ANDROGEN MISUSE AND ABUSE

David J Handelsman AO, MB BS, PhD, FRACP, FAHMS

ANZAC Research Institute, University of Sydney

& Andrology Department, Concord Hospital

Sydney, NSW, 2139

Australia

Correspondence:

Professor D J Handelsman

ANZAC Research Institute

University of Sydney

Sydney NSW 2139

Australia

T: +61-2-9767 9100

E: djh@anzac.edu.au

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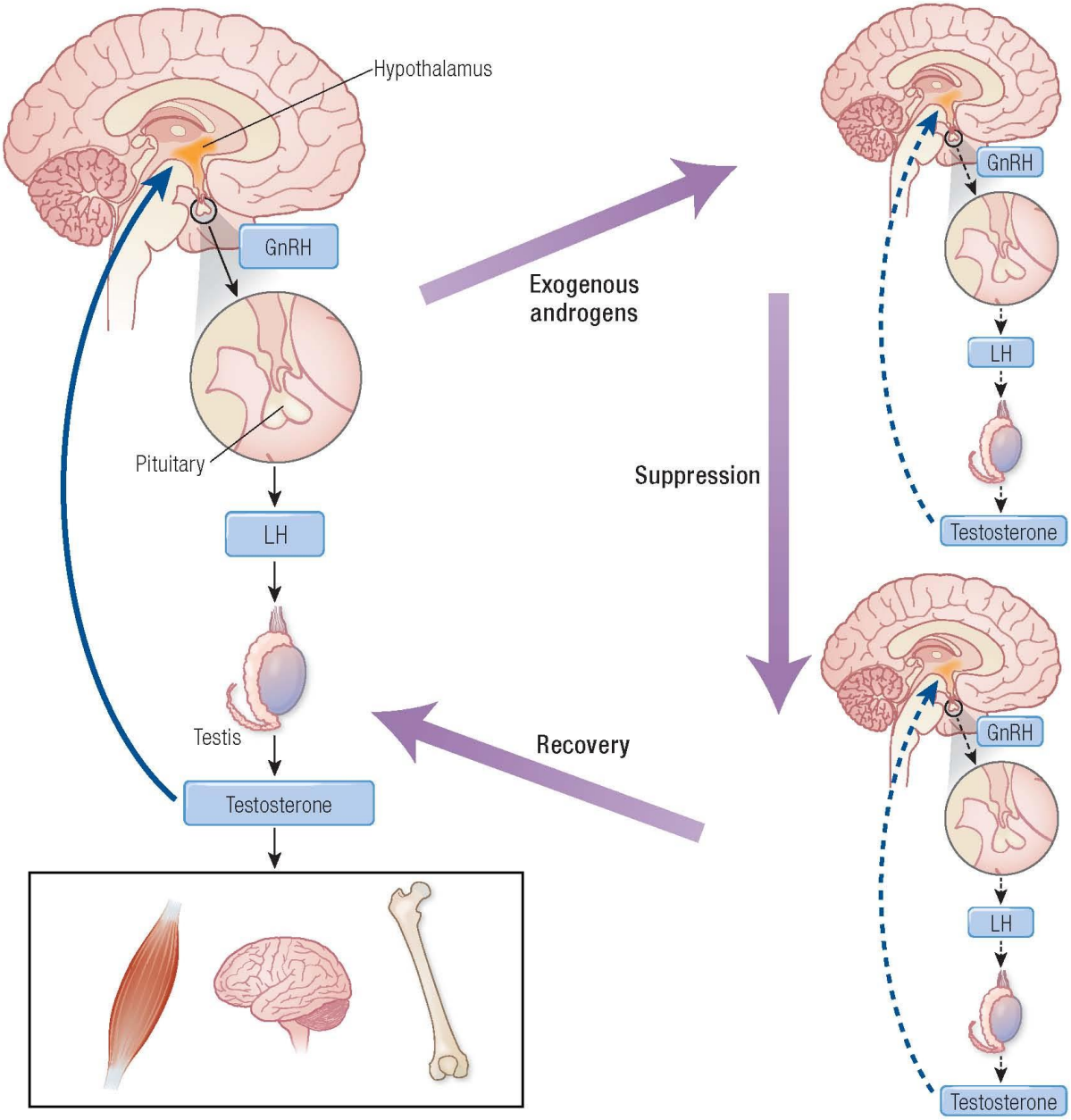
Abstract

Androgens are potent drugs requiring prescription for valid medical indications but are misused for invalid, unproven, or off-label reasons as well as being abused without prescription for illicit non-medical application for performance or image enhancement. Following discovery and first clinical application of testosterone in the 1930s, commercialisation of testosterone and synthetic androgens proliferated in the decades after World War II. It remains among the oldest marketed drugs in therapeutic use, yet after 8 decades of clinical use the sole unequivocal indication for testosterone remains in replacement therapy for pathological hypogonadism, organic disorders of the male reproductive system. Nevertheless, wider claims assert unproven, unsafe, or implausible benefits for testosterone, mostly representing wishful thinking about rejuvenation. Over recent decades this created an epidemic of testosterone misuse involving prescription as a revitalizing tonic for anti-ageing, sexual dysfunction and/or obesity, where efficacy and safety remains unproven and doubtful. Androgen abuse originated during the Cold War as an epidemic of androgen doping among elite athletes for performance enhancement before the 1980s when it crossed over into the general community to become an endemic variant of drug abuse in sufficiently affluent communities that support an illicit drug industry geared to bodybuilding and aiming to create a hypermasculine body physique and image. This review focuses on the misuse of testosterone, defined as prescribing without valid clinical indications, and abuse of testosterone or synthetic androgens (androgen abuse), defined as the illicit use of androgens without prescription or valid indications, typically by athletes, body-builders and others for image-oriented, cosmetic or occupational reasons.

Keywords: androgen, ageing, testosterone, synthetic androgens, SARMs, anabolic steroid, drug abuse

Graphical Abstract



1. Introduction

Androgens are potent pharmacological drugs requiring a legal prescription for valid medical indications, but they are also misused for invalid, unproven and off-label medical reasons as well as abused without prescription for illicit non-medical application for performance or image enhancement. Following the discovery (1) and first clinical use of testosterone (2) in the 1930's, medical uses and commercialisation of androgens proliferated in the post-World War II decades, the Golden Age of Steroid Pharmacology, overlapping with the early years of the Cold War (Figure 1). Testosterone remains among the oldest marketed drugs in therapeutic use. Yet after eight decades of clinical use, the sole unequivocal indication for testosterone remains in replacement therapy for pathological hypogonadism, organic disorders of the reproductive system (3). Yet the application of testosterone and its synthetic androgen analogs remains clouded by various wider claims asserting unproven and/or implausible benefits, often representing the wishful thinking about rejuvenation and with undefined safety risks. This review focuses on the misuses of testosterone, defined as prescribing without valid clinical indications, and abuse of testosterone or synthetic androgens (androgen abuse), defined as the illicit use of androgens without prescription for non-medical reasons, typically by athletes, bodybuilders, and others for image-oriented, cosmetic, or occupational reasons (table 1).

2. Historical background

Testosterone is the principal molecule responsible for the striking sex-based dichotomy between masculine and feminine physical features in adults. The precise molecular basis for these obvious distinctions was not understood prior to identification of testosterone as the principal mammalian male sex steroid of testicular origin in 1935 (1) followed rapidly by its first clinical use in 1937 (2), discoveries marked by a 1939 Nobel Prize in Chemistry. Yet androgens had an ancient pre-history long pre-dating that birth of modern androgen pharmacology. The role of the testis as the source of virility and fertility was known since antiquity. Castration of men has been practiced since ancient times to generate obedient slaves, harem guardians, as punishment for sexual crimes, religious self-mutilation and reinforced by the experience of castrating domesticated and agricultural male animals to render them more docile. The Chinese eunuch system, a tradition dating from the imperial period, persisted into the turn of the 20th century (4) as did the European practice of castrating boys to preserve their high-pitched voices combined with adult large lung capacity for opera singing (5). Castration to punish sexual crimes continues in some European countries by

orchidectomy (6-8) or, increasingly, by chemical (non-surgical) castration (9-11) including the first strong evidence from a randomized placebo-controlled clinical trial of a GnRH antagonist (12).

Since ancient times declining virility and fertility as men age, together with vague perceptions of the function of the testis, coupled to the desire for rejuvenation have repeatedly fostered attempts to revive youthful virility by boosting testicular functions. Rejuvenation fads have erupted whenever social affluence allowed indulgence in health hobbies including fantasies of life extension. Prominent episodes included the 16th century expeditions of Juan Ponce de Leon to the Caribbean, landing in Florida searching for the fabled Fountain of Youth, famously depicted in Lucas Cranach's 16th Century fantasy landscape (http://lucascranach.org/DE smbGG_593) in which the legendary spring waters restore youthfulness. Characteristically, in Cranach's painting ailing elderly women are carried to enter the waters then to emerge from the Fountain magically restored as attractive young women reflecting the prevailing communal beliefs that rejuvenation of men merely required that the female form was restored to youthful attractiveness. Notably, Ponce de Leon's royal patron had recently married a woman 35 years his junior and, even if that tale is apocryphal (13), its persistence reflects the popularity of latent rejuvenation fantasies.

Other imagined life extension schemes have proliferated (14). Undoubtedly the greatest flowering of rejuvenation quackery occurred over the turn of the 20th century as organotherapy (15). Organotherapy garnered credence in the late 19th century when Berthold, replicating John Hunter's 18th century experiments, demonstrated experimentally the androgen dependence of male secondary sexual characteristics by transplanting testes into the abdominal cavity of castrated roosters (15, 16). Wishful thinking transmuted these findings into a quasi-scientific basis for rejuvenating virility by organotherapy. Its original proponent, Charles Edouard Brown-Sequard, a genuine pioneer of experimental medicine during his working life (17), claimed at a post-retirement College de France meeting that self-injection of crude extracts of animal testes restored his vitality, virility and intellectual capacity for prolonged periods. These claims were derided by peers on both sides of the Atlantic as fantasy (18, 19) including noting that they could not be replicated without effects of expectation (20), an early inkling of the now known roles of expectation and suggestibility as components of the placebo response (21-23). Once testosterone could be measured, these claims were proven to be placebo effects because Brown-Sequard's aqueous extract yielded no hydrophobic constituents such as testosterone (24). Nevertheless, the promise of revitalization guaranteed enormous popularity for rejuvenation quackery (25, 26). Brown-Sequard's organotherapy became highly popular among the in turn-of-the 20th century Europe and North America by affixing a façade of scientific respectability to revitalization (26). Subsequently, the

Austrian surgeon Steinach promoted an “autoplastic” procedure (unilateral vas ligation) as an alternative rejuvenation procedure, reportedly performed in Vienna on 100 University professors including Freud and the Nobel Prize-winning Irish writer WB Yeats (27, 28). Yet another alternative was developed by Serge Voronoff grafting testis slices from various non-human animals onto the capsule of the human testis (29-31). At the same time in the USA, transplantation of human testis was reported (32) using organs from accidentally deceased donors with testis slices implanted into abdominal wall muscles (33) or whole testes from executed prisoners implanted into the scrotum without revascularization (34, 35). These procedures produced subjective improvements in a few men but only necrotic tissue on histopathology (35). These popular delusions disappeared in the 1930’s with the coincidence of the Great Depression which removed both the motive (discovery of testosterone removing organotherapy’s façade of scientific credibility) and opportunity (eliminated discretionary spending on frivolous pursuits) for organotherapy. Yet, hope never springs eternal more than when it comes to rejuvenation. Rather than vanishing without a trace, rejuvenation went into decades-long hibernation to re-emerge in an upscale make-over as testosterone treatment for “andropause” (also known as viropause, male menopause, late-onset hypogonadism, age-related or functional hypogonadism among many neologisms) around the turn of the following century, an ironic centennial recurrence of the rejuvenation mystique as millennial madness.

Most pharmaceutical developments of testosterone were deferred until after the hiatus of World War II. During the following 25 years, the Golden Age of Steroid Pharmacology, produced the successful commercial development of synthetic glucocorticoids and oral contraceptives which remain major modern pharmaceuticals. However a third major quest, for the development of a non-virilizing androgen (“anabolic steroid”) suitable for use in women and children, based on dissociating the virilizing from the anabolic effects of androgens failed comprehensively (36). This failure is now understood as being due to the discovery of a singular androgen receptor together with the mis-interpretation of non-specific whole animal androgen bioassays employed to distinguish between anabolic and virilizing effects (37). The term “androgen” is used herein for both endogenous and synthetic androgens including references to chemicals named elsewhere as “anabolic steroids”, “anabolic-androgenic steroids” or “specific androgen receptor modulators (SARM)”, which continue to make an obsolete and oxymoronic distinction between virilizing and anabolic effects of androgens where there is no difference (36).

3. Androgen Use, Misuse and Abuse

Table 1 here

The nature and significance of androgen misuse and abuse are best appreciated when contrasted with the appropriate uses of testosterone and synthetic androgens in physiological or pharmacological applications, respectively (table 1).

3.1. Physiological Treatment: Testosterone Replacement Therapy for Pathologic Hypogonadism

The sole unequivocal indication for testosterone use remains as replacement therapy for organic hypogonadism due to defects in the hypothalamo-pituitary testicular axis arising from pathological disorders. Within the framework of medicine based on the pathological basis of disease, testosterone treatment is justified when pathological disorders of the reproductive system render it incapable of maintaining androgen-sensitive tissue functions. Such defects may be due either to testicular damage disrupting Leydig cell testosterone synthesis and secretion or else to hypothalamo-pituitary disorders that reduce pituitary LH secretion, the principal drive to Leydig cell testosterone production. Testosterone is used exclusively for androgen replacement therapy as synthetic androgens lack the full spectrum of testosterone's effects involving the amplification and diversification pathways (figure 2). Testosterone effects are mediated by not just direct testosterone effects on androgen receptors, but also via indirect effects of its bioactive metabolites, usually generated within the androgen target tissues as local paracrine mechanisms. These bioactive metabolites comprise testosterone's amplification by 5α-reductase enzymes to the more potent, pure androgen dihydrotestosterone (DHT) and diversification by local conversion to estradiol via the enzyme aromatase (aromatization) to act on estrogen receptors. At the tissue level, androgen action is exerted by androgen binding to and activating the androgen receptor (AR) so genetic mutations impairing AR function can produce complete or partial androgen insensitivity syndromes, depending on the residual function of the mutated AR (38, 39).

Testosterone replacement therapy requires an accurate diagnosis of pathological hypogonadism. Hypogonadism is a clinical diagnosis, with a pathological basis and confirmed by hormone assays. The clinical diagnosis relies on history and physical examination to identify underlying irreversible disorders of the testis, pituitary or hypothalamus that require lifelong testosterone replacement. To confirm the diagnosis and assess the severity of hypogonadism requires measuring a reproductive hormone profile (serum testosterone, LH and FSH) at least twice on separate days. Concurrent

measurement of serum sex hormone binding globulin (SHBG) is required to evaluate if a low circulating testosterone simply reflects a low SHBG, the major carrier protein for circulating testosterone (40). Circulating LH and FSH in the mid-normal range are a useful indicator of adequate tissue androgen exposure as circulating LH is an effective and useful androgen sensor analogous to circulating TSH for evaluating thyroid hormone status. The pattern of low serum testosterone with proportionately low serum SHBG with normal serum LH and FSH is characteristic in the pseudo-hypogonadism of obese men, which may be mistaken for hypogonadism based solely on the low serum testosterone. Men with untreated structural hypothalamo-pituitary disorders causing a low serum testosterone typically have concomitant undetectable or very low serum LH and FSH. However, unlike TSH which has well defined lower limits of normal so that hyperthyroidism can be diagnosed, serum LH immunoassays have no well-defined lower limit of normal. The pulsatility of serum LH requires multiple samples to verify the ambient serum LH levels. Additionally, serum FSH usually provides a synergistic estimate of integrated gonadotropin secretion, unless there is concomitant independent spermatogenic damage which may disproportionately increase serum FSH.

A glaring failure of identifying pathological hypogonadism warranting testosterone replacement therapy is the striking under-diagnosis of Klinefelter's syndrome (KS, 47XXY), the most frequent cause of pathological hypogonadism and genetic disorder of male reproductive function. KS occurs in about 1 in 650 male births (152 per 100,000) in all populations surveyed (41, 42) yet registry data shows that, despite virtually pathognomonic small, firm testes (<4 ml), and a near normal life expectancy (43) the large majority (~75%) of men with KS go through life undiagnosed. This occurs because, in contrast to females of comparable age who undergo pelvic examinations regularly from adolescence onwards, most men never undergo medical examination of genitalia and thereby missing out on simple diagnosis and effective testosterone treatment. The minority of men with mosaic KS may have some preservation of spermatogenesis and larger testes thereby escaping clinical attention. Although genetic screening of neonates for KS is feasible, it has not been implemented for lack of evidence for cost-effectiveness for pre-pubertal diagnosis (44) in contrast to diagnosis from puberty onwards. The underdiagnosis of KS is a poor reflection on contemporary medical care of male reproductive health, especially contrasting with massive, wasteful testosterone misuse elsewhere and the better example of female reproductive health care.

