Position Statement

Use, misuse and abuse of androgens

The Endocrine Society of Australia consensus guidelines for androgen prescribing

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on behalf of the Endocrine Society of Australia

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Abstract

- Androgen replacement therapy (ART) is usually life-long, and should only be started after androgen deficiency has been proven by hormone assays. The therapeutic goal is to maintain physiological testosterone levels.
- Testosterone rather than synthetic androgens should be used.
- Oral 17α-alkylated androgens are hepatotoxic and should not be used for ART.
- There is no indication for androgen therapy in male infertility. Although androgen deficiency is an uncommon cause of erectile dysfunction, all men presenting with erectile dysfunction should be evaluated for androgen deficiency. If androgen deficiency is confirmed, investigation for the underlying pathological cause is required.
- Contraindications to androgen therapy are prostate and breast cancer. Precautions include using lower starting doses for older men and induction of puberty. Intramuscular injections should be avoided in men with bleeding disorders. Androgen-sensitive epilepsy, migraine, sleep apnoea, polycythaemia or fluid overload need to be considered. Competitive athletes should be warned about the risks of disqualification.
- ART should be initiated with intramuscular injections of testosterone esters, 250 mg every two weeks. Maintenance requires tailoring treatment modality to the patient's convenience. Modalities currently available include testosterone injections, implants, or capsules. Choice depends on convenience, cost, availability and familiarity.

- There is no convincing evidence that, in the absence of proven androgen deficiency, androgen therapy is effective and safe for older men *per se*, in men with chronic non-gonadal disease, or for treatment of non-specific symptoms. Until further evidence is available, such treatment cannot be recommended.

Androgens are hormones that are based on the structure of testosterone, the major male sex hormone, and are capable of developing and maintaining masculine sexual characteristics (including the genital tract, secondary sexual characteristics, and fertility) and the anabolic status of somatic tissues. All androgens have similar biological effects because they all act through the single androgen receptor. Their effects in different tissues are diversified by metabolism of testosterone to its active metabolites by the enzymes 5α reductase (which converts testosterone to 5α-dihydrotestosterone, an androgen with enhanced potency acting on the androgen receptor) and aromatase (which converts testosterone to oestradiol, which acts on the oestrogen receptor).

Use of androgens

The main medical use of androgens (Box 1) is as androgen replacement therapy (ART) for established androgen deficiency.[1-3] Classical androgen deficiency occurs in about 1 in 200 men, due to testicular disorders that directly reduce testosterone output, or hypothalamic-pituitary disorders that reduce pituitary luteinising hormone (LH) secretion, which is the main drive to testosterone production by the interstitial (Leydig) cells of the testes. Although classical androgen deficiency is relatively easy to recognise, diagnosis of less severe androgen deficiency can be more difficult. Owing to its subtle and variable clinical features, the diagnosis may easily be missed, denying patients simple and effective medical treatment with often striking subjective benefits.

Potential extensions of classical indications to partial androgen deficiency remain to be fully evaluated for clinical safety and efficacy. These indications include age, androgen deficiency secondary to a chronic medical condition or its treatment, hormonal male contraception, and postmenopausal symptoms.[4-6] Until more definitive objective evidence is available regarding the safety and efficacy of prescribing androgens for these indications, they remain suitable for carefully monitored, controlled clinical research trials, but not for routine medical treatment.

Pharmacological applications of androgens (Box 1) usually represent second-line therapy where more specific treatments are not yet available or have failed.

Androgen treatment can evoke a strong placebo response. In men without genuine androgen deficiency, this placebo effect invariably wanes with time, leading to confusion and dissatisfaction with treatment. In addition, once androgen therapy has commenced, the biochemical changes can cloud further interpretation of results for months. Therefore, androgen replacement therapy should be commenced only after androgen deficiency is clearly established.[2,3]

Diagnosis of androgen deficiency[1-3]

Diagnosis of androgen deficiency involves the recognition of appropriate clinical features, with confirmation by biochemical testing. Important clinical features required to evaluate testicular function

include reproductive history (including pubertal development), fertility status, changes in sexual function and body hair growth, known testicular pathology, drug use, and occupation. Physical examination should record androgenisation (secondary sexual characteristics, especially body hair distribution, musculature and gynaecomastia) and testis volumes (by orchidometry).

