Testosterone: use, misuse and abuse

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ABSTRACT

- Testosterone is among the oldest drugs in medicine. It has a long efficacy and safety record for its prime role of androgen replacement therapy in men with androgen deficiency.
- Testosterone and synthetic analogue androgens have also been used in pharmacological androgen therapy (PAT) to produce androgenic effects on marrow, muscle or bone. Although PAT is increasingly being superseded by newer, more expensive drugs, androgens remain cost-effective in many older applications.
- Androgen misuse is the systematic over-prescribing for unproven medical indications. Misuse is increasingly evident for male ageing ("andropause") and some other clinical conditions.
- Further trials for new indications for androgens require reliable safety data, but rising costs may make it increasingly attractive to circumvent the need for evidence by promoting off-label mass marketing.
- Androgen abuse is the illicit self-administration of often massive doses of androgens for non-medical purposes — notably power sports and body building. In parallel with effective detection reducing androgen abuse in elite sports, more focus is needed on non-sporting cosmetic, recreational and occupational androgen abuse.
- Despite ongoing androgen misuse and abuse, testosterone remains under-prescribed for younger men with classical androgen deficiency that frequently remains undiagnosed.

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Testosterone, an androgen, was first characterised as the male sex hormone in the mid 1930s, a feat quickly earning the 1939 Nobel Prize in Chemistry (and finally ending the fin-de-siècle rejuvenation quackery associated with the names of Brown-Sequard, Steinach and Voronoff).[1] Its clinical use flourished in the post-War decades (the golden age of steroid pharmacology), and by 1965 all currently marketed testosterone and synthetic androgen products had been patented. In that era, the pharmaceutical industry had three principal commercial development goals for testosterone: the development of an orally active analogue, an anabolic steroid devoid of virilising properties, and a long-acting depot form.

In hindsight, the first goal proved unsafe, and the second, an unphysiological fantasy; only the third was a durable success. Now in clinical use for nearly seven decades,[2] testosterone is among the oldest marketed drugs, with a long record of safe and effective use for its principal indication of testosterone replacement in androgen deficient men. In addition, testosterone and synthetic androgens have long been used pharmacologically to obtain specific anabolic or other effects in non-androgen-deficient men with chronic diseases. Finally, over recent decades, testosterone and other androgens have increasingly been used as drugs of abuse, complete with an illicit market and their own folklore.

Nevertheless, despite decades of use and tremendous advances in understanding the molecular and cellular basis of androgen action, we have far to go to achieve optimal use of testosterone. Here, an approach to this challenge in men is outlined, which involves defining and optimising appropriate clinical use, while minimising misuse and, hopefully, eliminating the abuse of testosterone.

Use: appropriate indications

Testosterone is used clinically in two distinct modes, as androgen replacement therapy (ART) and as pharmacological androgen therapy (PAT).[3] With ART, the aim is to replicate, for the remainder of life, endogenous androgen exposure of all tissues using titrated doses of testosterone. PAT uses androgens like any other drug, judged by the same safety, efficacy and cost-effectiveness standards as any xenobiotic.

Androgen replacement therapy

Androgen deficiency (AD), due to hypothalamus, pituitary or testis disorders of genetic or acquired aetiology, is the principal clinical indication for ART.[3] Testicular testosterone production may be reduced by gonadotrophin deficiency or Leydig cell dysfunction. In ART, testosterone is used at doses designed to reproduce endogenous blood testosterone concentrations and physiological exposure of tissues to androgen. To the extent this is achieved, ART has the inbuilt safety of replicating long-term health outcomes of eugonadal men. Used in this way, testosterone can rectify all the clinical features of AD, with prominent effects of improving quality of life through enhanced energy, motivation and endurance, as well as restoring structural or functional deficits in muscle, bone, marrow and psychosexual activity.[4] Specific time-limited variations of ART include treatment of delayed male puberty[5] and hormonal male contraception.