3.2. Pharmacological Androgen Treatment

Pharmacological androgen treatment is the clinical use of androgens, usually synthetic androgen analogs of testosterone, as xenobiotic drugs aiming to influence the natural history and morbidity of a wide variety of systemic (non-reproductive) illnesses (Table 2) (45). Synthetic androgens include chemical classes with distinctive structural and pharmacological features including 17α- alkylated androgens, 1-methyl androgens and, most recently, non-steroidal androgens (synthetic androgen receptor modulators, SARM). In general, the desirable pharmacological features include oral bioavailability (considered desirable for marketing based on user convenience and acceptability) and tissue-selectivity (a modern reframing of a pure "anabolic" – i.e. non-virilizing - androgen). The undesirable features include the class-specific hepatotoxicity of 17α-alkylated androgens and the inability of synthetic androgens to undergo paracrine local tissue amplification or aromatization.

Pharmacological androgen treatment mainly aims to exploit the prominent pharmacological features of androgens, notably their myotrophic effects to increase muscle mass and strength, but in other setting for increasing hemoglobin, bone mass, hepatic C1 esterase inhibitor concentrations or reversible suppression of gonadal function (shrinking endometriosis, hormonal male contraception) (45) (Table 2). Unlike testosterone replacement therapy which is constrained to physiological dose, pharmacological androgen therapy would aim to use the most effective and safe doses of synthetic androgens, often at higher effective doses than would be used for replacement therapy. In most current clinical settings, pharmacological androgen therapy is now an affordable, cost-effective, second line option as an alternative to more expensive and/or less available but often more specific mechanism-based treatments, such as bisphosphonates for osteoporosis (46), erythropoietin and its analogs for renal anemia (47), GnRH analogs for endometriosis (48), and recombinant C1 esterase inhibitor for hereditary angioedema (49).

Physiological uses of testosterone serve as replacement therapy in men whose endogenous testosterone production capacity is absent or severely limited. By contrast, use of exogenous androgens in men with an unimpaired underlying reproductive system induces profound and sustained suppression of endogenous testosterone via androgenic negative feedback effects on the hypothalamus and pituitary (Figure 3). This pharmacological impact leads to characteristic undetectable or low serum LH and FSH due to profound and sustained suppression of pituitary gonadotropin secretion. While often overlooked, serum LH and FSH recovery are valuable indicators of the status of recovery of the hypothalamus-pituitary unit from suppression by exogenous androgens.

3.3. Androgen Dependence

Androgens have potent, dose-dependent psychoactive effects on mood, inducing hypomania in healthy individuals (50). Androgen abuse, typically involving massive doses, is associated with heightened impulsivity, aggression and violence (51), dysphoria (depression, anergy) and precipitating psychosis (52). Androgen abusers display addictive behaviors (53) such as reinforcement, tolerance, withdrawal and craving-driven drug-seeking and loss of control regardless of consequences (52). Their behavior also features impaired emotion recognition (notably fear) from body movements which may contribute to their social and personal problems reflected in antisocial behaviors (54).

Extensive experimental research on experimental rodent models that investigate the behavioural effects of androgens has been well reviewed elsewhere (55-60). These have employed various anthropomorphic paradigms aiming to identify any fundamental biological basis for the observations of indiscriminate aggression reported in a significant minority of androgen abusers. For example, cognitive effort discounting (testing the “win-at-all-costs” mentality) was assessed in testosterone treated rats reporting that dopaminergic reward mechanisms (61) and serotonin-depletion impulsivity (62) that may underlie androgen-induced mood and aggression changes . Other experiments have focussed on complex mechanisms of high dose androgen effects (including testosterone or synthetic androgens with variable aromatizability (63)) may exert both direct effects mediated via AR, cross-reactivity with ERs and progesterone receptors in the brainstem as well as indirect effects via changes in neurotransmitter release of receptor sensitivity involving serotonergic, dopaminergic and glutaminergic hypothalamic signalling pathways (57). The ultimate role of these exploratory experimental paradigms is to develop testable hypothesis for interpreting motivation and molecular mechanisms in androgen abuser behaviors geared towards therapeutic interventions to break the vicious cycle of their androgen dependence.

Transient withdrawal symptoms during recovery are a crucial reinforcing feature (64). Androgen dependence, recognized in ICD-10 and DSM-5, is well described by Brower’s two stage model (65) starting with voluntary recreational use transforming into compulsive drug-seeking habits as a gateway to addiction (66). The first stage (drug instrumentalization) is androgen use to enhance perceptions of appearance (67), followed by second stage (neuropsychological dependence) reinforced by withdrawal (androgen deficiency, regression of desired muscle growth effects) effects

making it difficult to quit (Figure 3). These non-fatal withdrawal symptoms are comparable with caffeine, nicotine and benzodiazepine dependency but less intense than for cocaine, amphetamines or opiates (60), congruent with less intense androgen effects *vs.* the "high" of acute intoxication of amphetamines or opiates. A consistent spectrum of psychological phenomena including cyclical behaviour patterns, repetitive reward-punishment dyad, reinforcing addictive behaviour by reward for repetition and by withdrawal dysphoria (anti-reward) with avoidance (68), have an indisputable basis in unobserved brain processes. However, objective biomarkers to track addiction for analytical, prognostic or therapeutic purposes are lacking, a key knowledge gap limiting understanding of the biology of addictive neurobehaviours (66, 69). These considerations have prompted the speculative proposal of stable circulating microRNAs as a biomarker read-out for androgen abuse (70). Uniquely in the case of androgen dependence, the suppression of serum LH and FSH due to prolonged exogenous androgen abuse, provide readouts of the state of recovery from androgen-induced hypothalamic suppression (71). These features make experienced psychological support an essential component of managing both the underlying psychological drivers to androgen abuse as well as the transient withdrawal symptoms during recovery. Effective rehabilitation must overcome the ingrained abuser folklore, quasi-scientific but usually baseless advice circulating on the internet and relayed through "bro-science" buddy networks (72). Although quasi-regulatory impact of reimbursement policy deters and reduces unjustified testosterone prescription (73), prolonged use of unjustified testosterone treatment creates a state of iatrogenic androgen dependence in leading to short-term withdrawal (androgen deficiency) symptoms after stopping treatment which encourages the vicious circle of ongoing treatment to alleviate withdrawal symptoms when the original objective of treatment is already forfeit (74). Fortunately, the natural history suggests that most androgen abusers eventually grow out of the habit and discontinue. Most abusers commence androgen intake in their adolescence or early 20s, continue for several years but very few remain active androgen abusers over the age of 50 years (71, 75, 76). No systematic studies of the reasons for discontinuing androgen abuse have been reported.

3.4 Free Testosterone: Dogma and Reality

The FT hypothesis is widely disseminated but controversial and unproven concept that may contribute to misunderstanding of testosterone use and misuse. The FT hypothesis, recently comprehensively restated (40), asserts that the non-protein bound fraction of circulating testosterone (about 2%) is the only biologically active moiety capable of entering tissues to exert androgen action. This contrasts with bound testosterone representing an inert reservoir (40, 77, 78) with most being firmly bound to SHBG (about 60%) and the remainder loosely bound to albumin and

other proteins (about 38%) constituting an buffer reservoir of biologically inactive circulating testosterone.

The FT hypothesis originated from the earliest, now obsolete, 1970's pharmacology theory of drug interactions. That focused on mutual displacement of drugs bound to circulating proteins (79) invoking the concept of a hypothetical unbound ("free") drug fraction (77, 78, 80, 81) but is now discarded in modern pharmacology (82) in favour of physiological mechanisms of drug interaction due to molecular receptor binding, cytochrome P450 induction/inhibition, P-glycoprotein and ion channel blockade (83). Nevertheless, the enshrining of the FT hypothesis in Endocrinology was secured by the fortuitous coincidence of the developing calculational formulae for the recently invented immunoassays in the 1970s. These focus on separating antibody-bound from unbound ("free") fractions (84) lending plausibility to the questionable physiological extrapolation of in vitro binding equation theory. Subsequently, despite the abandonment of its pharmacological underpinnings, this simple illustrative heuristic of "free" hormones evolved into an unquestioned dogma, passing uncritically from one paper to another without ever undergoing rigorous clinical evaluation of its validity, application, and interpretation. Long now considered an unchallengeable, quasi-axiomatic panchreston (explain-all), the FT hypothesis has been widely and prominently invoked to suggest (a) wider scope for testosterone treatment in male ageing because FT levels fall faster with age than accurately measured testosterone observed in population-based studies (85-91)and (b) obesity is not a state of testosterone deficiency warranting testosterone treatment because FT is normal (92-94). A parallel argument from thyroidology raised in favor of the FT hypothesis is that thyroid function testing routinely includes measurements of "free" thyroxine (T4) and triiodothyronine (T3). Yet, the FT hypothesis lacks basis in theory, measurement, and empirical clinical application (for details see review (95, 96)).

The FT hypothesis asserts that the small moiety of circulating testosterone not bound to any circulating protein (or loosely bound to albumin and other low-affinity binding proteins) is the most "biologically active" fraction of circulating testosterone due to its greater accessibility to tissues compared with tightly bound steroid. Yet unbound testosterone is also equally more accessible to sites of degradation, so this theory cannot explain why unbound hormones would be more rather less biologically active (95). Corollary assumptions of the FT hypothesis include that the rapid transfer of testosterone from its bound state to circulating carrier proteins moving into tissues

occurs passively and identically in all capillaries. While equilibrium binding theory may be reasonably assumed for testosterone during its relatively long time in the circulation, its application is dubious to the dynamic unloading of testosterone during fleeting capillary transit, an inherently non-equilibrium state. Each assumption has been invalidated by empirical evidence (for details see review (95)). For example, rather than being biologically inert protein-bound testosterone is actively transferred to androgen-sensitive tissues (97-102) and the varying thresholds for testosterone effects in different tissues (103) makes it unlikely that the capillary transfers are identical in all tissues or if they are, they do not determine androgen action in those tissues.

Despite the misconceived and ambiguous theory, dialysis-based laboratory measurement of "free" testosterone is feasible. However, dialysis-based laboratory methods lack a certified standard, quality control or validated reference range. They are also laborious and vulnerable to artefact so are not widely used in high throughput automated chemical pathology laboratories or, if available, costly. Instead, lab measurements are replaced by formulae based on serum testosterone and SHBG concentrations combined into equilibrium binding equations (104, 105). However, aside from the untenable assumption of equilibrium for testosterone unloading into tissues, these formulae are inaccurate relative to laboratory measurements due to their reliance on arbitrary plug-in constants and erroneous stoichiometry for testosterone binding to SHBG (106, 107). Amusingly, to glamorize these formulae the equilibrium binding equations have been referred to as calculations by the "Law of Mass Action" (108-112), analogous to claiming to measure weight by the Law of Gravity or temperature by the First Law of Thermodynamics. Nevertheless, flawed formulae are easy to calculate and widely but uncritically used. Crucially, through its formulaic dependence on two age-dependent variables, such calculated "free" testosterone is a deterministic (inverse) function of age. Hence, introducing this calculated variable, a masked surrogate for "age", confuses rather than clarifies any clinical evaluation androgen status, especially for older men. Direct empirical testing reveals that calculated "free" testosterone provides no clinically meaningful prognostic information beyond accurately measured serum testosterone (96). Given the unsound theoretical and empirical basis, recourse to such derived measures of circulating testosterone do not contribute to sound clinical decision-making regarding androgen status notably in male ageing.

Commercial free T4 and T3 immunoassays have an established role in diagnosis of thyroid dysfunction having overtaken measurement of total T4 and T3 apparently to account for potential

changes in circulating TBG concentrations. However, like the invalid free testosterone analog assays, free thyroid hormone analog assays violate the fundamental assay criterion of comparing like with like because there is no authentic standard for either “free” measurand. Instead, these surrogate methods introduce chemically non-authentic T4 or T3 analogs into the cognate free T4 and T3 immunoassays and then rely on complex recalibration to achieve credible clinical results. Inevitably, violating basic assay theory renders analog immunoassays vulnerable to errors and artefacts (113, 114) reflected in the difficulties of establishing a consensus common reference intervals for commercial free T4 immunoassays (115), as recognized by one of the pioneers of the “free” hormone thinking (77, 116). Fortunately, the clinical diagnosis of thyroid dysfunction relies almost exclusively on highly sensitive TSH assays. Modern TSH immunoassays feature well defined lower and upper limits of normal with the lower limit clearly distinct from zero (unlike serum LH) and all assays readily conform to a common reference interval (117). This reliance on TSH for diagnosis of thyroid dysfunction covers hyperthyroidism (suppressed TSH) and primary hypothyroidism (elevated TSH). The serum TSH assay in isolation may not provide a diagnosis of secondary hypothyroidism; however, as a late feature of panhypopituitarism, that state is usually accompanied by hypofunction in other pituitary-dependent axes (gonadal, adrenal, GH/IGF-I). Hence, the diagnosis of thyroid dysfunction is not dependent on the error-prone “free” analog T4 or T3 assays but rather on the highly sensitive TSH assay. In any case, this tangential issue provides no counterpart justification for the dubious FT hypothesis and its implementation in actual or surrogate measurements.

Nevertheless, FT hypothesis remains controversial in retaining some support from many experienced endocrine investigators (118-123). The most concerted application of the FT hypothesis to male ageing has been in the observational EMAS study which reports that calculated FT correlates with sexual (dys)function symptoms in cross-sectional and longitudinal analyses (91, 124); however, being unable to ascribe causality these observational data leave it unclear if the FT changes are cause or effect of the sexual (dys)function, especially considering the often overlooked evidence of reverse causality in that sexual activity maintains circulating testosterone (125-129). Despite its weak theoretical rationale and limited empirical clinical evidence base, the consistent unreflective repetition of the FT hypothesis in papers as an unchallengeable dogma with a façade of biochemical sophistication fosters confirmation bias among those schooled on an unquestioned verity. For those with second-hand knowledge of endocrinology pathophysiology derived from such textbooks and reviews, the FT hypothesis creates an attractive and facile, no-cost tool to eke statistical significance

from otherwise insignificant relationships of testosterone with age-related variable(s) – with strength of belief inversely proportional to the distance from first-hand knowledge of the field.

4. Androgen Misuse

4.1. Introduction

Androgen misuse is defined as the prescription of androgens without a valid indication. As a medical practice at variance with sound evidence, off-label testosterone prescription for wrong, unproven and/or unsafe reasons can lead to harmful, ineffective, or counterproductive results. Androgens are highly susceptible to wishful marketing and promotion for sexual dysfunction or an anti-ageing tonic. Specific misguided applications of testosterone include treatment for (i) male infertility, (ii) sexual dysfunction, obesity, type II diabetes, osteoporosis, depression or states of low energy, motivation or vitality in the absence of proven organic androgen deficiency and, by far the most frequent, (iii) age-related functional hypogonadism (aka "LowT", "Andropause", "Late-onset hypogonadism") as a tonic for age-related symptoms of sexual dysfunction and/or non-specific energy-related symptoms. While the exact boundary between justified off-label prescription and misuse may be hard to define for individual patients, mass marketing and promotion in absence of reliable evidence is clear.

4.2. Pharmacoepidemiology

There are virtually no estimates of the prevalence of testosterone misuse overall, or for its specific misapplications. The most visible manifestation of testosterone misuse is the phenomenal increase in testosterone prescribing over the start of the 21st century despite no new approved indications.

Figure 4 here

Based on sales data, testosterone prescribing has increased 100-fold from $18 million in the late 1980's (130) to $1.8 billion over 3 decades (131). This epidemic of off-label testosterone prescribing is predominantly for treatment of "age-related or functional hypogonadism" (132-134), most prominent in North America with parallel but lesser changes in most other regions (131, 135). This "andropause" bandwagon has been propelled by permissive prescribing guidelines by professional scientific societies (118, 136), direct-to-consumer-advertising (137), single issue men's health clinics and tendentious misinterpretation of testosterone measurements and surrogate calculations.

