Guidelines on the management of sexual problems in men: the role of androgens

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Please note these guidelines are summarised from the following journal articles (dual publication):

Wylie K., Rees M, Hackett G, Anderson R, Bouloux PM, Cust M, Goldmeier D, Kell P, Terry T, Trinick T, Wu F. (2010) Androgens, health and sexuality in women and men. Maturitas. 67, 275-89
Wylie K., Rees M, Hackett G, Anderson R, Bouloux PM, Cust M, Goldmeier D, Kell P, Terry T, Trinick T, Wu F. (2010) Androgens, health and sexuality in women and men. Human Fertility, 13, 277-297.

Separate guidelines are issued with regard to the management of sexual problems in women.

BACKGROUND

- An active and satisfactory sex life is beneficial for health, but there is often a reluctance on the part of professionals (in primary and secondary settings, including gynaecology, urology, psychiatry and endocrinology) to enquire about sexual symptoms.

- Reduced androgen levels (a feature of ageing in both sexes) may have somatic, psychological and sexual effects, sometimes severe enough to compromise a patient's general well-being or sex life in particular. Androgen replacement is used in the treatment of sexual disorders, in both women and men. The principal androgen is testosterone; its precursors include dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S) and androstenedione. Testosterone itself is a precursor of estrogens; in women it is produced by the ovaries and adrenals.

- Health-care professionals need to be careful that they use terms such as sexual 'problems', 'concerns', 'difficulties' and 'dysfunctions' appropriately. Labelling the patient as suffering from a dysfunction may lead to over-medicalisation, whereas classifying a severely distressed patient as having a 'concern' may be equally unsatisfactory.

MEN

- The role of androgens in maintaining well-being in men is well established. Low androgen levels in men are chiefly the result of hypogonadism. Hypogonadism (primary or secondary) can occur at all ages, including in elderly men.

- The most common presentation of hypogonadism arises from screening investigations for patients presenting with erectile dysfunction and/or reduced sexual desire. Consideration should be given to routinely asking men if they have any sexual concerns, especially those at high risk. These include men with diabetes, osteoporosis (fragility fractures), chronic opiate therapy, cardiovascular disease, metabolic disorder, erectile dysfunction and depression.

- The diagnosis of hypogonadism is based upon appropriate symptoms combined with reliable measurement of testosterone in the morning on more than one occasion.

- The demand of the patient to achieve a satisfactory sexual response is a major driver for testosterone therapy, either alone or in conjunction with erectogenic therapy. Psychosexual therapy may also be indicated.

ANDROGENS AND MALE PHYSIOLOGY

- Late-onset hypogonadism (LOH), also referred to as age-associated testosterone deficiency syndrome (TDS), is a clinical and biochemical syndrome associated with advancing age; it is characterised by a serum testosterone level below the young healthy adult male reference range. The condition may greatly reduce quality of life and may adversely affect the function of multiple organ systems.

- Common symptoms of LOH include fatigue, reduced well-being, depression, loss of concentration, hot flushes and sweats, reduced muscle mass and weakness and reduced body hair. The sexual symptoms include low libido, erectile dysfunction and ejaculatory dysfunction. Poor morning erection is often reported by the man.

- Hypogonadal men restored to the eugonadal state with testosterone replacement may experience: a general improvement in sexual function, particularly ejaculation, orgasm and penile sensation; improved erection; restored or enhanced responsiveness to PDE5 inhibitors. The last is an important indication for androgen replacement, especially if restoration of erectile function is a priority for the patient. This issue is particularly relevant to men with type 2 diabetes, where response to PDE5 inhibitors alone may be little more than 50%.

EPIDEMIOLOGY AND RISK FACTORS

- Problems of sexual function are relatively common in men, but persistent problems are much less so. Sexual problems lasting at least six months in the previous year are estimated to have a prevalence of 6%; the most common problem is premature ejaculation/orgasm. Over 8% of men between the ages of 50 and 79 years are hypogonadal.