Serum LH, follicle-stimulating hormone and testosterone levels should be measured, on at least two separate days and preferably in the morning, to minimise the effects of random and laboratory fluctuations and diurnal rhythms. Direct measurements of free testosterone, if available, may help establish the diagnosis of androgen deficiency, but require extensive validation. Indirect measurements of free testosterone, such as the free androgen index (testosterone/sex hormone binding globulin [SHBG] ratio), correspond poorly with direct measurements and lack empirical validation as a diagnostic test.

Additional tests that may be required to identify underlying disorders include karyotyping, pituitary radiology and measurement of prolactin levels, serum ferritin levels, iron saturation and, increasingly, genetic diagnosis.

Androgen deficiency is unlikely in men with mean testis volume > 20 mL without atrophy, with a plasma testosterone level consistently above 20 nmol/L, or presenting with erectile dysfunction and a plasma testosterone level consistently above 8 nmol/L (Box 2). Where the diagnosis is not clear, referral to a clinical endocrinologist with experience in this area is recommended.[1]

Androgen replacement therapy[1-3]

ART is indicated to rectify androgen deficiency of any cause sufficient to cause clinical consequences. After puberty, there is no age limit to ART. Androgen-deficiency effects may manifest as changes in one or more androgen-sensitive functions; for example, psychosexual function, or loss of anabolic effects on bone, muscle, blood-forming marrow and other androgen-responsive tissues. Apart from decreased spermatogenesis, ART can rectify all clinical features of androgen deficiency, which usually respond within 1-2 months of starting therapy, although the full effect may take longer.

Dosage: Standard ART is either testosterone enanthate (Primoteston in castor oil; Schering) or mixed testosterone esters (Sustanon in arachis oil; Organon) as 250 mg in 1 mL oil at 14-day intervals. Deep intramuscular injections are usually given into the upper and outer quadrant of the buttock, although some patients prefer the deltoid or lateral thigh muscle sites. Few men can manage self-injection with the viscous oil vehicle.

For all ART, testosterone and its esters should be used in preference to synthetic androgens, because of their established safety and efficacy, as well as ease of dose-titration and assay monitoring.

Lower starting doses may occasionally be needed, especially in previously untreated elderly men and during first induction of puberty. Less frequent dosing intervals (eg, every three weeks) are occasionally necessary for those unable or unwilling to have standard dosage, but are accompanied by more extreme peaks and troughs in blood testosterone levels, which may exaggerate symptom fluctuations.

An inadequate clinical response raises doubt about androgen deficiency as the cause of recalcitrant

symptoms. Rarely, an inadequate clinical response may require increased dosage. If suboptimal symptomatic benefit is supported by biochemical evidence of inadequate maintenance of androgen levels (low trough testosterone levels with or without persistently supranormal LH levels in primary hypogonadism), the same dose may be injected at 10-day intervals. Persistently inadequate responses indicate that unresponsive symptoms are not due to androgen deficiency; further escalation in dose or frequency is not warranted. Men with mild or partial androgen resistance due to androgen-receptor mutations may benefit from high-dose androgen therapy.

As the underlying disorders are almost always permanent, life-long ART after the age of puberty is usually necessary. Long term therapeutic compliance depends on an acceptable regimen. Crossover studies indicate that patients strongly prefer the stable testosterone levels and smoother clinical effects provided by implants or transdermal formulations, compared with the wide fluctuations in testosterone levels and symptoms during intramuscular testosterone ester injections. Thus, although ART should commence with injections, alternative modalities (Box 3) may improve compliance. Factors to consider include cost, convenience, availability, familiarity with alternatives, and tolerance for frequent injections.