Patterns of testosterone prescribing are most reliable in countries where prospective data is available from single-payer national or regional health schemes, private or national public health insurance or comprehensive health systems databases (reviewed in (138)). A global

pharmacoepidemiology analysis of testosterone prescribing for 41 countries (figure 4) shows a major, progressive increase in per capita testosterone usage for every region and most countries over the first decade of this century (131), all without any new approved indications. That included a 40-fold increase in Canada and 10-fold in USA in per capita testosterone usage. Quasi-regulatory curbs through reimbursement policy for off-label testosterone prescribing have proved to be transient and/or partially effective in Australia (73, 74, 135, 139) and Canada (140). The Australian national health scheme displays striking but medically inexplicable differences between states (139) consistent with marketing-driven prescribing. Corroborative findings of progressive increase in testosterone prescribing based on nationally representative data are reported from Australia (135, 139), Canada (141), UK (142, 143) and Switzerland (144). Analogous findings are also reported from more selective sources like private health insurance databases (143, 145) or the Veteran Administration medical system (132, 146); however, the participation bias of those databases means their findings cannot necessarily be extrapolated to national prescribing. Discrepancies between these selective system-based estimates and those of national sales data (131) indicates they under-estimate prescriptions, likely a reflection of having effective formulary rules. A Veterans Administration study revealed that 94% of men receiving testosterone prescription did not meet even their lax local clinical guidelines (134). Testosterone prescribing in the absence of pathological hypogonadism is principally for men aged 40-70 years of age in the national Australian data (73, 74) and aged 40-60 years of age in more selective US data from VA studies (132, 134).

Testosterone usage accelerated in the second half of the decade since 2010 reflecting the impact of permissive US (147) and European-based (148) prescribing guidelines published in 2005-6 and republished virtually unchanged 4 years later (136, 149) in multiple journals and again updated in 2018 with minimal changes (118). In a classical form of disease mongering (150, 151), these expanded the definition of “hypogonadism” from a condition due to pathological disorders of the reproductive system to any condition associated with a low serum testosterone and any non-specific symptoms, regardless of underlying diseases or whether the symptoms are caused by the low serum testosterone (152). This provides tacit endorsement of testosterone prescribing for functional or age-related hypogonadism (153) regardless of reproductive pathology, bypassing the need for high quality evidence for off-label indications (154) and contributing to the major upsurge in testosterone prescribing. In 2015 the FDA criticised this *de facto* bypass of regulatory controls against marketing off-label uses in a safety warning (155, 156) making it clear that testosterone was approved only for pathological hypogonadism and that age-related hypogonadism was neither an accepted diagnosis

nor warranted testosterone treatment as efficacy and safety had not been established. Evidence is accumulating that this epidemic of off-label testosterone prescribing has peaked and is declining at a national level in Australia (73) as well as from selective private insurance-based US databases (157, 158). However, recent evidence from Australia indicates that quasi-regulatory reimbursement policy changes may change patterns of testosterone prescribing but that overall testosterone usage persists (74). This suggests that men initially prescribed testosterone for invalid, off-label indications display androgen dependence reflecting unwillingness to stop testosterone treatment, likely due to the iatrogenic androgen deficiency withdrawal symptoms (74).

4.3 Specific misuses of testosterone

Male infertility: The most egregious misuse of testosterone is prescription for treating male infertility where it can only be detrimental. Historically, in the 1970s testosterone rebound therapy was proposed as a treatment for male infertility based on uncontrolled clinical experience series (159, 160). In this approach spermatogenesis was suppressed by exogenous testosterone administration on the basis that it would rebound to higher than pre-treatment baseline and produce more pregnancies than expected; however, clinical trials indicated that it was no more effective than placebo for inducing pregnancies (161, 162). Administration of testosterone reliably and reversibly suppresses spermatogenesis for hormonal male contraception (163, 164). Yet, over 30% of Nigerian doctors (165) and North American urologists (166, 167) report prescribing testosterone to treat male infertility with 70% believing that such testosterone treatment stimulates sperm production (165), perhaps an unjustified persistence of beliefs in testosterone rebound therapy despite its refutation or misunderstanding of the physiological role of testosterone in spermatogenesis. This iatrogenic cause of male infertility (167, 168) is regretted by men who used androgens while unaware of this risk (169). There is no basis for testosterone treatment of male infertility and such harmful mismanagement should be avoided.

Obesity: Although gonadal function in obese men remains incompletely defined, obesity is not a cause of pathological hypogonadism (170). As most testosterone is bound to SHBG, inevitably, serum T and SHBG are consistently reduced in male obesity, both in inverse proportion to the degree of obesity with these changes reversible by substantial weight loss (93, 94, 170, 171) notably after bariatric surgery (93). Based on the FT hypothesis, it is commonly asserted that FT is normal in

obesity (92-94, 172) thereby concluding that testosterone treatment is not justified in obese men. Yet that interpretation of FT in obese men (92-94) is, at best, only true for surrogate FT calculations in mild obesity but it is not an accurate generalization of available data based on the reference dialysis-based laboratory method. The dialysis-based laboratory method requires skilled, non-automatable manual procedures so are not widely available and in recent years has been largely supplanted by surrogate methods. Over the last 25 years only a single study reported investigating FT by equilibrium dialysis in obese men with or without diabetes (173). This study showed that FT was reduced in obese men, regardless of diabetes. These findings reinforce the older empirical equilibrium dialysis studies of limited sample size showing FT is reduced in obese men depending severity of obesity (174-178) supported by classical studies using calculated rather than measured FT (179, 180). The alternative methods used to substitute for the dialysis-based laboratory reference method are based on equilibrium binding equation formulae (Sodergard, Vermuelen) that calculate FT from serum T and SHBG measurements (104, 105, 181) or FT analog immunoassays (182-186). However, equilibrium binding formulae provide consistently inaccurate FT estimates (106, 107, 187-189) due to their multiple flawed assumption of equilibrium binding, approximated plug-in affinity and mistaken stoichiometry for testosterone binding to SHBG (106, 107). Similarly, the testosterone analog method is an invalid assay because it violates the basic assay principle of comparing like with like lacking any FT standard. Ultimately, the FT analog method provides results an order of magnitude lower than dialysis-based measurement (40, 190-195) while also lacking any quality control program or consensus reference ranges. Hence while accurate measurement of FT may be normal in mild obesity, this interpretation is not generally correct for obesity. However, circulating LH and FSH concentrations remain consistently mid-normal range in men with obesity signifying a eugonadal status (170). The typical conjunction in obese men of a low serum testosterone and SHBG with normal serum LH and FSH may be misinterpreted as hypogonadotropic hypogonadism (196) and is better understood as pseudo-hypogonadism.

The few well-designed randomized clinical trials of testosterone in obese men show minimal (197, 198) and non-sustained (199) benefits of testosterone over placebo that are insufficient support the pharmacological androgen therapy as effective treatment for obese men. Clinical studies showing small increases in muscle mass (and strength) with comparable small reductions in fat mass and increases in hemoglobin are expected effects of testosterone treatment in any men regardless of obesity, diabetes or other disease states so such expected changes do not provide evidence that the men had any testosterone deficiency state prior to testosterone treatment. Furthermore, such

treatment risks the consequences of sustained exogenous testosterone treatment in men without underlying pathological hypogonadism including androgen dependence and possibly cardiovascular disorders.

Overall the available evidence does not support the interpretation that obesity represents any state of hypogonadism with the possible exception of extreme obesity for which bariatric surgery rather than testosterone may be the most effective treatment (170). The question-begging conclusion that testosterone treatment is not justified in obesity, based on the FT hypothesis, is an interpretation reaching the right conclusion by the wrong reasoning. Overall, there is no sound basis for testosterone treatment of obese men. This makes it pointless to screen individual obese men for low serum testosterone especially if it relies on inaccurate formulae for calculated fractions of testosterone. Rather, they should undergo a full clinical evaluation (including testicular examination) together with multi-sampling of reproductive hormones to identify or exclude any reproductive pathology, a recommendation echoed by the cognate European Society of Endocrinology Clinical Practice Guidelines (200).

Diabetes: As type II diabetes is so strongly based on obesity, the conjunction of the characteristic pseudo-hypogonadism changes of obesity (low serum SHBG and testosterone, normal serum LH and FSH) is frequently observed among obese men with type II diabetes whereas such changes are not evident in men with type I diabetes (201, 202). However, these changes have been misinterpreted as "hypogonadotropic hypogonadism" on the basis that serum LH and FSH are "inappropriately normal" and that "free" testosterone concentrations are low (196). However, both interpretations are spurious because normal circulating LH and FSH are consistent with eugonadal status as untreated men with hypogonadotropic hypogonadism usually have low LH and FSH when testosterone concentrations are low. Accordingly, a meta-analysis review of randomized controlled trials of testosterone in type II diabetes has shown minimal or no benefit over placebo for glycemic control (203). Other well-known effects of testosterone on sexual function, body composition, hemoglobin and bone density are equally evident in men with diabetes as in non-diabetic men. While these effects may represent side-benefits of testosterone treatment if it was warranted, they do not provide a basis to initiate testosterone treatment in men with type II diabetes. Hence there is no basis for testosterone treatment of men with type II diabetes who do not have pathological hypogonadism making it pointless to screen men with type II diabetes for low serum testosterone.

Osteoporosis: Testosterone has important impact on male bone growth and maintaining bone density. This is dependent on not only direct effects of testosterone and dihydrotestosterone on androgen receptors but also via the aromatization of testosterone to estradiol to act via estrogen receptors (204). This is most clearly illustrated in the bone deficits characteristic of men with pathological hypogonadism and their reversal with testosterone replacement. Osteoporosis in men is less studied than in women so that reviews and guidelines often provide ambivalent and weakly substantiated recommendations regarding testosterone treatment for osteoporosis in men without pathological hypogonadism (205, 206). Empirical treatment with testosterone for men unexplained (idiopathic) osteoporosis but without pathological hypogonadism was once advocated as a form of pharmacological androgen therapy but lacks any solid foundation from well-controlled clinical trials of fracture prevention and is now known to risk long-term androgen dependence. Given the availability of potent non-steroidal bone protecting and anabolic agents (207), studies of testosterone effects suggest minimal effects in older men (208) so that empirical testosterone treatment continues to lack a sound basis. Hence, beyond testosterone replacement therapy for men with pathological hypogonadism presenting with osteoporosis, there is no basis for testosterone treatment of idiopathic osteoporosis for men without pathological hypogonadism. This makes it pointless to screen men with osteoporosis for low serum testosterone other than as part of a comprehensive clinical evaluation (including examination of testicular size) to identify or exclude pathological hypogonadism.

Depression: Testosterone's long-known mood elevating properties, which led to its patenting as an anti-depressant in 1948 prior to the modern anti-depressant era (209), have recently resurfaced with recognition of testosterone's psychoactive, mood elevating effects (210, 211). These produce pleasurable mood and sensations that may explain its modest efficacy as an adjuvant antidepressant for mild depression (212, 213). Hypomania is also recognized as an idiosyncratic over-dosage side-effect affecting up to 5% of otherwise healthy individuals (214). Hence, testosterone treatment of men with non-specific symptoms may improve symptoms or tolerance for minor disabilities, regardless of androgen status, just like any anti-depressant or other mood-elevating drug does; however, this does not justify testosterone prescription for depression.

Drugs: Treatment with some drugs is an important reason for off-label testosterone prescribing for men without pathologic hypogonadism. In an enlightening epidemiological study of the US Veterans Administration health system (134), Jasuja et al studied a large cohort of men (excluding HIV) who had received a testosterone (162,092) or prescribed a drug other than testosterone (648,594) over a 4 year period when there was no formulary restriction on testosterone prescribing. Of men prescribed testosterone, 93.7% did not have pathologic hypogonadism and only 20% had two low blood testosterone measurements before starting testosterone treatment. Testosterone prescribing was more frequent among men treated with opioids and systemic glucocorticoids but less often among men treated with anti-psychotics or who were substance abusers. Concomitant systemic diseases significantly increased (chronic pulmonary disease, diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, mental disorders) or decreased (cardiovascular diseases, psychotic disorders, prostate cancer) the likelihood of testosterone prescribing. These findings illustrate the nexus between off-label testosterone prescribing with underlying systemic diseases, notably the co-morbidities of aging, and their drug treatments.

Among the drug classes that can lower circulating testosterone concentration, the most effective are drugs such as GnRH analogs and sex steroids used to induce medical castration for treatment of advanced prostate cancer, precocious male puberty or to reduce libido for forensic reasons. Other classes of drugs with off-target or unintended effects leading to usually lesser reductions in circulating testosterone raise a question whether testosterone treatment may be beneficial in aiming to restore circulating testosterone concentrations to eugonadal levels. Such modest lowering of circulating testosterone is often referred to casually as “hypogonadism” with all the implied license to prescribe testosterone. Other than exogenous androgens, the most frequently encountered drugs that cause significant lowering of circulating testosterone concentrations are opioids and systemic glucocorticoids. As highlighted in the Jasuja VA study, the lowering of circulating testosterone may be due to the drug treatment but there may also be important contributions from the underlying disease and/or a non-specific hypothalamic response to systemic illness. For example, severe weight loss due to HIV and other wasting diseases or anorexia/bulimia nervosa frequently cause reduced circulating testosterone concentrations, including in men (215), due to the common hypothalamic responses to undernutrition, effects which cause misinterpretation of testosterone treatment effects (216).

Men on long-term opioid treatments often display reduced serum testosterone due to the μ-opioid receptor effects of opioid agonists that reduce hypothalamic GnRH, pituitary LH, and consequently testicular testosterone secretion. The degree of testosterone suppression varies between drugs, according to their μ and/or other opioid receptor selectivity, and their pharmacodynamics. Such men may display other non-specific clinical features consistent with chronic androgen deficiency such as sexual dysfunction, low energy/motivation state, bone loss and fractures and impaired quality of life (217, 218). While uncontrolled observational studies suggest variable improvement in sexual function, pain tolerance and quality of life (219), there are just two small placebo-controlled RCTs which report modest and inconsistent benefits of pharmacological testosterone treatment in men treated with opioids for non-cancer chronic pain. One study of 64 men randomized to treatment with daily transdermal testosterone or placebo gel for 14 weeks found no significant benefit of testosterone on self-reported pain but improvement in two of four objectively measured pain sensitivity tests (220) and without benefit in sleep quality or pain catastrophizing (221). Among the anticipated testosterone effects, there was increased sexual desire but no other aspects of sexual function (International Index of Erectile Function) and improvement in only one of ten dimension of the SF36 quality of life scale. The other study randomized 41 men to testosterone undecanoate (1000 mg) or placebo injections at entry, 6 and 18 weeks with post-study evaluation of 38 men completing the study at 24 weeks (222). There were no improvements in clinical pain rating or in any of eight standardized measures of pain sensitivity despite expected changes in body composition, improvement in sexual function and one dimension of the SF36 quality of life scale. The investigators concluded there were no significant effects of testosterone treatment on clinical or experimental pain perception. Therefore, there remains at present no sound basis for routine testosterone treatment of men on chronic opioid treatment. Despite the well-established μ-opioid receptor mediated effects of suppression of endogenous testosterone, such negative findings may be understood because opioids exert much wider effects than the μ-selective opioid effects that reduce testosterone secretion so that reversing only a single dimension of opioid effects may have limited efficacy. Following these small, well-controlled studies, further evaluation involving well-powered placebo-controlled studies is required to investigate the sustained benefits, if any, of testosterone treatment in men on long-term opioid treatment. Such studies would need to account for the pharmacological diversity of opioid drugs (in terms of μ vs other opioid receptor selectivity), routes of administration, dosage, and duration of treatment as well as the degree and persistence of suppressing endogenous testosterone and the various indications for opioid use (cancer, non-cancer chronic pain) as well as illicit street opiate addiction and methadone or buprenorphine maintenance. A limitation of the previous observational and controlled studies is the lack of rehabilitation as an

outcome measure to determine whether improved quality of life including sexual function could enhance societal efficacy from a community perspective. The disastrous recent crisis of addiction and overdose deaths from prescription and illicit opiates creates urgency to resolve these challenges. In principle, this could include a role for adjunctive treatments like testosterone aiming to ameliorate quality of life as part of effective rehabilitation; however, more convincing efficacy would be required for this to become recognized as a mainstream public health issue in response to the opiate crisis (223).

Although men taking long-term systemic glucocorticoid treatment often display modest reduction in circulating testosterone (224-228), there is little evidence to support the use of adjunctive testosterone treatment. Only two small, controlled studies of testosterone treatment in men on long-term systemic glucocorticoid treatment are reported. One study randomized 51 men taking systemic glucocorticoid treatment to treatment with mixed testosterone esters (200 mg), nandrolone decanoate (200 mg) or matched placebo injections every 2 weeks for 12 months (229). Compared with placebo, both androgens significantly increased muscle mass (3.5% & 5.8%) and strength as well as bone mineral density in lumbar spine (by 4.7%) but not hip or total body. Testosterone, but not nandrolone or placebo, improved overall quality of life. Similar findings were reported in a randomized cross-over study of 15 men having systemic glucocorticoid treatment for asthma. These participants were treated with 250 mg of mixed testosterone ester injections monthly or had no treatment for 12 months before switching to the other study arm for a further 12 months after a 4-month washout period (230). Testosterone produced increased bone mineral density at the lumbar spine (by 5%) but not at the hip or total body. The congruent findings of the two studies indicate testosterone has a consistent, small effect on lumbar, but not hip or total body bone density as well as muscle mass and strength and quality of life; however, the magnitude of the increase in bone density (~5%) is small relative to the detrimental effects of glucocorticoids (231). As a result testosterone is not often recommended for treatment of glucocorticoid-induced bone loss (232) and testosterone treatment has never gained wide usage in this setting. Given the modest magnitude of effects, the potential role of pharmacological testosterone treatment is reduced by the availability of alternatives such as using minimally effective doses and duration of systemic glucocorticoids (eg reducing dosage, switching to inhalational steroids for asthma) and the use of dose-sparing alternatives such as non-hormonal, disease-modifying immunosuppressants (including biologics) for inflammatory diseases and/or bone anabolic drugs to prevent early glucocorticoid-induced bone loss

(233). Therefore, there remains at present little basis for routine testosterone treatment of men on chronic glucocorticoid treatment.

