Men's Sexual Health Research Review™

Making Education Easy

Issue 11 – 2013

In this issue:

Abbreviations used in this issue:

ED = erectile dysfunction

IIEF-EF = International Index of Erectile Function – Erectile Function

PDE = phosphodiesterase

PE = premature ejaculation

Welcome to the eleventh issue of Men's Sexual Health Research Review.

European researchers have demonstrated that despite similar efficacies, tadalafil (once daily or as needed) as initial ED therapy was associated with better adherence than as-needed sildenafil. US researchers showed that unlike topical testosterone replacement, enclomiphene citrate for secondary hypogonadism appears to normalise testosterone production, and therefore restores sperm counts via the hypothalamic-pituitary-testicular axis. Research out of NSW highlights the importance of raising the issue of PE with men in general practice. This issue concludes with an interesting review of advances in vascular regenerative therapies for ED.

I hope the selection for this issue is valuable for your everyday practice, and I look forward to your ongoing comments and feedback.

Kind Regards,

Dr Michael Lowy

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Sexual dysfunction in men suffering from genital warts

Authors: Kucukunal A et el

Summary: This prospective cross-sectional pilot study investigated whether genital warts increased the likelihood of sexual dysfunction, and if this was associated with depression or anxiety, in 116 men with and 71 without genital warts. Men with genital warts were found to be significantly more likely to have sexual dysfunction than controls ($p<0.001$). Significant between-group differences were seen for Arizona Sexual Experience Scale (ASEX) subscores ($p<0.001$), and men with genital warts had significantly higher Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) scores than controls. BDI and BAI scores were significantly correlated with ASEX total and subscores ($p<0.001$).

Comment: Genital warts are a common concern for people seeking treatment for sexually transmitted infections. This study tells us that treating genital warts should go further than the usual medical treatments, but rather addressing the psychosexual aspects of this condition. This study tells us that male patients with genital warts have a higher rate of sexual dysfunction, depression and anxiety when compared with the normal population. A more holistic approach in the treatment of sexually transmitted infections will address the physical and psychosexual aspects of the condition.

Reference: J Sex Med 2013;10(6):1585–91
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12132/abstract

Adherence to initial PDE-5 inhibitor treatment: randomized open-label study comparing tadalafil once a day, tadalafil on demand, and sildenafil on demand in patients with erectile dysfunction

Authors: Buvat J et al

Summary: PDE-5 inhibitor-naïve men with ED were randomly allocated to receive tadalafil 5mg once daily (n=257), tadalafil 10mg as needed (n=252) or sildenafil 50mg as needed (n=261) for 8 weeks with dose adjustment possible, followed by 16 weeks of pragmatic treatment during which switching between PDE-5 inhibitors was allowed, in this open-label study. Kaplan-Meier estimated rates for discontinuation of randomised treatment were 52.2%, 42.0% and 66.7% in the tadalafil once daily, tadalafil as needed and sildenafil groups, respectively. Compared with sildenafil, the tadalafil once daily and as needed groups had significantly longer median times to randomised treatment discontinuation (130 and >168, respectively, vs. 67 days; respective hazard ratios 0.66 [97.5% CI 0.51–0.85] and 0.49 [0.37–0.65]; p<0.001), with the following significantly different reasons for discontinuation: i) 'lack of efficacy (duration of erection)' (4.3% and 2.8 vs. 9.2%); ii) 'time constraints due to short window of action' (0% and 0.4% vs. 4.2%); and iii) 'feel medication controls my sexual life' (0% [tadalafil once daily] vs. 2.7%). There were no significant differences among the groups for change in baseline IIEF-EF domain score and discontinuations due to adverse events.

Comment: As a generalisation, one can say all PDE-5 inhibitors work effectively, that is in most cases they provide an erection firm enough for sexual activity. Yet why are they so often discontinued when they work so well? This study tells us the reasons are 'lack of efficacy', 'time constraints', 'medication controls sex life', etc. The answer lies in the fact that successful sex is clearly more than a firm erection. However, it does appear that daily dosing promotes longer adherence to ongoing use of the medication, probably due to the spontaneity issue of not having to time intercourse around the taking of a tablet. The longer action of the as-needed tadalafil may explain its preference over the shorter acting (yet still very effective) sildenafil.