Monitoring: Monitoring of ART is mainly to ensure effective androgen replacement by a regimen tailored to the patient's needs, aiming to maintain adequate therapeutic compliance by continuation of treatment. Serial clinical observation of clinical well-being and major symptoms of androgen deficiency, together with limited numbers of hormonal assays, is usually adequate. Restoration of sexual function has a low threshold for androgen action, so adequate libido and potency is a necessary, but not sufficient, indication of clinically adequate androgen replacement.

Blood hormone assays have limited utility in optimising an ART regimen at the start of treatment and in evaluating androgen replacement. Trough blood testosterone levels (ie, before the next scheduled dose) within the eugonadal reference range can be a valuable guide to the adequacy of parenteral androgen replacement, but random blood testosterone levels are not useful for monitoring with either oral or injectable testosterone. In men with hypergonadotropic hypogonadism, suppression of blood LH levels into the eugonadal reference range indicates adequate ART, whereas persistent non-suppression of LH after 3-6 months of regular treatment indicates inadequate dosage or compliance. In hypogonadotropic hypogonadism, blood gonadotropin levels are uninterpretable. Serial evaluation of bone density (especially vertebral trabecular bone) by dual-photon absorptiometry at 1-2-year intervals may be useful in evaluating the adequacy of long-term androgen effects on bone. Other biochemical indices of androgen action, such as haemoglobin, SHBG, and high density lipoprotein cholesterol levels, reflect only supraphysiological effects and are too insensitive for routine monitoring of ART.

Androgen deficiency is protective against prostate disease, and ART may restore the risks to those equivalent to, but no more than, eugonadal men of similar age. Screening of men receiving ART for cardiovascular and prostate disease need be no more intensive than for men of similar age not on ART.

Precautions and side effects[14-17]

Adverse effects of androgen treatment are uncommon. Virilisation may occur with androgen therapy in women or children; androgen therapy in these settings requires expert management. Truncal acne and hair growth, weight gain, gynaecomastia and male-pattern hair loss may be observed, and should be managed symptomatically. Certain side effects are characteristic of specific therapeutic modalities (eg,

discomfort from intramuscular injections, extrusion of subdermal implants, gastrointestinal disturbance from oral testosterone undecanoate). Polycythaemia may occur disproportionately often in older men treated with testosterone ester injections. In addition, certain testosterone formulations have distinctive effects due to their pharmacokinetic features (eg, reduced levels of SHBG, high density lipoprotein cholesterol and other hepatic proteins due to supraphysiological hepatic testosterone exposure). This may be due to injectable testosterone esters (via high peak blood testosterone concentrations) or oral testosterone undecanoate (via high first-pass portal testosterone concentrations), whereas more steady formulations (transdermal, implants) exhibit fewer or no such effects.

Oral synthetic androgens that have a 17α-alkyl substituent (oxandrolone, fluoxymesterone, danazol) are inherently hepatotoxic, causing cholestatic hepatitis, peliosis hepatis and hepatic tumours. Other classes of synthetic androgen, such as 19-nortestosterone derivatives (nandrolone, MENT) and the 1-methyl androgens (mesterolone, methenolone), are not hepatotoxic.

Absolute contraindications to androgen therapy are prostate or breast cancer in men. Androgen therapy should be started in men over the age of 40 only after exclusion of undiagnosed prostate disease. Precautions are required for:

- older men starting androgen treatment, where it may precipitate urinary obstruction or unfamiliar increases in libido;
- pubertal boys, in whom excessive dosage may accelerate epiphyseal closure, leading to shortened final stature;
- parenteral androgen therapy in men with bleeding disorders;
- competitive athletes, who may be disqualified;
- androgen-sensitive epilepsy, migraine, sleep apnoea or polycythaemia; and
- cardiac or renal failure or severe hypertension susceptible to fluid overload from sodium and fluid retention.