4.4 Rejuvenation and the Invention of Andropause: Age-related Functional Hypogonadism

In continuity with the pre-history of androgen pharmacology (see Section 2), the major current misuse of testosterone is its promotion for rejuvenation as an unproven anti-ageing tonic to combat declining male sexual function and/or loss of energy or vitality. Modern marketing to revive the turn-of-the-20th century rejuvenation fad (organotherapy) required social branding to legitimize off-label testosterone prescriptions (234). This has spawned coining a plethora of neologisms such as "male menopause", "climacteric", "andropause", "viropause", **"partial androgen deficiency in the aging male** , "LowT", "late-onset hypogonadism" and, most recently, "age-related or functional hypogonadism" to provide medical gravitas to this invented disorder (156) (Figure 5). The marketing drive coincided with recognition that, despite the modest prevalence of pathological hypogonadism (~0.5% (235)), "andropause" was present in up to 40% (236), or more usually 10-25% of men (88, 237, 238) with even the most modest estimates of 2-3% (124) representing major (5-100 fold) increases in potential market over pathological hypogonadism. Based on an FDA Advisory Committee review, in 2015 the FDA made clear its judgement that, while testosterone treatment for pathological hypogonadism was warranted, age-related or functional hypogonadism was not recognized as a genuine disease and that testosterone treatment for it was not justified (156).

The traditional definition of hypogonadism as pathological disorders of the male reproductive system, differs from a highly influential series of US (118, 147, 149) and European (136, 148, 239) clinical guidelines published over the last two decades. The three editions of the US guidelines between 2006 and 2018 have been cited over 3500 times and the three European guidelines published in 10 peer-review papers have over 1100 citations. These created a cascade of conforming subsidiary guidelines ramified through national and professional societies as well as organisations with commercial gains such as men's health clinics and pharma companies. These guidelines consistently widen the boundaries of the term "hypogonadism", with the elastic redefinition representing a form of "disease mongering" – expanding the market for drugs by widening acceptable indications (152). The first two versions of the US guidelines did not differentiate between pathologic and functional hypogonadism, a distinction that appeared in 2018. Yet, the

testosterone prescribing recommendations were largely unchanged across all versions in blurring the distinction between pathologic and functional hypogonadism regardless of formalizing the distinction. By recommending in 2018 against *"..routinely prescribing testosterone to all men 65 years of age or older with low testosterone concentrations.."*(emphasis added) this opens an influential imprimatur for discretionary prescribing testosterone for beyond pathologic hypogonadism. Endorsing discretionary testosterone prescription for men with any lowering of serum testosterone plus non-specific symptoms – when there is no way to know they are causally connected (in either direction) or both due to third factors (co-morbidities) –fosters testosterone prescribing whenever there is any doubt, which is almost always.

This permissive, wider redefinition substitutes an open-ended conjunction of virtually any non-specific clinical signs or symptoms coupled with a low circulating testosterone concentration regardless of underlying diseases and whether there the symptoms are caused by lower circulating testosterone concentrations. In assuming the non-specific clinical features are due to the low testosterone concentration, rather than the reverse or that both arise from underlying disease(s), the expansive re-definition abolishes the fundamental distinction between pathological and functional hypogonadism. The latter comprise numerous clinical states where a low serum testosterone is an adaptive dynamic hypothalamic response to systemic illness and/or its treatment. Hence it is unclear whether the clinical and hormonal features are cause, consequence or both arise from the underlying disease state(s). As such adaptive changes may beneficial, neutral, or detrimental to health, in contrast to pathological hypogonadism, testosterone treatment for male ageing needs rigorous evidence of safety and efficacy, which is largely lacking, and are displaced by influential manifestos tacitly sanctioning unproven treatment and effectively bypassing the need for sound evidence. Blurring the distinction between pathological and functional hypogonadism has been one contributory factor in the massive increases in testosterone prescribing over recent decades (131) as an unproven empirical tonic to counter sexual dysfunction and/or decreased energy, vitality or virility in ageing men (73, 74, 132-134). Additional important contributory factors have been the influence of direct-to-consumer-advertising (only legal in the US), inaccurate immunoassays for testosterone and calculations of “free” testosterone as well as the proliferation of commercial one-issue men’s health clinics together with congruent pharma promotion. Finally, evidence indicates that men treated with testosterone for unsound reasons (including ageing-related functional hypogonadism) have high rates of discontinuation of 80-85% after 1 year of treatment for ineffective treatment (240-245). Where symptom relief is reported during

administration of testosterone, persistent benefits reported after discontinuation of testosterone treatment (246, 247) indicates the presenting symptoms were not androgen related. This high turnover "churn" market risks patient dissatisfaction with their medical care.

The most ambitious attempt to define "andropause" was from the EMAS study (124), an observational population-based cohort of 3300 men from 8 European cities. In a cross-sectional analysis that produced estimates of "andropause" prevalence of 2-3%, there was no relationship between any physical or psychological features with serum testosterone concentrations. However, a post-hoc focus on three sexual symptoms (erectile dysfunction, frequency of morning erections or sexual thoughts) displayed a weak but significant negative correlation with serum testosterone concentrations but with high rates of false positive (25-50%) and negative (40-50%). For the 3 sexual symptoms, regression on blood testosterone levels produced shallow breakpoints at testosterone concentrations with the only consistent relationship between all 3 sexual symptoms and a serum testosterone concentration <8 nmol/L. These weak associations were nullified by adjustment for age, obesity and co-existing illnesses indicating any relationship of sexual function with reduced serum testosterone was mediated by impact of the co-morbidities of ageing, rather than ageing itself. Hence, if warranted, the objective to rectify reduced blood testosterone should be directed towards alleviating the underlying causes rather than testosterone administration (200, 248). Furthermore, the purported EMAS definition of "andropause" is further flawed by the false assumption of unidirectional causality - that low testosterone is a cause of sexual symptoms - ignoring evidence for reverse causality showing that sexual activity maintains blood testosterone concentration (125-129). Correspondingly, the FDA concluded in 2014-5 that this invented condition was not a genuine medical disorder, let alone warranted testosterone treatment (156, 249).

The dearth of convincing evidence for testosterone treatment for age-related hypogonadism led to the authoritative 2004 Institute of Medicine (IOM, now National Academy of Medicine) report (154) which concluded that the available efficacy evidence was not sufficient to justify public funding of a large-scale, randomized controlled clinical trial of testosterone in older men, comparable with the Women's Health Initiative for estrogen replacement in menopause (250). Instead, they recommended a series of well-controlled short-term efficacy studies. Accordingly, NIH funded a series of short-term placebo-controlled studies, the Testosterone Trials, to establish short-term (12 months) efficacy (251) which culminated in an efficiently designed series of seven interconnected,

overlapping studies (252, 253). Recruited from over 2 million mail-outs (Snyder, personal communication) resulting in over 50,000 telephone interviews, these studies recruited 790 men over 65 years of age, mostly obese, hypertensive ex-smokers, who had “LowT” (without pathological hypogonadism). The primary outcomes reported that daily treatment with testosterone or placebo gel for 12 months produced significant increases in sexual function, hemoglobin, and bone density but no improvements in physical or cognitive function or vitality (252). Secondary analyses have investigated the testosterone effects on hemoglobin (254), bone density (255), cognitive function (256) and mobility (257) and have been positively summarised by the investigators (258). The key endpoint of the T Trials was increased sexual function, in which the effect was modest in magnitude with about 1/3 increase over baseline, a smaller effect than that of PDE5 inhibitor treatment (259), and transient in duration with the benefits waning to non-significance by 12 months at the end of the trial (252). The small increases in hemoglobin and bone density are consistent with expected effects of testosterone treatment in anyone for any reason. A striking finding was a testosterone-induced increase in non-calcified coronary plaque, an unexpected and unprecedented adverse surrogate marker of coronary disease (260) although the study was too short to evaluate impact of testosterone on cardiovascular events or bone fractures. Further analyses of cardiovascular biomarkers has been reported (261, 262) and is inconclusive but warrants a larger, longer-term cardiovascular safety study. In summary, the accompanying editorial concluded that the improved sexual function did not warrant initiating testosterone treatment while the expected improvements in hemoglobin and bone density were useful side-effects but not sufficient to justify testosterone treatment (259). The consensus is that these short-term efficacy data do not warrant initiating testosterone treatment in older men without pathological hypogonadism (259, 263). Rather, they highlight the need for more definitive efficacy and safety studies of longer duration, larger sample size with greater power to determine substantial and safe patient benefit before such treatment can be recommended (264). Furthermore, they do not meet the mandate of the IOM report for sufficient short-term efficacy to warrant public funding for a large-scale clinical trial (154). Nevertheless, the FDA mandated a long-term cardiovascular safety study of testosterone treatment for age-related functional hypogonadism (TRAVERSE). This will investigate 6000 men from over 400 centres randomized to daily testosterone or placebo transdermal gel for up to 5 years and is scheduled for completion in 2022. Overall, age-related functional hypogonadism remains an invalid indication for testosterone prescription with the risk of adverse cardiovascular, prostate, and other effects including androgen dependence from unjustified testosterone treatment in men without reproductive pathology (74).

The prime motivation for this most frequent form of contemporary testosterone misuse, the impulse to prevent or reverse ageing deriving from the ancient rejuvenation mystique, represents a health hobby fetishizing testosterone as an elixir of youthful vigor to rekindle dwindling sexual function and vitality in ageing men and women. The medicalizing of ageing directs treatment at an ill-defined entity of "ageing" in contrast to authentic medical conditions, co-morbidities that accumulate during ageing. This reincarnation of hormonal rejuvenation fixated on testosterone has traditional analogies with other rejuvenation follies such as the Asian medicinal use of exotic animal body parts and the Western counterpart of overpriced placebos of the health food supplement industry. An interesting contrast is with another invented pseudo-medical entity, "adrenal fatigue", an imagined insufficiency of the adrenal glands to overcome stress, which has no genuine basis in medical science (265). Unlike "andropause", "adrenal fatigue" lacks the ingrained archetypal appeal of testosterone as the modern face of the rejuvenation mystique to the public (including doctors), as a generic tonic for ageing and sexual dysfunction. In more orthodox medical science, shorn of the rejuvenation mystique, a close analogy with 'andropause" is the sick euthyroid or non-thyroidal illness syndrome (NTIS) in which intercurrent illness leads to a reduction in circulating triiodothyronine (T3) that correlates with the severity of illness and prognosis (266). It remains controversial whether this syndrome represents an adaptive response to systemic illness not requiring any replacement therapy (267) or represents a form of central hypothyroidism warranting T3 replacement therapy (268). While each polar position has been referred to as "dangerous dogma" (267, 269), the present consensus is that thyroid replacement therapy for NTIS is not justified or practiced (266). Thus, in an analogous fashion, age-related functional hypogonadism may be better described as sick eugonadal syndrome or non-gonadal illness syndrome.

4.5 Public health and policy

The public health consequences of the present epidemic of unjustified off-label testosterone prescribing includes harm from such treatment, notably possible increases in the incidence of cardiovascular and prostate diseases as well as iatrogenic androgen dependence (74, 270, 271). Surveillance of event and death rates over the next decades will evaluate the impact of this large scale uncontrolled social experiment arising from prominent increases in testosterone usage by middle-aged and older men on these common, androgen-sensitive disorders of men's health.

Adverse effects of testosterone use in older men without pathological hypogonadism were highlighted by the premature termination of a clinical trial of testosterone in frail, elderly men (272).

Nevertheless, previous longer and higher dose studies produced no similar excess cardiovascular harms (248) although reporting bias in industry-sponsored studies reporting cardiovascular harm may under-estimate risk (273). Multiple meta-analyses aggregating the same limited set of short-term clinical trial data produce conflicting interpretations although with odds ratios for harm are mostly greater than unity, consistent with a small increased risk of cardiovascular events (273-277) within a set of still under-powered studies (278). Some of these differences may be due to the impact of short-term adverse effects (279-281) that may be partly nullified when averaged as if there was only uniform time-based risk over longer-term observations. As age-specific cardiovascular mortality is declining in many countries from its peak in the 1970's (282-286), investigating the potential testosterone-induced cardiovascular harm from the recent epidemic of testosterone prescribing requires surveillance of population cardiovascular morbidity and mortality rates. Ultimately resolving the cardiovascular harm from testosterone treatment of men who do not have pathologic hypogonadism requires well-designed, adequately powered, placebo-controlled randomized clinical trials of sufficient duration to evaluate testosterone-induced cardiovascular events. In that context, the FDA's mandated TRAVERSE safety study represents an important start.
Another public health concern is whether increased testosterone prescribing will increase benign or malignant prostate disease. Sustained post-pubertal exposure to adult male circulating testosterone concentration is required for full prostate development which in turn is necessary for the evolution of late-life prostate diseases. Nevertheless, beyond the requirement of testosterone exposure for prostate development, meta-analyses of observational studies suggest minimal risk that either endogenous or exogenous testosterone exposure predicts subsequent prostate cancer (287, 288). Similarly, pooling available randomized, placebo-controlled clinical trials of exogenous testosterone also showed no measurable risk of subsequent prostate cancer; however, exposure was only for up to 3 years, far shorter than the decades-long latency of prostate diseases (289). Consequently, further population surveillance of prostate diseases is warranted to detect any impact of the recent epidemic of testosterone prescribing. For prostate cancer, this require making the distinction between screened-detected, organ-confined and life-threatening advanced or metastatic cancers. Long-term interventional cardiovascular studies may provide information on prostate disease risk, but the even longer latency of life-threatening late-life prostate diseases creates some inherent limitations.

A third public health concern is the creation of iatrogenic androgen dependence when testosterone treatment is administered to men without reproductive pathology (74). In men with pathological hypogonadism, the irreversible underlying disorders require life-long testosterone replacement. In contrast, administration of testosterone to men with normal reproductive system suppresses

endogenous testosterone production due to androgenic negative feedback (Figure 3). When testosterone administration ceases this leads to withdrawal symptoms from transient androgen deficiency until the hypothalamo-pituitary unit axis recovers, which may take weeks to months, depending on the duration and dose of exogenous androgen used (71, 76, 290). Such withdrawal symptoms can lead to resuming testosterone administration to alleviate iatrogenic androgen deficiency creating a vicious circle of androgen dependence. Even after the man wishes to stop testosterone treatment, this cycle of dependence encourages continued testosterone administration and thereby perpetuates the underlying suppression of endogenous testosterone delaying ultimate recovery.

In the interim, testosterone prescribing for men without pathological hypogonadism should be confined to adequately powered, well-designed and placebo-controlled clinical trials geared to determining the efficacy and safety of testosterone prescribing for functional states, such as age-related hypogonadism defined solely by low serum testosterone levels with or without non-specific symptoms and mindful of the potential short and long-term adverse effects of testosterone treatment.

4.6 Avoiding Androgen (Testosterone) Misuse

Avoiding testosterone misuse is not easy for doctors in the present times (see Box for points to consider). It requires a sound understanding of testosterone physiology and familiarity with the available evidence on off-label testosterone treatment for the wide variety of applications advocated by enthusiasts. But in addition, uniquely in medicine, it also requires clear cognizance of the profound intuitive magnetism of the rejuvenation mystique to the public (including doctors) (see Section 2). Ageing impacts on the effects of every hormone and a myopic, tunnel-visioned case could be constructed for replenishment of any or every one of them to combat ageing. Yet there is no counterpart to the historically strong and regularly resurgent popular desire for testosterone supplementation. This largely derives from widely held and firmly entrenched subliminal fantasies of testosterone as the hormone of youthful manly vigour and sexual potency. Historically, this is reflected in the resilience of the rejuvenation mystique with its resurgence whenever socio-economic affluence favours indulgence in health hobbies, notably wishful chimeras of life-extension.

For medical disciplines other than reproductive endocrinology, most people accept their unfamiliarity with the complex technicalities of modern specialist practice and usually accept expert

advice. By contrast, virtually every person's individual experience of sex and reproduction often leads them to unrealistic confidence in folkloric beliefs assuming to understand testosterone's biological and clinical effects. Rather than representing contagious expertise, such ingrained misunderstandings may render them vulnerable to baseless beliefs promulgated through the vast echo chamber of the Internet and the scholarly slum of social media. Exaggerated, misplaced belief in the biological and clinical significance of testosterone, notably as an anti-ageing and sexual tonic, is a common and prominent misdirection not excluding medical professionals.

