638.
20. SHABSIGH R: The effects of testosterone on the cavernous tissue and erectile function. *World J. Urol.* (1997) **15**(1):21-26.
21. PARK K, KIM SW, KIM KD, PAICK L: Effects of androgens on the expression of nitric oxide synthase in mRNAs in rat corpus cavernosum. *BJU Int.* (1999) **83**(3):327-333.
22. PIERCE JG, PARSONS TF: Glycoprotein hormones structure and function. *A. Rev. Biochem.* (1981) **50**:465-495.
23. WOLLESEN F, SWERDLOFF RS, ODELL WD: LH and FSH responses to luteinizing releasing hormones in normal adult human males. *Metabolism* (1976) **25**(11):1275-1285.
24. LUGG JA, RAJFER J, GONZALEZ-CADAVID NF: Dihydrotestosterone is the active androgen in the maintenance of nitric-oxide mediated penile erection in the rat. *Endocrinology* (1995) **136**(4): 1495-1501.
25. MARIN R, ESCRIG A, ABREU P, MAS M: Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes. *Biol. Reprod.* (1999) **61**(4):1012-1016.
26. ZHANG XH, HU LQ, ZHENG XM, LI SW: Apoptosis in rat erectile tissue induced by castration. *Asian J. Androl.* (1999) **1**(4):181-185.
27. DAI YT, STOPPER V, LEWIS R, MILLS T: Effects of castration and testosterone replacement on veno-occlusion during penile erection in the rat. *Asian J. Androl.* (1999) **1**(1-2):53-59.
28. BANCROFT J: Hormones and human sexual behavior. *J. Sex Marital Ther.* (1984) **10**(1):3-21.
29. AHMED SR, BOUCHER AE, MANNI A: Transdermal testosterone therapy in the treatment of male hypogonadism. *J. Clin. Endocrinol. Metab.* (1988) **66**(3):546-551.
30. MCCLURE RD, OSES R, ERNEST ML: Hypogonadal impotence treated by transdermal testosterone. *Urology* (1991) **37**(3):224-228.
31. MEIKLE AW, MAZER NA, MOELLMER JF: Enhanced transdermal delivery of testosterone across nonscrotal skin produces

physiological concentrations of testosterone and its metabolites in hypogonadal men. *J. Clin. Endocrinol. Metab.* (1992) 74(3):623-628.

32. ARVER S, DOBS AS, MEIKLE AE: Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clin. Endocrinol.* (1997) **47**(6):727-737.

33. WANG C, SWEDLOFF R, KIPNESS M *et al.*: New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmakokinetics study in hypogonadal men. *J. Clin. Endocrinol. Metab.* (2004) **89**(8):3821-3829.

34. STEIDLE C, SCHWARTZ S, JACOBY K, SEBREE T, SMITH T, BACHAND R; NORTH AMERICAN AA2500 T GEL STUDY GROUP: AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J. Clin. Endocrinol. Metab.* (2003) **88**(6):2673-2681.

35. KORBONITS M, SLAWIK M, CULLEN D *et al.*: A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *J. Clin. Endocrinol. Metab.* (2004) **89**(5):2039-2043.

Affiliation

Dr Michael[2] Ohebshalom MD & Dr John P Mulhall MD[†1,2]
[†]Author for correspondence
[1]Weill Medical College of Cornell University, New York Presbyterian Hospital, USA
[2]Memorial Sloan Kettering Cancer Center, USA