- Risk factors for hypogonadism in older men include: chronic illnesses (including diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic, renal and HIV-related diseases), obesity, prolactinoma, excessive alcohol consumption, metabolic syndrome and haemachromatosis, as well as chronic opiate therapy and androgen deprivation therapy (for prostate cancer). Such chronic conditions should be investigated and treated.

DIAGNOSIS

- The diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency, as well as biochemical evidence. The symptom most associated with hypogonadism is low libido. Other manifestations include: erectile dysfunction, absence of morning erections, delayed ejaculation, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood. None of these is specific to the low-androgen state but each may raise suspicion of testosterone deficiency.

- The initial assessment of all men with erectile dysfunction and/or diminished libido should therefore include determination of serum testosterone. Whilst there are no generally accepted lower limits of the normal range for testosterone, there is general agreement that a total testosterone level above 12 nmol/l (350 ng/dl) does not require replacement. Patients with serum total testosterone levels below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol/l, repeating the measurement of total testosterone with sex hormone binding globulin (SHBG) and albumin to calculate free testosterone, or free testosterone by equilibrium dialysis, may be helpful.

- For total testosterone determination blood should preferably be taken at 9 am and certainly between the hours of 7 and 11 am, without fasting.

- The reference method for testosterone is isotope dilution gas chromatography mass spectrometry (ID-GCMS). Methods based on mass spectrometry are more accurate and precise and are increasingly recognised as the method of choice for serum testosterone measurement in men but they are currently not widely available. Equilibrium dialysis is therefore presently the gold standard for free testosterone measurement. Assays of free testosterone based on analogue displacement immunoassays are widely available but do not give an accurate measurement and should not be used.

- The free androgen index (total testosterone divided by SHBG, ×100) is of limited value in men. It might be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. There are no accepted lower limits of free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 225 pmol/l (0.225nmol/l or 65 pg/ml) can provide supportive evidence for treatment with testosterone.

- Since the various methods for the measurement of testosterone (both platform-based immunossays and mass spectrometry) are known to produce different results, it is imperative that health professionals use reliable laboratories and are acquainted with the reference ranges established by their local laboratory from healthy volunteers.

- Measurements of serum levels of luteinising hormone will assist in differentiating between primary and secondary hypogonadism, and a determination of serum prolactin level is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) or when secondary hypogonadism is suspected. The prolactin level should be measured to avoid missing a prolactinoma.

- Clinical assessment should be made in person by the consulting physician, who should not rely on non-specific unvalidated questionnaires. It may be undertaken over several consultations.

- In patients at risk of or suspected of having hypogonadism, a thorough physical and biochemical work-up is necessary. Transient decreases in serum testosterone levels, for example as a consequence of acute illness, should be excluded by careful clinical evaluations and repeated hormone measurement.

- Alterations in other endocrine systems occur in association with ageing (i.e. estradiol, GH and DHEA) but the significance of these changes is not well understood. Determinations of estradiol, thyroid hormones, cortisol, DHEA, DHEAS, melatonin, GH and IGF-I are not indicated unless other endocrine disorders are suspected, based on the clinical signs and symptoms of the patient.

- In men over the age of 40 years, prior to therapy with testosterone, the risk of prostate cancer must be assessed using digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA). If the PSA level is > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African-Caribbean or men with first-degree relatives who have prostate cancer), further urological assessment may be desirable. The pre-treatment assessment can be improved by incorporating other risk predictors, such as age, body mass index, family history and ethnicity/race. Pre-treatment prostate ultrasound examinations or biopsies are not recommended as routine requirements.

TREATMENT

- Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy. The diagnosis of hypogonadism should be confirmed before any androgen therapy is initiated. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short therapeutic trial (e.g. up to 6 months) of testosterone may still be justified.

- Once patients are on therapy, it is useful to monitor their levels of total testosterone, SHBG and albumin (to calculate bioavailable or free testosterone) to ensure normal serum testosterone concentrations are being achieved. The aim of therapy should be a total testosterone level of at least 15 nmol/l to ensure symptomatic improvement. Sustained supra-physiological levels should be avoided.

- An inadequate response to testosterone treatment requires reassessment of the cause of the erectile dysfunction and the discontinuation of testosterone. A satisfactory response may be generated by placebo, and so continued assessment is advisable before long-term treatment is recommended.