The best remedy is to reinforce confidence in sound clinical management and not to be beguiled by misplaced concrete thinking that substitutes reliance on simple formulae displacing clinical experience and evidence-based expertise. Excessive testing for circulating testosterone without proper indications or the right clinical setting leads to overdiagnosis and overtreatment. Unjustified testing creates needless dilemmas about whether testosterone treatment is justified when lowered serum testosterone concentrations are observed. This phony dilemma is worst when viewed in artificial isolation from full history and physical examination and additional reproductive hormone testing including gonadotropins and SHBG on multiple occasions. Critical awareness of the available evidence, crucially distinguishing pathologic from functional hypogonadism (and its various neologistic synonyms), is an important pillar of sound clinical practice. A common motive to prescribe off-label testosterone is the belief that other doctors would do so anyway fostering a vicious circle of mismanagement. This resembles one of the most frequent reasons for doping in elite sports, the usually baseless belief by athletes and trainers that their competitors are already drug cheats. Furthermore, reliance on inaccurate testosterone immunoassays, which feature method-specific bias and lack of specificity at low levels, should be replaced by the reference liquid chromatography-mass spectrometry methods that are increasingly widely available as the steroid immunoassay era of the 20th century closes.

5. Androgen Abuse

5.1. Introduction

Androgen abuse is the illicit use of androgens without prescription for non-medical purposes, typically increased muscular size and strength in the short-term, with the goal of either superior sports performance or bodybuilding to sculpt a hyper-masculine physique and image. Systematic androgen abuse first appeared as a Cold War epiphenomenon (Figure 1), an epidemic centred on Eastern European elite athletes in the mid-1950's confined to drug cheating ("doping") in elite power sports (291). Subsequently, in the 1980s androgen abuse crossed over into sufficiently affluent

communities as an endemic drug subculture for image-oriented, cosmetic or occupational purposes, mainly body-building to promote a fearsome muscular image and aggression rather than enhancing sports performance (234, 292).

The coincidence of the Cold War with the Golden Age of Steroid Pharmacology provided a fortuitous intersection of industrial means, unscrupulous operators, and ruthless political goals. This shaped the emergence of androgen abuse as a convenient tool by which socio-politically dysfunctional Eastern bloc countries could gain short-cut ascendancy through symbolic victories over Western political rivals on the sporting field as a surrogate for armed conflict. This challenge was quickly reciprocated by athletes and trainers from the advanced non-communist countries on an individual rather than national program basis. This bidding war escalated into a national sports doping programs operated covertly by Eastern European communist governments. These organized programs of flagrant cheating mixed competitive fraudulence with callous ruination of athlete's health and welfare sacrificed for national political goals. Till recently only the East German program, with its dire consequences for athlete's health, has so far been fully disclosed following the fall of the Berlin Wall (293) while other Eastern European programs have not yet been disclosed. This swindle was only matched and exceeded by the 2016 revelation of a Russian national doping programs that plumbed new depths of cynical and unscrupulous organized cheating (294-296).

5.2. Epidemiology

Accurate estimates of the natural history, prevalence and determinants of androgen abuse are difficult to acquire due to the unavoidable reliance on uncorroborated self-report of illicit activities. The best available epidemiological study of androgen abuse is a monumental meta-analysis of 271 studies involving 2.8 million participants. This reported that men were the predominant users (6.4% vs 1.6% in females) with the prevalence of androgen abuse highest among non-elite sports (18.4%), well ahead of athletes (13.4%), prisoners (12.4%), drug users (8.0%), high school students (2.3%) compared with the general non-athlete community (1.0%) (75). Aiming to compile the available literature on the prevalence of androgen abuse, this meta-analysis included diverse component studies including those with a population base as well as more selective studies with enriched niche populations of abusers. Consequently, while the prevalence estimates of this meta-analysis are credible, those estimates are subject to balance of component studies and thereby not necessarily universally extrapolatable. Given the higher incidence of violence (51, 297, 298), criminality (51, 299-301) and psychiatric disorders (302-304) as well as a wide variety of medical problems (305) including habituation or dependence (302), excess cardiovascular risk and premature death (306-

309), mood, behavioural and cognitive disorders including aggressive, irresponsible or violent behaviour possibly related to neurotoxicity (310) associated with androgen abuse, the growing prevalence of androgen abuse mainly among young men is a significant but underestimated public health concern (270). The potential confounding effects from using other illicit substances as well as prior mental disorders on adverse mental effects associated with androgen abuse need to be considered. Androgen abuse is a well-known habit among men in security related occupations (military, police, security, club doormen) where sculpting a fearsome, hyper-masculine body image is a prevailing aesthetic, a professional advantage, and an occupational hazard.

An important source of evidence on the prevalence of androgen abuse is from the captive, sentinel population of high school students. The best available long-term trend data among students is the Monitoring the Future (MTF) survey that has tracked annually since 1989 the self-reported prevalence of androgen ("steroid") abuse among a nationally representative sampling of 8^{th}, 10^{th} and 12^{th} year students (42,500 students in 396 US schools) (311). The MTF study reports the prevalence of lifetime (ever) androgen abuse varied between 1.3 and 3.3% peaking in 2001-2 with a progressive decline over the next decade to a lower plateau of 1.5% over the second decade of this century (Figure 6). Nevertheless, in US high schools androgen abuse is relatively uncommon compared with other drugs such as alcohol (59%), marijuana (44%), tobacco (22%), amphetamines (including cocaine) (12%), hallucinogens (7%), opiates (6%), tranquilizers (6%) (311). Among Australian male secondary students the prevalence has remained stable over the last two decades at 4-5% for lifetime (ever) or 2-3% for recent (last year) use (312, 313). As the median age at first use of androgens is 23 years of age (314), usage among high schoolers underestimates overall community prevalence (315). For community estimates, among Americans under the age of 50 years, the lifetime prevalence is estimated at 2.7-3.7% with recent use (within last year) about 60% of ever use (316). There is limited evidence available for criminal activity regarding illicit androgen marketing but the Australian Crime Commission reports a 10-fold increase over the last decade in customs seizures and arrests for illicit androgen importation, both growing at a faster rate than the data for opiates or amphetamines (317).

Androgen abuse is consistently higher among boys (316, 318), among American compared with non-American studies and subject to marked regional variability (75). An important caveat on epidemiological prevalence surveys is the limitation that they typically only record ever or recent

(last year) use and neither dose nor duration of use. Furthermore, the ambiguous term “steroids” may be confused with use of glucocorticoids for asthma or other valid medical indications leading to inflated prevalence estimates especially among females (319). Other reported risk factors for androgen abuse include minority ethnicity, sports participation, truancy and unsupervised recreation, unfulfilled desire to be "big" (“body or muscle dysmorphia”), steroid-using acquaintances, prior use of image or performance enhancing or other drugs (313).

5.3. Motivation and Patterns of Use

Among elite athletes the motivation for androgen doping is illicit performance enhancement with the goal of gaining ergogenic advantage to achieve fame and fortune arising from competitive success in elite sports (320, 321). Experimental evidence in mice indicates that androgen effects on muscle involves an irreversible increase in numbers of myonuclei (322-324) as well as effects mediated via neural pathways (325, 326). The excess myonuclei not only enhance muscular energetic function but also prime the muscles for future load or androgen exposure even after the initial exposure has ceased (327). This finding, yet to be confirmed in humans, raises the spectre that even a single episode of androgen doping may create irreversible advantages in androgen-dependent muscular performance and might warrant a lifetime ban from elite sports.

The World Antidoping Agency (WADA) undertakes surveillance and policing of the WADA Code to detect, deter and punish doping in elite sports (321). WADA’s banning of androgen abuse (doping) in elite sports is implemented by highly sensitive gas chromatography-mass spectrometry urine detection tests whereby positive anti-doping tests lead to banning rule-breakers from further competitions, a denial of access to their profession for elite athletes. Elite athletes agree in advance to the WADA Code with its strict liability provision so that a positive anti-doping test (including refusal or avoidance of testing or possession, attempts, trading and tampering with banned drugs) constitutes an anti-doping rule violation regardless of intent or negligence (321). The high numbers of androgen doping detections (293, 328) indicate the highly effective (albeit imperfect) deterrent is detailed elsewhere (321). The impact on sub-elite sports is less clear but the deterrence may be attenuated by the less frequent (if any) anti-doping testing coupled with youthful perceptions of invulnerability. In general, after many years of successful anti-doping detection of cocktails of synthetic androgens, contemporary androgen doping usually involves the surreptitious use of only a single androgen, including novel designer and nutraceutical androgens (291, 329-332), aiming for ergogenic advantage but within regimens largely oriented to evade detection. For example, micro-dosing or irregular patterns of administration (e.g. at night). Similarly, androgen misuse also usually involves a

single androgen, testosterone, prescribed at replacement doses but for the wrong reasons. These patterns pattern differ from androgen abuse in which the unrestrained concurrent use usually involves multiple androgens in massive doses.

The motivation for image-oriented androgen abuse in the community is gaining self-valued physical and/or psychological benefits (314, 333) including boosting low self-esteem (334) and muscular size and strength (320, 335, 336). The drive is entrained by promotional information in non-medical sources, mostly abuser internet folklore reinforced by the overlapping categories of friends, gym buddies, drug dealers and other androgen abusers. The goals include gaining greater visible muscular size, strength, and endurance in a sculpted hypermasculine body physique and image, allowing for more intensive training with less fatigue, all geared towards boosting self-esteem. In some men, the drive towards a hypermasculine, fearsome physique, often to cartoonish lengths, reflects a distortion of body image ("bigorexia" "body or muscle dysmorphia") analogous to women with anorexia or athletic nervosa (337). In these men, the muscularity achieved is not only never enough but virtually delusional (338-342). In professional bodybuilders, such sustained androgen abuse may be considered an occupational requirement and hazard (340).

Characteristically, image-orientated androgen abuse typically involves massive doses, much higher (10-100 times) than would be contemplated for any androgen use in medicine. The copious androgen abuse folklore encourages "cycling" regimes comprising "stacking" of multiple androgens in pyramidal ("pyramiding", dose tapering onset and offset) escalating and then de-escalating doses over a 6-12 weeks periods or else "blast and cruise" comprising a high loading dose with lower maintenance dose. Other variations including "bulking" and "cutting" phases where the goals are maximal weight gain and reducing fat, respectively. These drug use periods may be separated by drug-free periods purportedly to minimize side-effects and/or to recover sensitivity believed to arise from desensitization following sustained, massive supraphysiologic androgen exposure. Although there is no scientific evidence for these beliefs which arise from individual trial-and-error transmitted as subjective anecdotes. It remains wise to recall that, historically, androgen abusers through similar subjective trial-and-error had led them to disbelieve the conventional medical view held up to the 1990s, that high doses of androgens had no beneficial effects on muscle in eugonadal men (343), a belief comprehensively refuted in 1996 (335). Nevertheless, ritualistic quasi-scientific regimens are recorded in underground bodybuilding folklore described in publications (e.g. *Underground Steroid Handbook* & later replicas) and in unrestrained flamboyance on the internet whereby self-serving suppliers promote mislabelled illicit products (344), in an environment comparable with the 19th century selling of patent (proprietary) medicines in covered wagon medicine shows (345).

In evaluating such androgen abuse regimens, the specific androgen(s) administered, the doses and regimens used may not be reliably ascertained by an uncorroborated medical history; fortunately, such cataloguing of massive dosing does not matter other than whether androgens are the hepatotoxic oral 17α-alkylated variety or non-alkylated injectable or other products. The principal determinant of recovery from androgen abuse appears to be the time since cessation of androgen intake rather than duration or abuse or dose or regimen used (71, 76, 290).

Androgen polypharmacy is also linked to abuse of other drugs (346) as well as to other risk and criminal behaviours (51, 300, 301). Androgen abusers often self-administer a wide variety of non-prescription nutritional supplements (creatine, amphetamine stimulants) as well as prescription drugs (growth hormone, insulin, thyroxine, diuretics, phosphodiesterase type 5 inhibitors) illicitly sourced without prescription through the internet, gyms, and drug dealers (71, 76). Over a lifetime, androgen abusers have a higher rates of using other illicit substances and misuse of prescription drugs as well as being characteristically more involved in physical training but with lower educational attainment (347, 348).

Professional bodybuilders may use continuous high dose androgens for prolonged periods without drug-free intervals. Another variant is seasonal androgen abuse associated with a “body-beautiful” subculture where timing of cycles is timed to coincide with public display (eg summer, Mardi Gras). There is also a high prevalence of various “post-cycle treatment” which employs ad hoc treatment with human chorionic gonadotropin and/or anti-estrogens aiming to “restart” endogenous testosterone production suppressed by negative feedback from exogenous androgen exposure. Post-cycle therapies, typically given erratically and for short duration, lack any convincing evidence for their efficacy. The safety of anti-estrogens in this setting is particularly doubtful as androgen action in bone and the brain depend on aromatization of testosterone to estradiol to act upon estrogen receptors. While adverse effects on bone effects are relatively long-term, anti-estrogen effects may have more immediate adverse effects on male sexual function (336, 349).

The androgen regimens typically combine multiple androgens, extending beyond marketed synthetic androgens increasingly to never-marketed, designer, nutraceutical or non-steroidal (“SARM”) synthetic androgens. These are found in unregulated, over the counter and internet marketed food supplements often not identifying steroids on the label either due to deceit and/or cross-contamination during unaccredited drug manufacturing but promoted as purportedly legal and safe body-building “alternatives” to androgens (331, 350). Androgens are also manufactured illegally as unregistered, counterfeit, or inert products (351-353). Supplies are obtained mainly from illicit sources through leakage from the legitimate market (diversion, theft) via manufacturers, wholesalers, or

retailers or from local supply of smuggled imports sold by illicit drug dealers often linked to criminal gangs. Most supply is through underground networks including dealers linked to gyms. Only minimal supply of androgens for abuse arises from valid medical prescriptions, from well-meaning doctors who succumb to manipulation for prescribing on demand and/or the occasional androgen-abusing doctor.

These abuse patterns with alternating supra-physiological doses and androgen deficiency states during periods of active abuse and non-use, respectively, lead to fluctuating sexual dysfunction (reduced libido and sexual activity, erectile dysfunction) and poor general well-being (lethargy, reduced muscular power, depressed mood, emotional lability). This creates a cycle of dependency that reinforces continuing androgen abuse, a habituation (302) that results in longer and deeper, prolonged suppression of endogenous testicular function further delaying ultimate recovery. There is some early evidence from serial high school surveying (figure 6) that epidemic androgen abuse in the USA may have peaked (354) although it continues at lower levels.

5.4. Natural History of Androgen Abuse

As a relatively recent form of illicit drug taking, the natural history of image-oriented androgen abuse in the community is not well understood and sound data is lacking but badly needed. Reliable knowledge based on controlled studies is difficult to acquire when it depends on uncorroborated self-report of an illicit activity by individuals with limited accurate technical knowledge of the nature and dosage of the drugs they use. For example, abusers often simply sum the milligrams of all androgens used per week ignoring difference in potency of different androgens. Similarly, doses are often referred to in volume (ml) of injectable, without reference to the androgen, its potency or concentration. Among prospective controlled studies, well-designed randomized controlled studies of androgen abuse regimens are unlikely to be feasible, ethically, or legally. Although prospective observational cohort studies are theoretically feasible (318), they are subject to participation bias relying on self-selected volunteers who may not be representative of the general androgen abuser population. Retrospective case-control studies are the most feasible controlled study design available (71, 76) although they are subject to participation and recall bias, the latter clouding the drug history based on flawed and inaccurate recollections of current and past drug usage. A systematic review aggregating 33 studies reported the impact of mostly single androgens on sperm output and reproductive hormones (290); however, few studies in that meta-analysis investigated systematic androgen abuse.

One case-control study of 41 current and 31 past androgen abusers who had used various androgens for over 2 years compared with 21 non-user controls reported mostly reversible reproductive effects with recovery over 6 to 18 months (71). Current abusers had lower testis volume, sperm output, serum LH, FSH, SHBG. AMH, inhibin B, total inhibin whereas other serum steroids (serum testosterone, DHT, estradiol, estrone and 3α and 3β androstanediols) were elevated due to the testosterone-containing drugs administered. For suppressed variables, past users after an average of nearly one year since cessation of last androgen intake were no different from non-user controls although recovery of testis volume and serum SHBG was incomplete. The average time to recovery was shorter for reproductive hormones (7.3 months serum AMH, 10.7 months serum LH) than for spermatogenesis (14.1 months sperm output). Time since cessation of androgen abuse was more influential for rate and extent of recovery than duration of abuse (71). Age, anthropometric variables (height, weight, BSA, BMI), patterns (androgen abuse regimens including "post-cycle therapy") were unrelated rate or extent of recovery for reproductive functions.