Reference: J Sex Med 2013;10(6):1592–602
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12130/abstract

Distribution and factors associated with four premature ejaculation syndromes in outpatients complaining of ejaculating prematurely

Authors: Zhang X et al

Summary: These researchers conducted a verbal questionnaire in 1988 men reporting PE to assess the prevalence of, and factors associated with, four PE subtypes. The respective prevalence rates of lifelong PE, acquired PE, natural variable PE and premature-like ejaculatory dysfunction were 35.66%, 28.07%, 12.73% and 23.54%. The highest mean ages and body mass indices were seen in men with acquired PE, in whom sexual desire disorder, hypertension, diabetes mellitus, chronic prostatitis and ED were more frequently reported. Compared with other types of PE, men with premature-like ejaculatory dysfunction reported a lower mean frequency of sexual intercourse and higher anxiety and depression rates.

Comment: The four new proposed classifications of PE are helpful in diagnosing and treating this condition, which is defined as ejaculation within 1–1.5 minutes after vaginal penetration and associated with distress to the man and his partner. Primary lifelong PE has the highest prevalence, usually seen in younger men, and may have a neurobiological basis. Secondary acquired PE may be seen in older men with ED. Natural variable PE has an unpredictable ejaculatory time that varies between acceptable and not. Finally, premature-like ejaculatory dysfunction is a perception of PE when it does not exist by definition – a form of body dysmorphic syndrome associated with high levels of anxiety and depression.

Reference: J Sex Med 2013;10(6):1603–11
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12123/abstract

Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes

Authors: Hackett G et al

Summary: Men with type 2 diabetes and hypogonadism identified in a general practice setting (n=199) were randomised to receive long-acting testosterone undecanoate 1000mg or placebo for 30 weeks, followed by 52 weeks on open-label medication. Long-acting testosterone therapy was associated with: i) significant improvements in all IIEF domains of sexual function (erectile function, intercourse satisfaction, sexual desire, overall satisfaction and orgasm) at 30 weeks, with benefits seen as early as 6 weeks; ii) significant Ageing Male Symptom score improvements in men without depression, and a marked reduction in response to both sexual function and psychological scores in men with baseline depression; and iii) continued improvements in IIEF sexual function scores out to 18 months, with a 4.31 improvement in the erectile function score from baseline. Among men taking PDE-5 inhibitors (n=35), long-acting testosterone therapy was not associated with any change during the double-blind phase of the trial, but the IIEF-EF domain score improved by 9 points during the open-label phase. Compared with placebo, a greater proportion of testosterone recipients reported improvement in their health at 30 weeks (46% vs. 17%), and 70% of the cohort reported such improvements after open-label therapy. Response to testosterone therapy was better in less obese and older men, and no significant adverse events were reported.

Comment: Diabetic men often have other features of metabolic syndrome that can be associated with low testosterone levels. Men with low testosterone levels may present with low libido and ED and a poor response to PDE-5 inhibitors. This study found a marked improvement in quality of life and sexual function in men who were treated with the long-acting 12-weekly depot preparation of testosterone undecanoate. This is an expected finding and supports testosterone replacement when indicated. However, the level of 'low' testosterone chosen for this study was <12 nmol/L, a level advised in some overseas countries. In Australia, the level is <8 nmol/L when a man is said to be hypogonadal.

Reference: J Sex Med 2013;10(6):1612–27
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12146/abstract

Oral enclomiphene citrate stimulates the endogenous production of testosterone and sperm counts in men with low testosterone: comparison with testosterone gel

Authors: Kaminetsky J et al

Summary: Twelve men with secondary hypogonadism treated previously with topical testosterone received oral enclomiphene citrate or topical testosterone gel in this phase IIb open-label study. Both treatments were associated with significant increases in morning total testosterone levels at 3 months, which persisted at 6 months with levels of 545 and 525 pg/dL for the testosterone gel and enclomiphene citrate groups, respectively. However, increased luteinising hormone and follicular-stimulating hormone levels were only significantly increased in the enclomiphene citrate group. Moreover, sperm counts had increased to 75–334 × 10^6/mL at 6 months in all six enclomiphene citrate recipients, versus two of five testosterone gel recipients achieving sperm counts >20 × 10^6/mL. Elevated sperm counts persisted in only the enclomiphene citrate group at follow-up. Total testosterone levels had returned to baseline 1 month after treatment was discontinued.