Hormonal male contraception is a specific niche application of ART. Hormonal suppression of spermatogenesis requires inhibiting pituitary gonadotrophin secretion and depleting intratesticular testosterone. As this abolishes endogenous testosterone secretion, testosterone replacement is required for the pharmacologically induced AD.[6] Men in stable relationships wanting to share responsibility for family planning have to choose between methods that are either not completely reliable (condoms, withdrawal) or not intended to be reversible (vasectomy). No new male contraceptive methods were introduced in the 20th century, unlike the reliable, reversible female hormonal method widely available over the past four decades, which shifted contraceptive responsibility further onto women. In the long quest, carried out by the public sector, to develop a reliable, reversible hormonal contraceptive method for men, the landmark World Health Organization studies using testosterone alone[7,8] have been followed by an Australian study establishing proof of principle that a combination of prototype progestin with testosterone depots provides highly effective, reversible contraception with good short-term safety and acceptability.[9] Using this approach, commercial product development is underway in Europe.[10]

Elegant clinical research has identified pharmacogenetic modulation of androgen action involving a CAG triplet repeat polymor-

phism in the human androgen receptor, so that tissue sensitivity to both endogenous and exogenous testosterone is inversely correlated with length of the polyglutamine stretch.[11] This may contribute to explaining individual and population differences in susceptibility to androgen-dependent diseases, as well as guiding individual titration of testosterone dosage in ART — the latter consistent with recent evidence that men have widely different but individually consistent blood testosterone thresholds for androgen effects,[12] which change slowly with age.[13]

Recent Danish data linkage studies identified dramatic under-diagnosis of Klinefelter syndrome, an archetype of AD and its most frequent cause. Only about 25% of men with this syndrome are ever diagnosed during life,[14] depriving many men of effective treatment that enhances quality of life and may prevent their lifelong drift into poorer health and low socioeconomic status. These studies also imply that most men never undergo a full genital examination by a doctor during their lifetime,[15] in stark contrast with women — a facet of the neglect of male reproductive health as a whole.[16]

European population-based record linkage studies of men with Klinefelter syndrome also provided the first robust definition of lifetime health outcomes for androgen-deficient men.[15] Significantly reduced death rates from prostate cancer and ischaemic heart disease were balanced by increased deaths due to non-cardiac vascular and genitourinary disease, bone fracture and cancer, as well as excess hospitalisations.[17,18] In addition to the profound impacts of AD that do not precipitate hospitalisation or death, these findings outline numerous benefits in providing effective delivery of ART in conditions characterised by lifelong AD, which impoverishes the quality of life without shortening it.[15]

Pharmacological androgen therapy

PAT uses androgens without a priori regard to dose or class, aiming to achieve salutary androgen effects in men with chronic disease.[19] Many traditional PAT indications are now relegated to second-tier roles, having been overtaken by newer, more expensive drugs. As an adjunctive therapy, PAT would ideally improve survival by changing the natural history of underlying fatal disease — which has not yet been proven for any disease. Therefore, the objectives of PAT are limited to improving quality of life, and morbidity benefits have been proven in many settings. These include:

- anaemia due to marrow failure (maintaining haemoglobin, reducing transfusion requirement) or renal failure (augmenting and saving on erythropoietin);
- chronic respiratory or cardiac failure (quality of life, symptoms);
- steroid-dependent autoimmune disease (improving muscle and bone, symptoms);
- AIDS wasting (muscle gain, symptoms);
- preventing attacks of hereditary angioedema or urticaria; and
- palliating terminal breast cancer.[19]

Further controlled clinical studies are warranted to evaluate the safety, efficacy and cost-effectiveness of PAT in speeding rehabilitation from severe catabolic injury (burns, critical illness or major surgery) and chronic organ failure states for which there is promising but inconclusive evidence.

Key considerations for clinical research in PAT include distinguishing the mood-elevating properties of androgens. Testosterone has modest, positive psychological effects in most treated men and was one of the first antidepressants.[20] At high doses, a small minority of normal men become hypomanic.[21] In the context of PAT, such mood-elevating effects may non-specifically enhance quality of life without affecting the underlying disease,[22-24] rather like pharmacological glucocorticoid therapy used as a terminal palliative. This underlines the necessity for randomisation and placebo controls in future studies of adjuvant PAT. Nevertheless, even as new, expensive drugs overtake older indications, androgens may retain roles either for new adjuvant indications or because of their competitive cost-effectiveness.[25]

Misuse: prescribing for unproven indications

Systematic over-prescribing of androgens for unproven medical indications constitutes androgen misuse. Inevitably, the boundary between enthusiastic advocacy for novel but unproven use and misuse is vague, although either end of that spectrum would be readily recognisable. In the absence of any safe and effective indications, marketing by single-issue clinics and societies, sometimes with covert pharmaceutical industry support, may generate pressure for systematic over-prescribing. This may either be outside existing independent safety and efficacy guidelines or be related to "elastic guidelines", created to cater to ill-informed consumer demand. Areas of possible androgen misuse in men in Australia include increasing prescriptions of testosterone for "andropause" before there is convincing safety or efficacy evidence, as well as excessive androgen prescribing for men with HIV but without AIDS wasting.