Another case-control study of 37 current and 33 past androgen abusers with 30 non-user healthy controls, reported persistent reduction in testicular size and serum testosterone among past users compared with non-user controls (76). Past users displayed complete recovery of serum LH, FSH, inhibin B, AMH, androstenedione, SHBG, 17 hydroxyprogesterone to match non-user controls. The duration of androgen abuse correlated with residual reduction in testis size, serum inhibin B and AMH but not with serum testosterone. Although some past abusers reported non-specific symptoms resembling androgen deficiency, the mildly reduced serum testosterone (but in the upper range of non-user controls) with concomitant reduced serum SHBG but normal serum LH and FSH, indicated there was no relationship between those symptoms and serum testosterone concentrations (355).

These case-control findings are consistent with other studies showing recovery of circulating reproductive hormones (serum LH, FSH) in 19 past androgen abusers with a mean 6.9 years of active use and a median of ~18 months since cessation of androgen abuse compared with 36 non-users but with a modest degree of persistent reduction in testis volume (~10%) and serum testosterone (~30%) (356). Similarly, serum LH, FSH and SHBG as well as most lipids and liver function tests were restored to normal in 14 ex-abusers (median 2 years cessation) compared with 17 current abusers with both groups having abused androgens for over 8 years been bodybuilding for over 12 years (357). The impact of androgen abuse on sperm output is consistent with two previous reports that sperm output was reduced in 41 androgen abusers compared with 41 age-matched healthy controls (358) and in 30 bodybuilders of whom 15 admitted androgen abuse and were compared with 15

who denied use (359). Sperm output improved after cessation of androgen intake in one study (358) but neither studied recovery in past users.

Overall, these studies of androgen abuse report mostly reversible effects on the major male reproductive hormones (serum testosterone, LH, FSH, AMH, inhibin B) but taking from 6 to 18 months after cessation of androgen abuse. Persistent mild reduction in serum testosterone proportionate to reduced serum SHBG should not be confused with persistent androgen deficiency (355). By contrast, impaired spermatogenesis recovers more slowly and less completely after cessation of androgen abuse with a possible cumulative effect of past and/or prolonged androgen abuse on recovery of fertility. An important practical clinical issue is whether delayed recovery of reproductive function in individual men is due to undiagnosed prior reproductive disorders, ongoing but undisclosed androgen intake to alleviate androgen deficiency withdrawal symptoms or irreversible damage to testicular function by prolonged and/or high dose androgen abuse. Clarification of these important issues requires prospective studies that would characterize reproductive function prior to onset of androgen abuse while also screening for ongoing androgen abuse during the recovery period.

5.5. Medical management

5.5.1. Clinical Identification and Management

Androgen abusers are typically males from mid teenage to 50 years of age with the prevalence among females at 1-2% of that among males (316, 318, 360). The median age of onset is 23 years of age (314) and, as few are over 50 years of age, most androgen abusers eventually discontinue intake usually within a few years although the motivations to discontinue remain to be explored. Characteristically, they undertake bodybuilding through weightlifting in gyms and/or combat sports. Despite drug-free policy of some “clean” competitive bodybuilding organisations, membership is based on self-assessment and not verified by drug testing so many participants still use androgens and other drugs without disclosure.

The possibility of androgen abuse, whether acknowledged or not, should be considered when seeing an otherwise healthy young man with prominent muscularity complaining of stereotypical androgen deficiency-like symptoms (loss of libido, sexual dysfunction, loss of energy etc) flavoured with distinctive internet jargon and requests for androgens or related drugs (hCG, anti-estrogens). Androgen abusers are usually aware of, but disregard, health risks and consider doctors as unsympathetic gatekeepers of prescriptions and health monitoring. A more empathetic attitude may

be exploited, with the hunter captured by the prey. As a result, medical history taking may be incomplete, deceptive, or manipulative with the objective of acquiring prescriptions and/or monitoring. Characteristically, while presenting with infertility, sexual dysfunction, or androgen deficiency symptoms and, despite unusual muscularity, they may display body image dissonance, be preoccupied with exercising, and exhibit tell-tale stigmata such as adult-onset truncal acne and/or gynecomastia. The history should focus on the frequency and intensity of gym, body-building or athletic training sessions, the goals of such training (eg competing in elite sports or bodybuilding), their perceptions of their body image, and if they have been offered or used “steroids” and whether they desire to stop.

The physical examination may identify the degree of muscularity, truncal striae consistent with prior cycles of rapid body weight gain and loss, gynecomastia or peri-areolar plastic surgery scars and adult-onset truncal acne (and/or a history of anti-acne retinoid prescription), the latter virtually pathognomonic of androgen abuse when it occurs after the age of 20 when adolescent acne, if any, has subsided. In contrast to predominantly facial adolescent acne spreading to the trunk when severe, adult-onset truncal acne due to androgen intake typically involves the upper back and midline chest but with much less facial involvement. Similar findings have been noted in androgen abusers (361, 362)as well as in female-to-male transgenders (363).

Measurement of circulating reproductive hormones can be very informative. Suppression of serum LH and FSH to undetectable or very low levels with low serum SHBG levels in men with otherwise normal prior reproductive function (completed puberty, established paternity, normal sexual function) and without overt hypothalamic-pituitary disorders, is virtually diagnostic of androgen abuse. Screening using serum LH, FSH and haematocrit has a high (>91%) reliability in distinguishing current from past or non-users. Adding serum AMH and inhibin, if available, increases the discrimination of the screening profile to 96% (71). Exceptionally, a similar hormonal pattern of high serum testosterone with suppressed serum LH and FSH has been reported in a man credibly denying exogenous androgen use but having a very small steroid-producing testicular tumour, only diagnosed after selective venous sampling for diagnosis based on steroid concentration gradients when imaging was not informative (364). With use of synthetic androgens (i.e. excluding testosterone), serum testosterone will also be fully suppressed; however, if exogenous testosterone is included in the regimen, serum testosterone may also be non-suppressed or elevated. Detection of specific synthetic androgens in urine by mass spectrometry is useful if available. However, these tests are not usually available outside accredited sports antidoping programs, which are contractually obliged to not offer such testing outside commissioned antidoping testing to avoid

gaming by athletes intent on gaming the windows of detection for doping substances (365, 366). Fortunately the use of convenient and readily available serum gonadotropin assays provides a generic test for exogenous androgen exposure.

5.5.2. Harm from Androgen Abuse

Testosterone is unique among the major human hormones in having no naturally occurring pathology due to excessive secretion in men. Unlike some other drugs of addiction, androgen abuse does not produce deaths directly from overdose. Nevertheless, androgen abuse, typically using massive doses, can cause harm to the user as well as to those around them, the latter through prominent adverse psychological effects leading to violence, criminality, assaults, and deaths. Major adverse effects of androgen abuse include universal suppression of reproductive function as well as harmful effects on numerous other non-reproductive organs and tissues, effects well reviewed elsewhere (305, 367). Prominent non-reproductive adverse effects include mental effects such as habituation and dependence (214), neuropsychiatric and psychological (303), cardiovascular (368), hepatic (369-371), and various musculoskeletal, connective tissue and metabolic disorders as well as deaths (308, 372).

Hepatotoxicity is among the most serious adverse medical effects of androgen abuse. Other than androgen type, its prevalence, mechanisms, and risk factors remain poorly understood (373). Hepatotoxicity is a risk from any 17α-alkylated androgens (369-371), the main class of orally active synthetic androgens, as well as from SARM's (374), a novel class of non-steroidal androgens structurally derived from anti-androgens (375). By contrast, other natural androgens (unmodified or esterified testosterone, nandrolone) or other synthetic androgen classes (1-methyl androgens) do not exhibit hepatoxicity other than coincidental (376-379). The 17α-alkyl substitution creates oral bioavailability but causes class-specific hepatotoxicity including hepatic tumors (adenoma, carcinoma, cholangiosarcoma, angiosarcoma), peliosis hepatis and drug hepatotoxicity (usually cholestasis) (369, 370, 372, 380-382). Biochemical hepatotoxicity after short-term usage may be reversible (383). Most hepatic tumors are benign, slowly progressive, and reversible with cessation of androgen ingestion, but fatal cancers are reported. Peliosis hepatis, a benign pattern of focal hepatic necrosis causing vascular cysts, causes hepatic and/or splenic enlargement and serious, even fatal, bleeding either spontaneously or following liver biopsy (384, 385). Post-mortem studies show that hepatic tumors and peliosis are frequently undetected clinically during long-term therapy with oral 17α-alkylated androgens. This class of synthetic androgen, marketed prior to the 1970's, would not be considered safe for modern drug registration and is progressively disappearing from clinical usage.

Reproductive effects of exogenous androgens in men involve profound, although usually reversible, hypothalamic suppression of pituitary-testicular function manifest as impaired spermatogenesis, infertility, sexual dysfunction and androgen deficiency (367). The hypothalamic suppression is initially reversible although the transient androgen deficiency withdrawal symptoms after cessation of androgen abuse recover slowly, lasting for prolonged periods of 6-18 months (71). Some studies report persistent mild reduction in serum testosterone over longer periods (76, 356); however, this may due to persistent adverse effects of androgen abuse on hepatic SHBG secretion leading to low serum SHBG with proportionate reductions in serum testosterone without necessarily signifying testosterone deficiency (355). However, neither undisclosed androgen intake to alleviate androgen deficiency withdrawal symptoms or permanent testicular damage due to prolonged, high dose androgen abuse remain difficult to exclude and further studies are required.

In women, androgen abuse causes acne, breast atrophy, menstrual disturbances and infertility which are usually reversible but virilisation (hirsutism, voice change, male-pattern balding, clitoral enlargement) may be irreversible depending on the dose and duration of androgen exposure. Irreversible voice change may be very disturbing to women who use their voice professionally or value highly their phone contact with family and friends. Biochemical effects such as suppression of SHBG, lipid changes and hepatotoxicity are equally prevalent in female androgen abusers.

Acne and gynaecomastia are frequent side-effects of androgen abuse. Male-pattern baldness may be precipitated in susceptible men and women. Androgen-induced acne in adults is typically truncal but rarely facial, the reverse of adolescent acne. Hence adult-onset truncal acne is almost pathognomonic for androgen abuse. Gynecomastia may become evident during or even soon after stopping androgen abuse but usually regresses spontaneously as testicular function recovers. Abusers with gynecomastia, rather than stop androgens, often seek to continue usage by adding treatment with anti-estrogens or non-aromatizable androgens but ultimately cosmetic surgery is often taken up for persistent symptomatic gynecomastia especially among those who do not stop androgen abuse.

Mental disturbances are a major adverse effect of androgen abuse. They correspond to the severity of the abuse (386) but are complex to interpret as to causality and mechanisms (52). Florid mood and/or behaviour disturbances including hypomania, aggression, depression and sleep disturbance are reported among androgen abusers (303). These may be aggravated features of pre-existing psychopathology and/or confounding effects of intensive weight training that predispose to, or are precipitated by, androgen abuse rather than, or in addition to, authentic drug effects. Prospective, placebo-controlled studies of testosterone at replacement doses in healthy young men show minimal or no changes in mood or behaviour (387) whereas supraphysiological doses of androgens produce

hypomania in a minority (~5%) of individuals (50). These disparities suggest behavioural disturbances of androgen abusers (“roid rage”) involves either an idiosyncratic reaction in an unusually susceptible minority and/or individuals whose recollections are coloured with exculpatory motivation ("drug excuse", "dumb-bell defense"). Androgen abuse often represents an obsessive behavioural pattern analogous to eating disorders and fanatical exercising where distorted self-perception and dissonance between body image and reality drives an insatiable desire for, or addiction to, continuous body shaping towards an idealised goal never achieved. The withdrawal effects after cessation of androgen abuse, arising from transient androgen deficiency symptoms while the endogenous system recovers, often including lethargy, loss of vitality, easy fatigue, and sexual dysfunction. These androgen deficiency withdrawal symptoms together with the loss of acquired muscle mass and strength, usually the objective of the androgen abuse, lead to a cycle of habituation and dependence which discourage cessation (302) and, by perpetuating the androgen abuse, delay ultimate recovery.

The cardiovascular consequences of androgen abuse are classified into four potential mechanisms (accelerated atherogenesis, thrombosis, vasospasm, direct cardiotoxicity) but most evidence remains based on anecdotal case reports (388). Adverse cardiovascular outcomes associated with androgen abuse include cardiomyopathy, premature atherosclerosis, myocardial infarction, cardiac tamponade, cardiac failure, sudden death, thrombotic and hemorrhagic stroke, subdural hematoma, peripheral artery or venous thrombosis and pulmonary embolism. Procoagulant effects of androgen abuse may contribute to these adverse cardiovascular effect (389). Case-control studies have shown fully (71) or incompletely (390-392) reversible cardiac effects but, like the reproductive effects, lingering adverse functional effects many years after apparent cessation of androgen abuse may reflect either surreptitious or undeclared ongoing use of androgens or irreversible adverse cardiac effects. With cardiac disorders presenting at an early age, incidental genetic (393, 394) or acquired (e.g. viral) heart disease need to be distinguished. In the absence of population-based studies and adequate estimates of usage, it is unclear if atherogenic cardiovascular effects of androgen abuse exceed expectations for the general population (395).

Adverse effects of androgen abuse on the prostate have been little studied apart from anecdotal case reports and a single controlled study (396). One 30-year follow-up study of former androgen abusers reported a lower prevalence of prostate hypertrophy (397). Pooling prospective observational studies of circulating concentrations of testosterone or other androgens and pro-androgens show no consistent relationship with risk of subsequent prostate cancer (287, 288). Similarly, pooling available randomized, placebo-controlled clinical trials of exogenous testosterone also showed no measurable risk of subsequent prostate cancer although only for up to 3 years follow-up (398).

Further population surveillance of prostate diseases is warranted to detect any impact of the recent epidemic of testosterone prescribing. The apparent paucity of reported deaths from premature prostate cancer among former androgen abusers after an epidemic already lasting more than four decades, raises the possibility that no such excess will occur; however, quantitative epidemiological evidence of usage and outcomes is essential to draw reliable conclusions.

Infections associated with androgen abuse include local sepsis at injection sites and systemic viral infection (HIV, hepatitis) from needle sharing but more fulminant systemic infections (viral, fungal, endocarditis) and local abscess are uncommon. Musculoskeletal injuries arising from increased musculature may include tendon and ligament ruptures and rhabdomyolysis associated with over-training. Iliopsoas hypertrophy can present as an acute abdomen and nerve palsies can result from injection injury. In pre-pubertal adolescents, androgen abuse may prematurely foreclose the epiphyses and stunt final height.

Uncorroborated and/or idiosyncratic associations with androgen abuse include isolated case reports of colon, Wilms and renal cancer, bleeding esophageal varices, systemic lupus glomerulonephritis and transverse myelitis, psoriasis, and severe chickenpox. Without confirmation, these are best considered coincidental. Metabolic effects including changes in insulin sensitivity, lipid and other biochemical changes associated with androgen administration are reversible.

5.5.3. Rehabilitation and recovery

The management of rehabilitation from androgen abuse depends on its natural history which dictates the likely outcomes without treatment (399). While one case-control study reported that the reproductive and cardiac effects of androgen abuse may be slowly, but almost fully reversible (71), other case-control studies report persistent reproductive suppression (76, 356) and/or cardiac adverse effects (390-392) over longer period after apparent cessation of androgen exposure. Further studies are required to disentangle whether these discrepancies are due to undiagnosed pre-exposure pathology, surreptitious ongoing androgen intake to alleviate androgen deficiency withdrawal symptoms or irreversible effects of prolonged androgen abuse including on hepatic SHBG secretion.

While supportive counselling about the health effects of androgen abuse is warranted, prescribing testosterone or other androgens for abusers is not appropriate and such prescribing colludes with and perpetuates the androgen abuse. In some jurisdictions (e.g. Austria, France, Italy) such

prescribing is illegal and in many other jurisdictions it is considered professional misconduct. The 2020

Rodchenkov Anti-Doping Act gives US government extraterritorial power to prosecute individuals anywhere in the world for participating in doping schemes at international sports competitions involving American athletes, though not individual athletes. Rarely (e.g. in men with psychiatric disorders precipitated by androgen use or withdrawal), a tapering testosterone dose regimen may be justified. This should start with no more than a standard testosterone replacement dose which is then gradually reduced over weeks to months to zero (399). Higher doses or other drugs (hCG, anti-estrogens) are not justified in this safety salvage role.