- The combination of testosterone and phosphodiesterase-5 inhibitors (PDE5i) treatment should be considered in hypogonadal patients with erectile dysfunction who fail to respond to either treatment alone. It is suggested that men with hypogonadism and erectile dysfunction should be treated with testosterone prior to the introduction of a PDE5i.

- Men with severe symptoms of lower urinary tract symptoms, significant erythrocytosis (haematocrit >50%), untreated obstructive sleep apnoea or untreated severe congestive heart failure, breast or prostate cancer should not be started on treatment with testosterone without appropriate assessment and treatment of these co-morbid conditions.

- Although advanced age is not a contraindication to testosterone treatment, individual assessment of co-morbidities (as possible causes of symptoms) and of the potential risks versus benefits of testosterone treatment is of increasing importance with greater age. The situation is clearer in younger men, where hypogonadism is usually associated with specific clinical diagnoses.

- The use of testosterone in patients with locally advanced or metastatic prostate cancer is absolutely contraindicated. Men successfully treated for localised prostate cancer but suffering from confirmed symptomatic hypogonadism are potential candidates for testosterone substitution, after a prudent interval (at least two years), if there is no clinical or laboratory evidence of residual cancer. The risks and benefits must be clearly discussed with and understood by the patient, short acting preparations are advised and the follow-up monitoring must be particularly careful, with serial PSA estimations.

- Obese men are more likely to develop adverse effects.

- Preparations of natural testosterone should be used for substitution therapy. Intramuscular, subdermal, transdermal, oral and buccal preparations are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician. Risks of transfer should be discussed in advance of starting treatment.

- As any adverse events during treatment (especially elevated haematocrit or prostate carcinoma) require rapid discontinuation of testosterone substitution, short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism.

- Preparations of 17-α-alkylated androgens such as 17-α-methyl-testosterone are obsolete because of their potential liver toxicity and should no longer be prescribed. Dihydrotestosterone and androgen precursor preparations such as DHEA, DHEAS, androstenediol or androstenedione are not recommended. Human chorionic gonadotropin (hCG) stimulates the testosterone production of Leydig cells, albeit at a lower rate in older than in younger men, but it cannot be recommended in late-onset hypogonadism, except when fertility is an issue. Anti-estrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels but there is inadequate evidence to recommend their use. Selective androgen receptor modulators are in clinical development but not yet available; many of these compounds are non-aromatisable and the risks of long-term use are unclear.

- The risk, if any, of prostate pathologies in men on long-term testosterone therapy is currently unknown. Hypogonadal older men should be counselled on the potential risks and benefits of testosterone replacement before treatment and be carefully monitored for prostate safety during treatment.

- Patients should be monitored for prostate disease at 3–6 months, 12 months, and at least annually thereafter. Confirmed PSA increments >1.4 ng/ml during any one-year period after initiation of testosterone therapy or a PSA velocity >0.4 ng/ml per year during sequential PSA measurements for periods of more than two years should warrant a urological evaluation and more intensive future surveillance for prostate cancer. The combined application of PSA and digital prostate examination improves the prostate cancer detection rate over either test alone.

- Erythrocytosis can develop during testosterone treatment, especially in older men treated with injectable testosterone preparations. Haematological assessment is indicated before treatment, then at 3–4 months and 12 months, and annually thereafter. To keep the haematocrit below 52–55%, dose adjustments and/or periodic venesection may be necessary.

- Assessment of treatment outcome and decisions about continuing therapy should be based on improvement in signs and symptoms of testosterone deficiency. Failure to benefit within a reasonable time interval (up to six months is adequate for libido and sexual function, muscle function and improved body fat) should result in discontinuation of treatment. Further investigation for other causes of symptoms is then mandatory.