Misuse of androgens

Medical misuse of androgens involves prescription with no acceptable medical indication. Some common examples of misguided prescribing of androgens in the absence of established androgen deficiency include:

Male infertility: There is no indication for androgen therapy in male infertility. The only likely consequence is an adverse effect of suppressing spermatogenesis.

Male sexual dysfunction or impotence: Androgen deficiency (with or without hyperprolactinaemia) is an uncommon (< 5%) cause of men presenting with erectile dysfunction. In such men, excluding androgen deficiency as a readily treatable underlying cause is essential. In the unusual event of severe

androgen deficiency presenting with erectile dysfunction, the underlying cause needs to be identified, and plans for life-long ART need to be established.

"Male menopause" or "andropause": There is still no evidence that the modest decreases in circulating blood testosterone levels which commence during mid-life have any clinical importance. The risks and benefits of androgen supplementation for partially androgen-deficient older men require further evaluation by placebo-controlled studies. Androgen treatment may be inappropriate, wasteful, and involve placebo effects. Terms such as "male menopause" and "andropause" are misleading; they have little place in meaningful medical or scientific discourse.

Elderly men (> 65 years):[18] There is no basis for androgen therapy based on age *per se*. Further controlled clinical trials are needed to evaluate the potential role of androgen supplementation in ageing. While some preliminary placebo-controlled studies suggest short-term benefits for muscle, bone and quality of life, findings are not yet consistent and the identification of appropriate treatment objectives and target subgroups, as well as overall analyses of risks, benefits and costs, are lacking. Specifically, it remains to be determined whether androgen supplementation has significant and sustained clinical benefits in older men with low-normal plasma total testosterone and normal LH levels. At present, there is no basis for androgen treatment outside properly designed clinical trials.

Treatment of non-specific symptoms: There is no basis for androgen therapy based on symptoms in the absence of established androgen deficiency. In addition to the unproven safety and efficacy, the placebo effect of androgen injections may be confusing to both doctor and patient. When placebo effects wane, further confusion and dissatisfaction with treatment may be expected.

Abuse of androgens

Illicit use of androgens[19-24] ("anabolic steroids") depends largely on obtaining androgens without legal prescription to be used in the absence of any medical indication. Illicit androgen use became epidemic over the past four decades, since androgens were reportedly first used in elite competitive power sports. A recent placebo-controlled study has shown that high-dose androgen administration does improve muscle size and strength in healthy eugonadal men. Whether these changes enhance athletic performance, whether they are sustained, and whether they apply to older men remains to be clarified.

Medical prescription appears to support only a small proportion of illicit androgen use, but such activity has been formally ruled as a breach of professional standards by medical boards in most States and by the Royal Australasian College of Physicians. Highly motivated young men can be very sophisticated in manipulating and pressuring general practitioners while attempting to obtain prescriptions for androgens. The doctor is often led to believe that other practitioners are prescribing androgens for young men, and that he or she is being uncaring or negligent by not acceding to the patient's wishes. We recommend that general practitioners resist these pressures.

Fortunately, most people appear ultimately to lose interest in this form of drug abuse.

Background and evidence basis of recommendations

The Endocrine Society of Australia (ESA) Consensus Guidelines for Androgen Prescribing were written on behalf of the Endocrine Society of Australia. The ad hoc Writing Committee commissioned by the ESA's Council was Dr A J Conway, Professor D J Handelsman (Chair), Associate Professor D W Lording, Dr B Stuckey, and Associate Professor J D Zajac. The draft guidelines were extensively circulated for comment to active members of the ESA with clinical expertise or interests in male reproductive endocrinology. Comments were incorporated into the final document, which was ratified by the ESA's Council. Androgen therapy, in regular clinical use for over 60 years, is one of the oldest hormonal regimens in modern therapeutics. As a long established standard and effective form of hormone replacement for many decades, placebo-controlled studies are unavailable and now unacceptable. Consequently, the NHMRC Quality of Evidence Ratings for these recommendations are those appropriate to an expert committee reviewing all available evidence from controlled experimental and observational studies as well as clinical experience.