Similarly, ongoing ad hoc health monitoring is often sought by androgen abusers seeking reassurance they remain healthy while continuing to abuse androgens and other drugs; however, such monitoring lacks rational basis and may be counterproductive. The classic Wilson-Jungner criteria for health screening (400) require that prospective health monitoring uses cost-effective test(s) for which signals of adverse effect(s) will effectively alter health behaviour. Yet, some major dangers from androgen abuse (e.g. mental changes) are not susceptible to biochemical screening whereas the universal reproductive effects are disregarded by users and neither biochemical tests (401) nor imaging (402) are reliable to screen for liver damage. Moreover, androgen abusers are likely to misinterpret negative tests as a positive endorsement of health and safety while continuing abuse of androgens and other drugs. If they decline to stop the drug intake based on medical advice alone, it is doubtful they would do so for an adverse biochemical test. Rather than encouraging cessation of androgen abuse, ad hoc screening serves to collude with and perpetuate androgen abuse thereby delaying ultimate recovery. Health screening at the start of a program of supporting an abuser who has stopped drug intake and intends to remain abstinent may be justified.

Effective rehabilitation of androgen abusers is challenging. It requires knowledge of the likely time-course of recovery from suppressed hypothalamic-pituitary testicular function after cessation of androgen intake which, however, remains uncertain. Near complete recovery over 6-18 months has been reported (71) but other studies report prolonged incomplete recovery especially for spermatogenesis (76, 356). When recovery is very delayed, interpretation of outcome may be misinterpreted as persisting androgen deficiency if serum testosterone measurement is considered alone without considering long-term hepatic effects of androgen abuse in lowering hepatic SHBG secretion and serum SHBG as well as other issues like ongoing; however, undisclosed androgen intake or irreversible long-term adverse effects on the reproductive system also need consideration.

Managing rehabilitation of ex-androgen abusers requires understanding the cycle of dependency that androgen abuse creates, and that androgen abuse is an addictive state. The androgen dependency arises from withdrawal (androgen deficiency) symptoms which the ex-abuser may alleviate by resuming androgen intake creating an abuse cycle which, in turn, perpetuates the hypothalamic suppression and further delays ultimate recovery. Such androgen dependence may explain the persistence of testosterone prescribing for unjustified reasons even after insurance subsidy is withdrawn (74). The potent dose-dependent psychoactive effect of androgens on mood include inducing hypomania in healthy individuals (50) and heightened impulsivity, aggression and violence, dysphoria (depression, anergy) and precipitating psychosis (52). Addictive-type behaviors in androgen abusers (53) include reinforcement, tolerance, withdrawal and craving-driven drug-seeking and loss of control regardless of consequences (52). Transient withdrawal (androgen deficiency) symptoms during recovery are a crucial reinforcing feature (64). The non-fatal withdrawal symptoms are comparable with caffeine, nicotine and benzodiazepine dependency but less intense than for cocaine, amphetamines or opiates (60, 403), congruent with less intense androgen effects *vs.* the "high" of acute intoxication of amphetamines or opiates. These features make experienced psychological support an essential component of managing both the underlying psychological drivers to androgen abuse as well as support during the transient withdrawal symptoms during recovery and perceptions of losing the excess muscularity induced by androgen abuse (404). Effective rehabilitation must overcome the ingrained abuser folklore, quasi-scientific but usually baseless advice circulating on the internet and relayed through "bro-science" buddy networks. Fortunately, the natural history suggests that most androgen abusers eventually grow out of the habit and discontinue. The majority of androgen abusers commence androgen intatke during adolescence or early 20's and few remain active androgen abusers in their 50s (71, 75, 76, 290). At present, management of rehabilitation from androgen abuse is supportive care analogous to other forms of drug abuse without prescribing testosterone or providing pointless health monitoring. In the future improved rehabilitation requires more in-depth knowledge of motivation and effective supportive care of recovery androgen abusers (405).

Another issue in management of ex-androgen abusers is the use of "post-cycle therapy" which is propagated on the internet and advocated by illicit drug suppliers. In non-medical settings as advocated by internet blogs this treatment is often erratic and short-term. Requests from androgen abusers wishing to stop androgens may seek variations of "post-cycle therapy" to "re-start" the suppressed male reproductive axis. This involves the use of hCG and/or estrogen blockers which are believed to ameliorate the withdrawal symptoms at the end of cycles or in trying to recover reproductive function after ceasing androgen intake; however, there is no evidence that such

adjunctive treatment is effective with recommendations solely based on uncontrolled anecdotal studies.

The delayed recovery of testicular function interpreted loosely as a state of functional gonadotrophin deficiency has led to proposed treatments based on therapeutics of organic secondary hypogonadism (gonadotropin deficiency) due to hypothalamo-pituitary disorders (e.g. isolated hypogonadotropic hypogonadism, pituitary tumors and their treatment) using gonadotropin therapy (406) or estrogen blockade (407). Human chorionic gonadotropin (hCG) treatment usually in conjunction with FSH has well established efficacy for induction of spermatogenesis in men with genetic isolated hypogonadotropic hypogonadism (406, 408, 409). In a minority with lesser gonadotropin deficiency manifest by larger pre-treatment testis volume (>4 ml) or after a prior successful cycle of gonadotropin-induced spermatogenesis (408), hCG alone is sufficient to induce spermatogenesis. Although acquired gonadotropin deficiency due to androgen-induced hypothalamic suppression creates a transient state of functional gonadotropin deficiency, becoming clinically manifest after androgen intake ceases, the therapeutic significance of this functional state is unclear. An experimental basis for such hCG treatment was provided by studies showing that high dose hCG treatment (15,000 IU per week) rescued spermatogenesis after prolonged testosterone-induced suppression of sperm production in healthy men (410) whereas very low dose hCG (875 IU weekly, about 20% of standard dose) maintains intratesticular testosterone concentrations at the threshold required to maintain spermatogenesis (411, 412). However, hCG administration in men with a functional hypothalamo-pituitary-testicular axis would suppress FSH secretion and may hinder the hormonal drive to induce spermatogenesis. Furthermore, while anecdotal case reports (413, 414) and uncontrolled studies (415-417) suggest sperm output improves with hCG treatment of ex-androgen abusers, the timing of improvement also coincides with that of natural recovery (71, 418, 419) hence the efficacy of hCG treatment of ex-androgen abusers remains to be established. Finally, the deleterious effects of hCG on the testis and sperm (420-424) indicate that its unproven application to functional gonadotropin deficiency warrants well-controlled clinical trials to establish its efficacy and safety.

Similarly, estrogen blockade originally developed as adjuvant hormonal treatment for breast cancer (425) is achieved using either drug that blockade the estrogen receptor (anti-estrogens, SERMs) or inhibit estradiol synthesis (aromatase inhibitors). In men, experimental estrogen blockade unleashes additional GnRH secretion to simulates pituitary gonadotropin secretion thereby increasing testicular testosterone and sperm production. Adapted empirically as off-label treatment for male infertility (407) this has used mainly clomiphene or tamoxifen among a wide array of novel anti-

estrogens (426); however, evidence for efficacy of anti-estrogens (427) or aromatase inhibitors (428-430) for improving sperm output and fertility in male infertility is weak while well-designed, controlled trials lacking. Anti-estrogens create a reflex rise in pituitary gonadotropin secretion depending on interruption of estrogenic negative hypothalamic feedback; however, the dysfunctional hypothalamo-pituitary unit causing the transient gonadotropin deficiency of withdrawal from androgen abuse may display impaired responsiveness to estrogen blockade. The efficacy evidence of estrogen blockade in ex-androgen abusers is based on anecdotal case reports (431, 432) or uncontrolled retrospective series of men after androgen misuse and abuse (433). The long-term safety of estrogen blockade in men has not been studied so potential adverse effects remain to be better defined. Inhibiting the physiological requirement for aromatization of testosterone to mediate androgen effects on the brain and bone (434) warrants controlled studies of effects on bone density and fractures (204) as well as sexual function (336, 349) before off-label estrogen blockade treatment is adopted.

More speculative potential treatments to assist overcoming androgen abuse include the use of selective serotonin reuptake inhibitor (SSRI) anti-depressants based on the prominent mood disturbances in withdrawal (androgen deficiency) symptoms as well as the high prevalence of mood disorders in men castrated for advanced prostate cancer (435) where antidepressant treatment is frequently prescribed (436).

Finally, in any case, ad hoc adjunct “post-cycle” treatments such as hCG or anti-estrogens do not rectify underlying hypothalamic-pituitary suppression but rather reinforce it. In perpetuating the impact of androgen abuse as well as colluding with abusers in avoiding withdrawal, such treatment may further delay ultimate recovery from reproductive effects of androgen abuse.

5.6. Public health and policy

5.6.1. Performance enhancement

Androgen abuse among elite athletes is largely motivated by a "win-at-all-costs" mentality arising from the lucrative rewards of fame and fortune that success offers. In the competitive sports, WADA and international sporting federation have pursued the elimination of androgen abuse by programs of highly sensitive urinary drug screening (437). These aim to detect androgen abuse and to deter it by banning violating athletes (and/or coaches) from elite competition. Initially deployed during major competitions, there is evidence that stringent testing has reduced abuse of known synthetic androgens and testosterone during and immediately preceding elite competition (328). These developments have

depended on deterrence through the risk of detection. For example, the window of detection for exogenous androgens has been widened by the detection methods for urinary excretion of long-lasting metabolites of exogenous androgens so that some synthetic androgens can be detected up to months after the last dose (438-446). Similarly, the introduction of out-of-competition testing through the WADA's Whereabouts program, by which elite athlete must notify every quarter in advance a location where they will be available for no-notice testing on any day, is an important, albeit intrusive, initiative against surreptitious androgen doping. The strict liability of the WADA Code whereby athletes are responsible for the presence of any banned substances in their body regardless of intent, fault, negligence or knowing use has spawned exculpatory claims that meat or other foods may be contaminated with trace amounts of banned substances originating from their agricultural source. Wider application of unannounced, out-of-competition testing could eliminate virtually all androgens from elite sport but at a formidably expensive cost. Furthermore, in the high wealth environment of elite sports, such testing programs are susceptible to crippling by legal manoeuvres, as a tax-deductible cost of business.

Androgen abuse remains the most potent and prevalent form of sports doping detected (447). For example, among the 322,000 anti-doping tests conducted world-wide by WADA approved anti-doping laboratories in 2017, 4756 (1.5%) were positive tests (adverse analytical findings) with the majority (96%) being hormones, of which 96% were androgens (328). Within sports, androgen abuse may be direct androgen administration as well as indirect (administration of non-androgenic drugs to increase endogenous testosterone), both now readily detectable with mass spectrometry-based anti-doping urine tests (448). Yet, the ongoing temptation of fame and fortune coupled with the undoubted effectiveness of androgen abuse especially for power sports, continues to entice cheating via renewed approaches aiming to exploit androgens. Ongoing vigilance and innovation in anti-doping science is required to build resilience and deterrence against doping to maintain fairness in elite sport.

During the post-war decades, thousands of synthetic androgens were patented based on the steroidal structures of the natural androgens, testosterone and DHT (366) in the failed attempt to develop a pure non-virilizing androgen ("anabolic steroid"). The hepatotoxic class of synthetic 17α-alkylated androgens such as stanozolol, methandienone and oxandrolone retain their reputation for ergogenic advantages in power sports and for bodybuilding and are freely available via the internet for illicit use (344, 350, 449-453). However, all marketed synthetic androgens are readily identified by mass spectrometry-based urine anti-doping detection methods (366). Consequently, alternative strategies have been adopted to continue exploiting androgen doping without detection. As only a

tiny minority of synthetic androgens patented in the 1950s-70s were ever marketed, this large reservoir of non-marketed synthetic androgens in the expired patent literature provide a resource for development of apparently novel, designer androgens. These can initially evade detection by urine mass spectrometry-based anti-doping tests until their chemical structures become known, when they become detectable (350, 454, 455). The first designer androgen identified in an athlete's urine was norbolethone, a 17-α alkylated androgen originally synthesized in 1960 but never marketed (456). Soon after, tetrahydrogestrinone (THG), a previously unknown androgen produced illicitly by a one-step chemical reduction of a marketed alkylated progestin (gestrinone) was identified structurally (457) and then as a potent androgen by an *in vitro* androgen bioassay (458). Subsequently, desoxymethyltestosterone (Madol), another never-marketed androgen patented in 1960's was identified (459). A recent review notes at least six designer androgens available over the internet (453). Nevertheless, once identified, these designer androgens have rarely been detected again in regular doping tests reflecting effective deterrence. Numerous other schema to evade detection of doping have been reviewed elsewhere (321).

The first non-steroidal androgen invented was reported in 1998 (460) leading to a new class of structurally diverse mixed partial AR agonists/antagonists ("SARM") with the overall goal of tissue selectivity, reviving the older attempts to dissociate virilizing from anabolic effects of androgens (461). This new quest aims to replicate the serendipitous, but still largely unexplained, tissue selectivity of selective estrogen receptor modulators (SERM). So far, no non-steroidal androgens are yet approved for clinical use (462-464) but although their use in sport was prohibited pre-emptively in 2008, characteristically, they soon began to appear illicitly over the internet for doping or body-building, in breach of law, patents and anti-doping codes. For example, Andarine (S-4), widely advertised on the internet (465), has been identified in urine samples from athletes (466, 467). Given the limited clinical trial data available (463), the full safety profile of non-steroidal androgens, even at conventional let alone doping doses, remains little understood. As SARMs were developed by modification of the structures of non-steroidal anti-androgens which feature hepatotoxicity as side-effects, it is likely that SARMs will also feature hepatotoxicity (374, 468, 469).

5.6.2. Image enhancement

In contrast to the well-known impact of androgen abuse as ergogenic drug cheating in sport, the challenge of androgen abuse in the community among image-oriented abusers is only gradually being recognized and effective public health approaches to combat this relatively new form of drug abuse remain to be developed (302). Despite most governments introducing legislation to regulate illicit supply, possession and use of androgens, there is an awareness that effective programs for non-sporting, image-oriented androgen abusers will require different prevention and diversion focus from the effective deterrence of sports doping among professional elite sports. Interventions to prevent or halt androgen abuse requires understanding the motives for starting and continuing illicit drug intake. Yet, knowledge of the relevant social factors and motivations remains vague, so effective interventions do not yet exist. An important and little studied aspect of androgen abuse is the consistent evidence that minority ethnic or racial status creates higher risk for androgen abuse in US (470), UK (471), and Australian (313) communities. One educational program has proved capable of improving knowledge about androgen abuse but was unable to effectively deter initiation of new androgen abuse (472) and further innovation is required. For adolescents motivated by short-term goals of image enhancement and protected by the aura of invincibility, "scare tactics" are ineffective given the innate youthful belief in their invulnerability and immortality so more sophisticated, age-attuned approaches are required. Furthermore, androgen abuse creates a cyclical form of drug dependency due to androgen withdrawal effects after cessation of drug intake. Nevertheless, most androgen abusers appear to eventually discontinue thought the timing and motivations remain undefined. Fortunately, at least in one context outside sports, androgen abuse in US secondary schools shows signs of having peaked and abating (473) although the reasons for this time-course remain speculative (Figure 6). Hence with established androgen abuse, the most appropriate medical approach is supportive counselling and encouragement to discontinue without perpetuating abuse by prescribing androgens or purposeless medical monitoring, both of which collude with perpetuating androgen abuse rather than encouraging cessation.

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Figure Legends

Figure 1 – Historical timeline indicating the temporal overlap of the Golden Age of Steroid Pharmacology with the Cold War following World War II. The timeline from the 1930's originated with the discovery of testosterone and extends to the end of the Cold war around 1990. Landmarks in the Golden Age of Steroid Pharmacology are indicated above the timeline and those of the Cold war with its global confrontations below it.

Figure 2 – Pathways of testosterone action through direct interaction with the androgen receptor as well as through its bioactive metabolites, dihydrotestosterone (DHT) and estradiol. Dihydrotestosterone is a more potent, pure androgen that operates through the amplification pathway by interacting with the androgen receptor. Estradiol, the most potent estrogen, operates through the diversification pathway that modifies testosterone tissue effects to act on the estrogen receptor. Both active testosterone metabolites are mostly produced in androgen target tissues that express either 5α reductase or aromatase enzymes as mechanisms for local paracrine modulation of testosterone tissue effects.

Figure 3 – Impact of exogenous androgens in suppressing the hypothalamus, pituitary and testicular axis and its recovery. Any exogenous androgen (including testosterone) have powerful negative feedback effects on the hypothalamus to inhibit gonadotropin-releasing hormone release which reduced pituitary gonadotropin and consequently testicular testosterone secretion. The net effect of reduction of endogenous testosterone secretion has prominent deleterious effects on androgen-sensitive tissues.

Figure 4 - Global pharmaceutical sales of testosterone from 2000 to 2011 in monthly treatment doses per year per person. Despite no new approved indications there was a 100-fold rise in annual testosterone sales from $18 million in 1988 to $1.8 billion in 2011 indicating it was mainly for "andropause". Data obtained from IMS (now IQVIA) and adapted from Handelsman DJ (2013) Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. Med J Aust 199:548-551.