Male ageing

While blood testosterone concentrations decline slowly (about 1% per year) from midlife onwards, the clinical significance of so-called andropause remains unclear and contentious.[1] The risks and benefits of testosterone treatment in older men with only age-related functional decreases in blood testosterone differ markedly from those pertaining to younger men with gonadal disorders.

Firstly, the desired benefits are often misdirected, with older men seeking treatment prompted mostly by age-related decline in sexual (mainly erectile) function. Yet, erectile dysfunction has predominantly a neurovascular rather than hormonal aetiology, with testosterone unlikely to rectify such sexual dysfunction. Secondly, the background rates of cardiovascular and prostate disease are higher, so that even small increases in these adverse outcomes may negate quality-of-life benefits of androgen supplementation.

Ultimately, the balance of risk and benefit for testosterone treatment of older men can only be determined reliably by suitably powered, prospective placebo-controlled randomised controlled trials. A recent Institute of Medicine report noted that the existing efficacy evidence was so equivocal that it could not even recommend large-scale clinical trials without better short-term (about 1 year) evidence of efficacy (currently being commissioned).[26] The definitive answers are at least a decade away.

In the interim, in the United States, sales of testosterone have increased 20-fold since 1990,[27] whereas population-adjusted sales have remained virtually unchanged in Europe, Asia and Australia.[28] This radical dichotomy presumably reflects the effect of direct-to-public drug marketing in the US for a drug with literal sex appeal. Australia was the first country to develop national prescribing guidelines specifically geared towards restraining testosterone prescribing for andropause, when the Pharmaceutical Benefits Scheme adopted the best-practice recommendations developed by the Endocrine Society of Australia.[29] A pharmaco-epidemiological analysis of androgen prescribing patterns in Australia revealed gradual increases nationally in androgen prescribing, but with specific peaks

related to promotional activities by industry and, more vividly, by a single-issue andropause clinic.[28] Restraining inflated expectations of androgens in male ageing is a challenge for public and professional education to strengthen the focus on prudent management and to reinforce reliance on evidence-based practice.

Barriers to evidence

Distinguishing valid but unproven indications from unjustified or unsafe prescribing is made difficult by the formidable cost of the necessary, rigorous clinical trials geared primarily towards novel chemical entities. The post-Women's Health Initiative era mandates that newer indications for prolonged hormonal treatment be based on adequate long-term safety, so that important but infrequent adverse effects are not overlooked. Androgens are now relatively cheap, so there is little incentive for companies to undertake the costly clinical trials required for regulatory approval of new indications. As a result, many useful clinical applications of testosterone and androgens seem condemned to dwell in the limbo of off-label use, prone to misuse and possibly doing undetected harm when used with evidence-free enthusiasm.

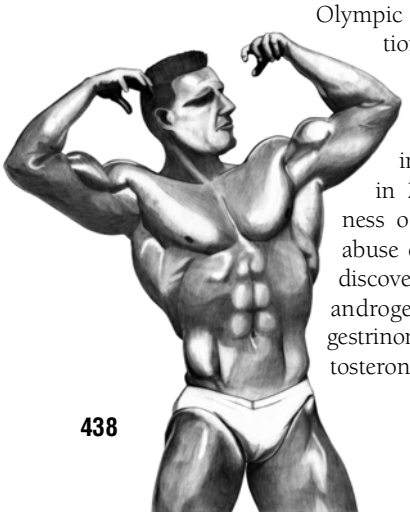
When circumstances foster off-label mass marketing, this lucrative option may circumvent the need for high quality but costly evidence — there remains a crucial role for vigilance by non-conflicted medical professionals.

Abuse: non-medical use

Androgen ("anabolic steroid") abuse is the use of androgens, usually obtained illicitly and often used in massive doses, for non-medical purposes. Abusers may use any available androgens, including veterinary, illegally manufactured, stolen and counterfeit steroids, in often bizarre, high-dose regimens advocated by folkloric underground publications. An unfortunate Cold War legacy, androgen abuse originated in international elite sports that became a proxy battleground for East European countries to cheat their way to public relations victory over the West — a challenge soon reciprocated. Androgen abuse is primarily attractive in power sports where increased muscle mass leads to greater strength, roughly proportional to androgen dose even in eugonadal men, a fact long denied[30] but proved by a seminal placebo-controlled study a decade ago.[31]