Comment: Clomiphene is a medication used in female fertility treatment. The use of clomiphene to increase testosterone levels has been abused by men whose levels are normal but purchase the medication online. These men often are weight lifters who also concurrently use illegally purchased testosterone. However there is a genuine benefit in off-label use of this medication in men who are hypogonadal and also have low sperm counts, as testosterone treatment will further suppress sperm production. This paper reveals the benefit of clomiphene on testosterone and sperm levels. Another paper with similar outcomes is Katz DJ et al. 'Outcomes of clomiphene citrate treatment in young hypogonadal men.' BJU Int 2012;110(4):573–8.

Reference: J Sex Med 2013;10(6):1628–35
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12116/abstract

Back to baseline: erectile function recovery after radical prostatectomy from the patients' perspective

Authors: Nelson CJ et al

Summary: This research explored postradical prostatectomy recovery of erectile function as defined by return to baseline in 180 men not receiving PDE-5 inhibitor therapy at enrolment. Return to baseline erectile function at 24 months was reported by 43% of men overall and 22% when the analysis was restricted to men who reported no PDE-5 inhibitor use during follow-up, and the respective rates among 132 men with baseline Erectile Dysfunction Domain score ≥24 were 36% and 16%, with a significantly higher rate among PDE-5 inhibitor nonusers aged <60 vs. ≥60 years (23% vs. 4%; adjusted odds ratio 6.25 [95% CI 1.88–50; p<0.001]).

Comment: The ability to return to presurgery erectile function after radical prostatectomy depends on the amount of nerves spared, the age at the time of surgery (better if <60 years) and the quality of the presurgery erections. This study tells us only 4% of men aged over 60 years returned to their former erectile ability and overall 22% returned to their former baseline function. Men tend to only seek sexual rehabilitation after prostate cancer surgery if they are not satisfied later on with the return of their previous erectile function, which sometimes can be nonexistent if the erection nerves were unable to be spared. The majority of men experience some form of ED after radical prostatectomy and this should be made clear before surgery.

Reference: J Sex Med 2013;10(6):1636–43
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12135/abstract

Premature ejaculation

Authors: Harrison C et al

Summary: This substudy of the BEACH (Bettering the Evaluations and Care of Health) programme, in which PE was managed in only 28 per 100,000 encounters with men, measured the prevalence of PE in 796 male general practice patients and explored the use of the Premature Ejaculation Diagnostic Tool (PEDT) for identifying the condition. Of the 463 men who indicated self-perceived PE status on a sexual activity questionnaire, 18.1% of currently or previously sexually active men reported PE, and of these, 45.2% reported PE since their first sexual activity and 11.9% reported developing PE in association with ED. PEDT scores suggested that 77.8% and 7.4% of respondents reporting PE did have and did possibly have the condition, respectively, and the respective rates for those not self-reporting PE were 3.6% and 8.7%.

Comment: PE is a common sexual dysfunction that is not often brought up in a general practice setting. This study reveals that when using a reliable and validated scale, PEDT, it is present in nearly 20% of male patients. The problem with diagnosing PE is the patient's often incorrect perception of ejaculation time, but the distribution of the scores is consistent with the incidence of PE in the general community. The message from this study is that there are always a significant number of men attending general practitioners who have a sexual dysfunction such as PE or ED and would benefit from a discussion of these problems but don't know how to do so. Here the observant doctor should be proactive in bringing up these important male topics.