Figure 5 – Annual PubMed citation rates over decades. The left panel shows the citation rates per year for “Andropause” and its most widely used neologisms. The right panel shows the citation rates per year of “Andropause” and “LowT” illustrating their contemporaneous evolution. While the remarkable temporal coincidence in these rising rates makes it unlikely to be due to chance alone, it cannot be determined from these data whether one topic stimulates the other (in either direction) or whether both are the product of a third factor, namely uncritical and wishful rejuvenationist thinking about male ageing.

Figure 6 – Prevalence of androgen abuse in US high school students in years 8, 10 and 12 from annual surveys from 1991 to 2019. Left panel is the data displayed as lifetime (ever) use per high school class years. The right panel is the lifetime and recent (last year) use pooled over class years over the same survey period. Data adapted from the Monitoring the Future Surveys (311).

Tables

Table 1 - Classification of Use, Misuse and Abuse of Androgens

Table 2 - Pharmacological Androgen Therapy

Box 1 – Avoiding Androgen (Testosterone) Misuse

Table 1: Classification of Use, Misuse and Abuse of Androgens

	Therapeutic Status	Application
USE	Physiological replacement therapy	Pathological (Organic) Hypogonadism Female-to-male transgender
	Pharmacological androgen treatment	Non-reproductive disorders including functional low testosterone states Masculinizing female-to-male transgender (transmen)
MISUSE	Invalid indication	Misinformation &/or misapplication Male infertility; obesity, diabetes, osteoporosis, erectile dysfunction in absence of pathological hypogonadism “ Andropause”, “LowT”, “Late-onset hypogonadism”
ABUSE	No medical indications	Elite sport performance Image enhancement and body building for cosmetic, recreational, occupational reasons

Table 2 – Pharmacological Androgen Therapy

Target Tissue	Clinical Indication	Status
Spermatogenesis	Hormonal male contraception	Proven principle (phase II-III trials of prototype), no product
	Male infertility	Disproven
Hemoglobin	Renal or marrow failure	Proven 2nd line therapy, cost-effective vs erythropoeitin
Bone	Osteoporosis	Proven 2nd line therapy, less effective than bone anabolic drugs
	Steroid-induced bone loss	Proven adjuvant therapy, not widely used
Muscle	HIV wasting/cachexia	Proven 2nd line therapy
	Genetic myopathies	Disproven
Psychosexual	Male sexual dysfunction	Disproven (eugonadal men)
	Female sexual dysfunction	Proven (at supraphysiological levels)
Transgender	Female-to-male transgender	Widely adopted standard of care
Mood	Depression, quality of life	Modest efficacy (dysthymia), not tested vs anti-depressants

Anti-estrogen	**Advanced breast cancer** **Endometriosis**	**Proven, last resort** **Proven, 2nd line therapy vs GnRH agonists**
Liver	**Angioedema (C1 esterase deficiency)**	**Proven, cost-effective vs recombinant C1 esterase**

BOX

Avoiding Testosterone Misuse

- Testosterone is highly susceptible to wishful thinking, marketing and promotion leading to its use as an anti-ageing or sexual dysfunction tonic and for cyberchondria
- Hypogonadism is a clinical diagnosis with a pathological basis, confirmed by hormone assays – not the other way around
- Testosterone misuse is prescribing for wrong reasons: harmful, invalid, or unproven off-label indications, most often for inappropriate or unproven clinical context
- The invented condition known variously as “Andropause”, “LowT”, “Late onset hypogonadism” or “age-related or functional hypogonadism” is a fiction in search of a definition
- Functional hypogonadism is not a disease and testosterone treatment is not justified without sound evidence of efficacy and safety from placebo-controlled clinical trials
- Take care to distinguish pathological from functional hypogonadism
- Beware of disease mongering: watch the objective evidence and beware of indications stretched beyond valid evidence
- Be prepared to say you do not know when you do not
- Avoid testosterone prescribing solely because another doctor might do so or that underlying non-reproductive causes of a low testosterone might seem irremediable

Mismeasure leads to Misuse

- There is no basis for population screening for low testosterone
- Avoid “case-finding” in men with non-specific clinical features without evidence of pathologic hypogonadism
- Without likely underlying reproductive pathology, there is no reason to measure serum testosterone
- To measure serum testosterone, the testes should be examined and underlying reproductive pathology suspected
- Always measure serum LH, FSH and SHBG with testosterone for interpretation and obtain multiple samples
- Encourage pathologists to provide accurate serum testosterone by LCMS – steroid immunoassay era of 20th century is ending
- Imaginary, derived fractions of testosterone (“free”, “bioavailable”) are a numerical artefact signifying nothing and provide no reliable clinical guidance on androgen status

- Androgens are potent drugs requiring prescription for valid medical indications but are also misused for invalid, unproven or off-label reasons as well as being abused without prescription for illicit non-medical application for performance or image enhancement.
- Testosterone remains among the oldest marketed drugs in therapeutic use, yet after 8 decades of clinical use the sole unequivocal indication for testosterone remains in replacement therapy for pathological hypogonadism, organic disorders of the male reproductive system.
- Nevertheless, wider claims assert unproven, unsafe, or implausible benefits for testosterone, mostly representing wishful thinking about rejuvenation which have over recent decades created an epidemic of testosterone misuse involving prescription as a revitalizing tonic for anti-ageing, sexual dysfunction and/or obesity, where efficacy and safety remains unproven and doubtful.
- Androgen abuse originated during the Cold War as an epidemic of androgen doping among elite athletes for performance enhancement before the 1980s when it crossed over into the general community to become an endemic variant of drug abuse in sufficiently affluent communities that support an illicit drug industry geared to bodybuilding aiming to create a hypermasculine body physique and image.

Figure 1

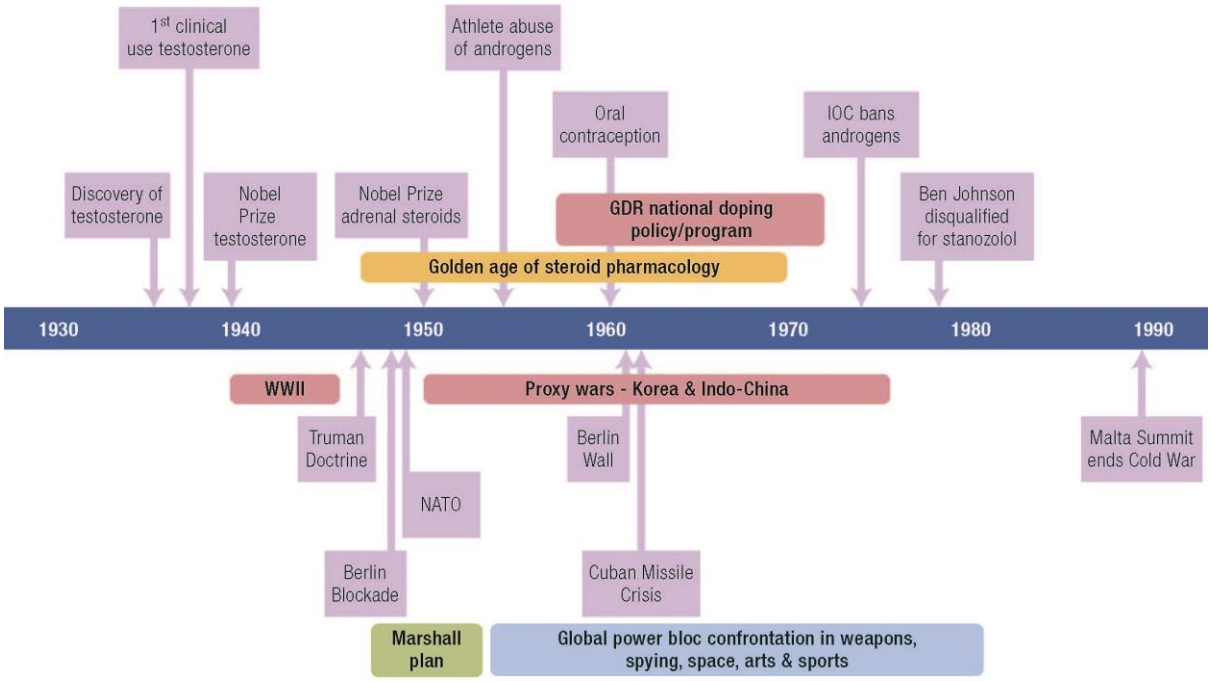


Figure 2

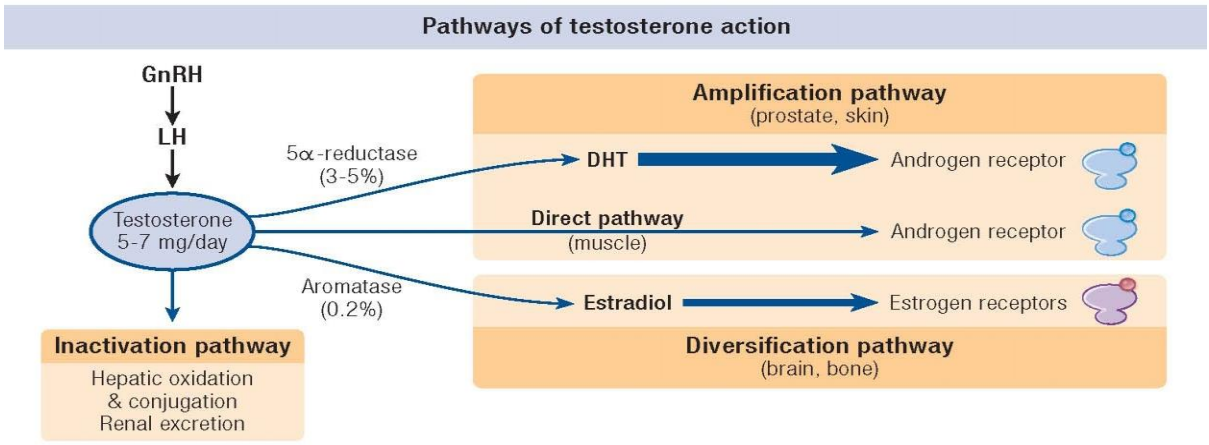


Figure 3

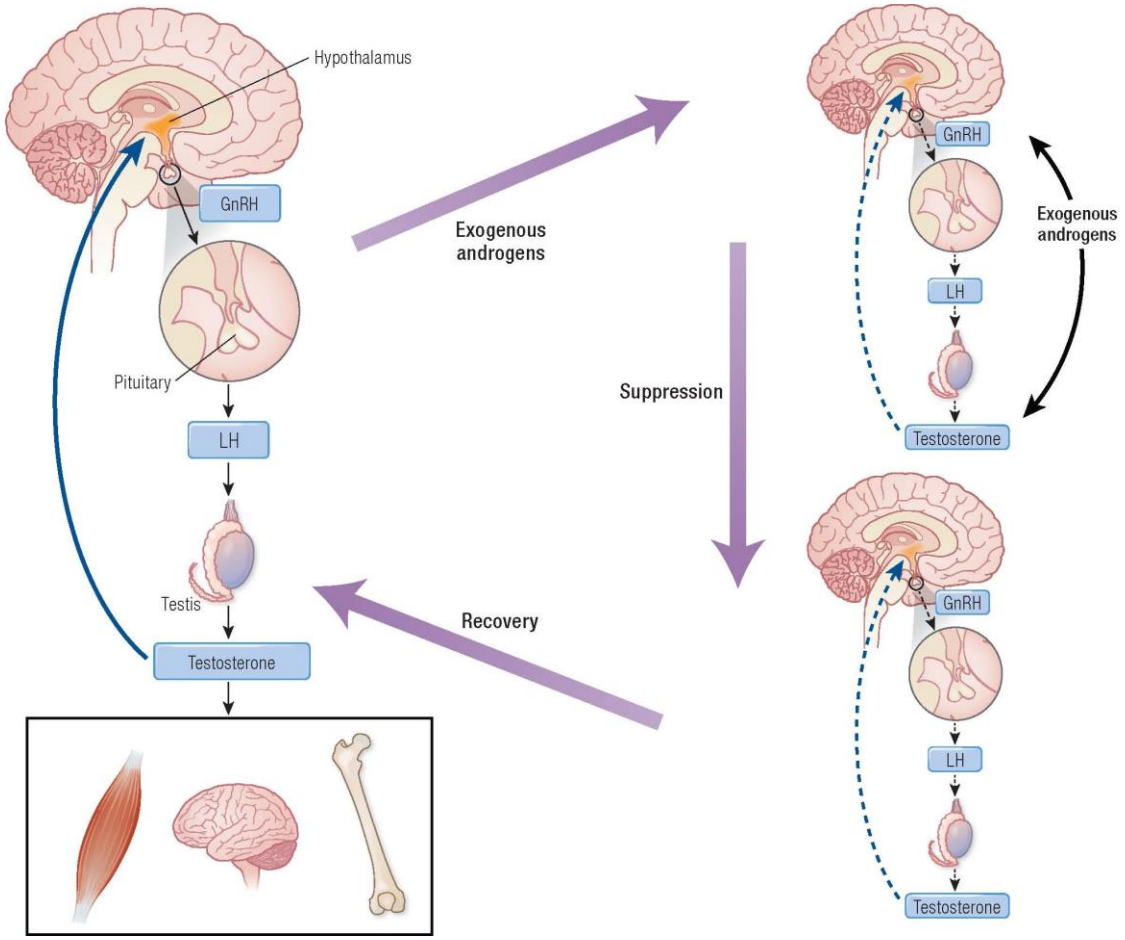
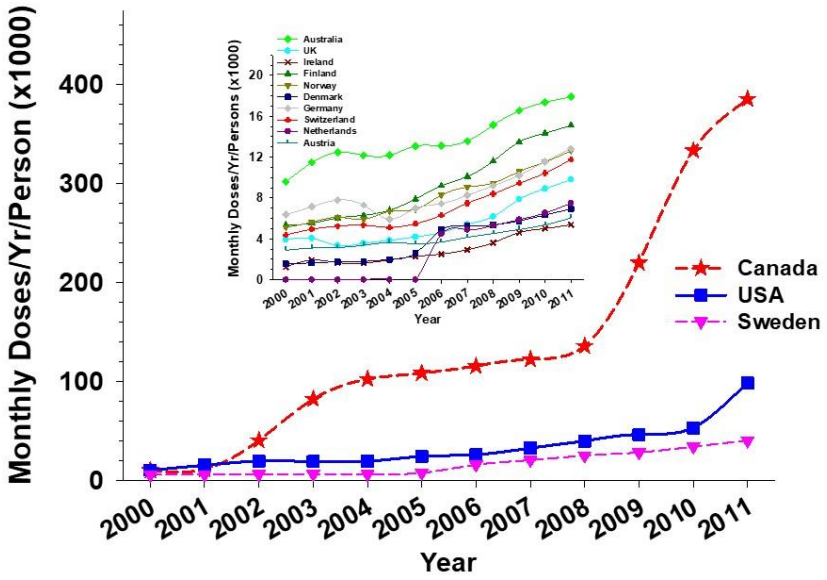


Figure 4



Global Pharma Sales of Testosterone

1988 - $18 million
2011 - $1.8 billion
100-fold rise in 30 yr.

No new indications Approved

Mostly prescribed off label for "andropause", "LowT", "LOH"

Figure 5

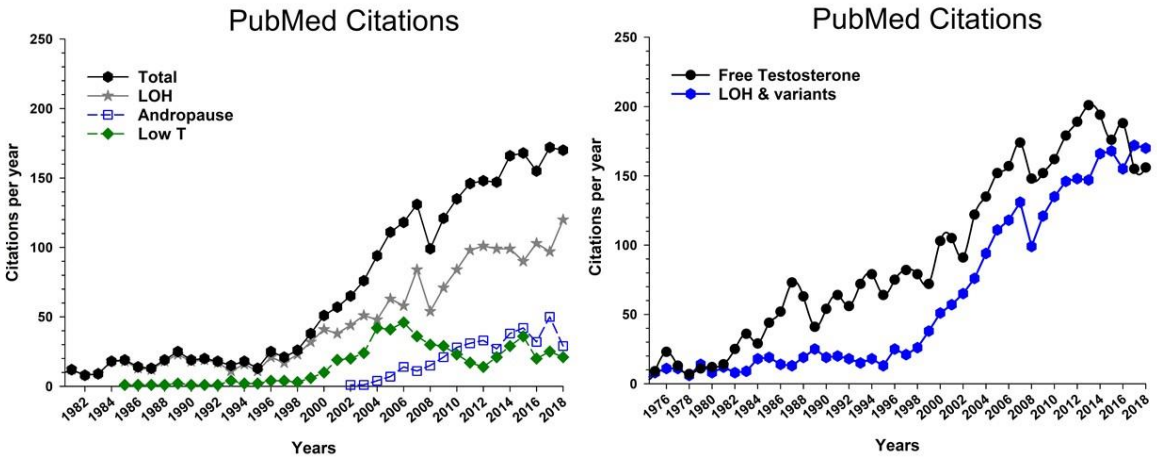


Figure 6