Abuse in sport

Androgen abuse in elite sports is policed by the World Anti-Doping Agency (WADA), which standardises sports doping tests internationally. The effectiveness of drug screening in competition is shown by the very low rate of positive tests (<2% of about 170 000 tests performed by 32 laboratories in 2004) on random testing at the Olympic Games and other major international events. The most frequently detected drugs are androgens, with three (testosterone, nandrolone and stanozolol) accounting for about 80% of positive results in 2004. Testimony to the effectiveness of WADA screening to stamp out abuse of all marketed androgens are the discoveries since 2002 of three designer androgens (norbolethone,[32] tetrahydrogestrinone [THG],[33] and desoxymethyltestosterone [DMT][34]) purpose-manufactured to evade WADA detection. These designer androgens are manufactured illegally in clandestine laboratories, with access to unpublished commercially confidential data from the 1960s allowing minor chemical modification of commercially available steroids to form potent androgens.[35] Once identified, effective detection methods are added so rapidly to routine screens that there is evidence of only one (THG) ever used in competition. Although requiring continued vigilance, the opportunities for androgen abuse in competition are virtually closed for athletes. Further elimination of androgen abuse from training by random out-of-competition testing is a formidable task still to be more fully developed.



A vision of the consequences of removing the WADA doping control regime is provided by the rampant androgen abuse in US baseball and football — national sports providing sufficient fame and fortune without an international dimension so they remain outside WADA jurisdiction. By tacitly accepting androgen abuse through failure to institute effective drug screening, these sports illustrate how androgen abuse would effectively become mandatory for elite athletes without effective policing. Responsible medical authorities cannot regard such a scenario as of no concern[36] in the light of the appalling health toll recorded from the one national doping program using systematic androgen abuse that has released its files.[37]

Abuse in the wider community

From the epicentre of drug cheating in sport, androgen abuse has diffused to the wider community, where it has become an entrenched modality of drug abuse, predominantly a masculine form of cosmetic consumerism appealing to a narcissistic, body building subculture. In addition, a smaller group of security professionals such as police, security guards and bouncers seek occupationally useful intimidating muscularity and enhanced strength in cartoonish caricatures of muscle-bound hyper-masculinity. Androgen abuse is now widely entrenched as a low-level endemic among economically developed countries where an illicit trade in steroids is sustainable. Surveys of Australian high school students[38] indicate a prevalence about half that reported in the US,[39] but levels of abuse among Australian secondary students remained stable over the 1990s.[40]

The doctor's role

In combating the communal problem of drug abuse, doctors can recognise, deter and avoid propagating androgen abuse. Doctors may identify androgen abuse in men who usually readily acknowledge intense, obsessive gym and exercise patterns and have tell-tale active truncal acne, often with additional features such as unusually prominent muscularity, testicular atrophy and gynaecomastia outside adolescence. Persistent suppression of blood luteinising hormone and follicle-stimulating hormone can confirm use of exogenous androgens, together with a low blood testosterone level indicating use of synthetic androgens. Recovery from prolonged testicular axis suppression can be lengthy (up to 12 months), but is eventually successful if exogenous androgens or human chorionic gonadotropin are not resumed in the interim. By themselves, medical professionals have limited scope to combat the societal phenomenon of androgen abuse, but must at least avoid perpetuating it by prescribing androgens without valid medical indications — a practice deemed professional misconduct by several state medical boards. It is fortunate that the professional defeatism of drug legalisation has not gained momentum for androgens, as it would

undermine efforts to deter such health-damaging behaviour, and corrode rational drug prescribing.

Therapeutic ironies

As a therapeutic drug, testosterone suffers simultaneously from both overuse and underuse. There is clear evidence of under-diagnosis of AD in affected young men, warranting more systematic efforts for efficient detection and testosterone treatment for an easily rectifiable condition that has lifelong consequences on quality of life. At the same time, the lay mystique of testosterone as a sex hormone encoding the virile properties of masculinity attracts male consumers of drugs for panacea or pleasure. This has created a boom in testosterone treatment for older men despite serious doubts about safety, probably fuelled by promotional activity of enthusiasts, single-issue clinics and societies running well beyond prudence in the post-Women's Health Initiative environment. It is a major challenge for our future as to whether the key tools of mass health education can straddle the subtlety of goals, which appear, simplistically, to be in conflict with each other.

Competing interests

Over more than 20 years, my clinical and laboratory research groups have received funding on a costs-recovery basis for research into many basic and clinical aspects of androgen physiology and pharmacology. This includes support from every company marketing testosterone products. No payment was received personally.

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