MANAGEMENT ALGORITHM (MEN)

	Yes	No
1. Man presenting with erectile dysfunction and/or diminished libido.	Candidate for testosterone therapy, but confirm diagnosis of treatable hypogonadism.	
2. Are there symptoms and signs suggestive of testosterone deficiency: low libido, erectile dysfunction, delayed ejaculation? Look also for decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood.	Establish a diagnosis of hypogonadism by the documentation of low serum total testosterone.	
3. Is the total testosterone level above 12 nmol/l (350 ng/dl)?	Does not require replacement treatment.	Patients with serum total testosterone levels below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment. (If the serum total testosterone level is between 8 and 12 nmol/l, consider repeating the measurement).

	Yes	No
4. Is the serum testosterone lower than 5.2 nmol/l (150 ng/dl)?	The prolactin level should be measured to avoid missing a prolactinoma.	
5. Is there a co-morbidity such as diabetes mellitus, hyperprolactinaemia, metabolic syndrome, bladder outlet obstruction and peripheral vascular disease, significant erythrocytosis (haematocrit >50%), untreated obstructive sleep apnoea or untreated severe congestive heart failure, breast or prostate cancer?	Do not start treatment with testosterone without appropriate treatment of the co-morbid condition. The use of testosterone in patients with locally advanced or metastatic prostate cancer is absolutely contraindicated. Severe symptoms of lower urinary tract symptoms due to benign prostate hyperplasia represent a relative contraindication.	
6. Is the patient taking any medication that could cause the complaint?	Consider if there are alternative medications which may have a different sexual side effect profile whilst maintaining effect	
7. Determine the serum level of luteinising hormone, to differentiate between primary and secondary hypogonadism.		
8. Is secondary hypogonadism suspected?	The prolactin level should be measured to avoid missing a prolactinoma.	
9. Are other endocrine disorders are suspected, based on the clinical signs and symptoms of the patient?	Determinations of estradiol, thyroid hormones, cortisol, DHEA, DHEAS, melatonin, GH and IGF-I are indicated.	
10. Once patients are on therapy, testosterone levels should be monitored to ensure normal concentrations are being achieved. The aim of therapy should be a total testosterone level of at least 15 nmol/l.		

	Yes	No
11. Erythrocytosis can develop during testosterone treatment, especially in older men treated with injectable testosterone preparations. Haematological assessment is indicated before treatment, then at 3–4 months and 12 months, and annually thereafter. To keep the haematocrit below 53% (48% if history of thrombosis), dose adjustments and/or periodic venesection may be necessary.		
12. Review after 6 months (and thereafter). Has there been an adequate response to testosterone treatment?	Continue therapy.	Failure to benefit within 6 months should result in discontinuation of treatment. Reassess the cause of the sexual dysfunction. Further investigation for other causes of symptoms is then mandatory. Note, however, that the combination of testosterone and phosphodiesterase-5 inhibitors (PDE5i) should be considered in hypogonadal patients with erectile dysfunction who fail to respond to testosterone alone.
13. Hypogonadal older men should be carefully monitored for prostate safety during treatment, at 3–6 months, 12 months, and at least annually thereafter.		

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Mike Cust - Previous member of P&G advisory board on transdermal testosterone patches

Frederick Wu - FCWW served on advisory boards and acted as consultants for the following companies: GSK, Organon bv, Bayer-Schering Pharma, Ferring, TAP, Eli-Lilly, Proctor & Gamble, Ardana Biosciences, Pierre Fabre Medicaments in the last 10 years. He has been awarded research grants from Organon bv, Bayer-Schering Pharma

Phillip Kell - Worked for Bayer/Prostrakan as an advisor and have done research trials

Geoff Hackett - No conflicts. Occasional speaker for Lilly, Bayer and Boehringer-Ingleheim

Tom Trinick - No conflicts of interest

Pierre-Marc Bouloux – No conflicts of interest

Richard A Anderson – Served on advisory boards for Organon/Schering Plough and Roche

Margaret Rees - MR has received honoraria, research grants and support to attend medical conferences from Bayer Schering Pharma, Boehringer Ingelheim, GlaxoSmithKline, Meda Pharmaceuticals, Procter and Gamble and Wyeth. Neither she nor his any immediate family member has a current financial arrangement or affiliation with any organization(s) that may have a direct financial interest in the subject matter of the guideline

David Goldmeier - Consultant to Boehringer Ingelheim

Tim Terry – No conflicts of interest

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