Reference: Aust Fam Phys 2013;42(5):265
http://www.racgp.org.au/afp/2013/may/premature-ejaculation/

Retrospective analysis of the efficacy and safety of once-daily tadalafil in patient subgroups: men with mild vs moderate ED and aged <50 vs ≥50 years

Authors: Seftel AD et al

Summary: The effects of tadalafil 5mg once daily for 12 weeks in men with mild or moderate ED aged <50 versus ≥50 years were explored in this *post-hoc* analysis of pooled data from three randomised controlled trials. Compared with placebo, tadalafil was associated with significant increases in mean IIEF-EF by 6.8 points, successful penetration attempt rate from 70.1% to 91.3% and successful intercourse attempt rate from 33.4% to 76.8% (p<0.001 for all). However, the effects of tadalafil were not different in men aged <50 years compared with those aged ≥50 years.

Comment: Oral PDE-5 inhibitors are generally regarded as effective treatments for most causes of ED, except in men with neurogenic and severe vasculogenic ED. This analysis looked for evidence whether the benefits were any different for men aged under and over 50 years using the well-established IIEF. The findings showed a higher success rate with tadalafil over placebo, with no difference in both age groups. Tadalafil was well tolerated. These results are consistent with our clinical experiences, but I would have liked a comparison between as-needed tadalafil 20mg, daily tadalafil 5mg and placebo.

Reference: Int J Impot Res 2013;25(3):91–8
http://www.nature.com/ijir/journal/v25/n3/full/ijir201240a.html

Comparison of efficacy and satisfaction profile, between penile prosthesis implantation and oral PDE5 inhibitor tadalafil therapy, in men with nerve-sparing radical prostatectomy erectile dysfunction

Authors: Megas G et al

Summary: Men with ED 6 months after nerve-sparing retropubic radical prostatectomy for prostate cancer (evaluable n=54) received tadalafil three times weekly or penile prosthesis implantation in this study. While both groups experienced a significant reduction in preoperative IIEF score at 6 months, the penile prosthesis arm had a significantly greater change than the tadalafil arm at 2 years (20.4 vs. 8.1; p<0.001).

Comment: The insertion of a penile prosthesis is regarded as the last of the line of treatments for ED, because of the inability to reverse this treatment. Counselling is recommended for the man and his partner. However, a penile prosthesis is a well-engineered product that works very effectively when placed in the appropriate patient providing years of satisfactory sexual activity. These days it is often recommended in men after prostate cancer surgery where ED is a common occurrence, particularly when nerve sparing of the cavernous nerves has not been possible. This study shows acceptable sexual function in the tadalafil treated group, but an even better result in the men who had a penile prosthesis. Men who wish a superior erectile response after prostate cancer surgery should consider this treatment.

Reference: BJU Int 2013;112(2):E169–76
http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11561.x/full

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Independent commentary by Dr Michael Lowy, who is a men's health physician with a special interest in sexual medicine (male sexual dysfunction), relationship counselling and the general health issues of men. Dr Lowy began his medical career in general practice.

Michael became a sexual health physician in 1996 (FAChSHM) and obtained a Masters in Psychological Medicine in 2001, and is currently a director of Sydney Men's Health in Bondi Junction.

Vascular regenerative therapies for the treatment of erectile dysfunction: current approaches

Authors: Condorelli RA et al

Summary: These authors reviewed vascular regenerative ED therapy with mesenchymal or adipose tissue stem-cell transplantation and endothelial nitric oxide synthase or vascular endothelial growth-factor gene therapy. They also discussed two other aspects of interest in ED therapy, including the potential vascular regenerative effects of PDE-5 inhibitors and therapeutic strategies for patients with diabetes, who often don't respond to conventional ED therapies.

Comment: ED treatment is well established with PDE-5 inhibitors. ED is especially present in diabetes and other conditions that feature endothelial dysfunction. Another major cause of ED is neurogenic, with cavernous nerve damage following radical prostatectomy for prostate cancer. Newer proposed treatment strategies are intracavernosal injections of therapeutic genes derived from endothelial nitric oxide synthase or mesenchymal cells. These stem cells may be derived from adipose tissue or bone marrow. Another outcome of this research was to confirm the hypothesis that PDE-5 inhibitors may counter endothelial dysfunction, not only in patients with ED, but also those with cardiovascular disease.

Reference: Andrology 2013;1(4):533–40
http://tinyurl.com/lw4o5o2

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