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1: Use, misuse and abuse of androgens

Use
Physiological (androgen deficiency)[1-3]

- Classical androgen deficiency ("hypogonadism")
- Age-related partial androgen deficiency
    - Micropenis (neonatal)

- Delayed puberty
- Aged men*

- Androgen deficiency secondary to chronic disease*
- Induced androgen deficiency
  - Hormonal male contraception*

Pharmacological (non-androgen deficiency) [4-6]

- Osteoporosis
- Anaemia due to marrow or renal failure
- Advanced breast cancer
- Excessively tall stature in boys

Misuse
Inappropriate indications

- In absence of proven androgen deficiency:
  - Male infertility
  - Sexual dysfunction/impotence
  - "Male menopause", "andropause"
  - Older men (>65 years)
  - Non-specific symptoms

Abuse [19-24]
Absence of medical indication

Sporting	Competitive power sports (athletics, weightlifting, football, swimming, rowing, boxing)
Recreational	Bodybuilding
Cosmetic	"Body beautiful" subculture
Occupational	Security, police, armed forces, professional sports

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* These indications remain to be fully evaluated for safety and efficacy in controlled clinical trials.

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2: Biochemical evaluation of the diagnosis of androgen deficiency in men with clinical features consistent with hypogonadism*

Testosterone level†	Luteinising hormone	Diagnosis

	level†	
<8 nM	High‡	Androgen deficiency (hypergonadotropic hypogonadism§)
<8 nM	Not high	Androgen deficiency (hypogonadotropic hypogonadism§)
8-15 nM	High‡	Androgen deficiency (Leydig cell failure)
8-15 nM	Not high	Androgen deficiency not confirmed: unproven therapeutic benefit of androgen replacement therapy
>20 nM	Any	Excludes androgen deficiency
>30 nM**	High‡	Androgen resistance

*There is necessarily an arbitrary component to this type of table. It is based on current experience and should be subject to changes according to further clinical evidence. †Blood sample classification based on at least two separate morning blood samples. ‡"High" luteinising hormone level is defined as > 1.5 times the upper limit of the eugonadal reference range for young men. §Hypergonadotropic and hypogonadotropic hypogonadism are also referred to as primary and secondary hypogonadism, respectively. Compensated Leydig cell failure is a form of partial androgen deficiency in which androgen replacement is often beneficial. **Elevated testosterone is defined as above the upper limit of the eugonadal reference range for young men.

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3: Androgen treatment modalities [7-13]

Testosterone implants

- Fused cylindrical pellets of pure crystalline testosterone that form a subdermal depot
- Provide stable, physiological levels of testosterone for 4-6 months following a single implantation of four 200 mg (800 mg) implants
- Implantation uses a trochar and cannula technique under office sterile conditions, and requires local anaesthesia
- Main adverse effect is extrusion of implants via the insertion site 1-2 months after implantation
- Extrusion rate (about 10%) depends on operator experience and patient's physical activity
- Minor adverse effects related to the minor office surgery (bleeding, infection) are infrequent (<5%)
- Should only be used for patients who have demonstrated satisfactory tolerance of androgen effects with shorter-acting preparations

Transdermal testosterone

- Administered daily via androgen-impregnated adhesive skin patches or hydroalcoholic gels (not yet available in Australia)

Other depot testosterone formulations

- Newer injectable esters (testosterone undecanoate, testosterone buciclate)

- Testosterone-laden biodegradable microspheres
- Both these formulations deliver stable, physiological testosterone levels for 2-3 months following injection

Oral testosterone undecanoate

- Useful where parenteral testosterone is undesirable (eg, bleeding disorders or anticoagulation) or poorly tolerated
- Administered as 160-240 mg (four to six 40 mg capsules), divided into 2-4 doses per day
- Second-line formulation for routine ART, because of frequency of administration, high hepatic load, gastrointestinal intolerance, and higher cost

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