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Characteristics and Consequences of Use of Anabolic Androgenic Steroids in Poly Substance Abuse

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2008

ISSN 1651-6206
ISBN 978-91-554-7270-2
urn:nbn:se:uu:diva-9261

Dissertation presented at Uppsala University to be publicly examined in Hörsalen, Dag Hammarskjölds väg 17, Uppsala, Thursday, September 25, 2008 at 10:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

Abstract

Petersson, A. 2008. Characteristics and Consequences of Use of Anabolic Androgenic Steroids in Poly Substance Abuse. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 372. 81 pp. Uppsala. Uppsala. ISBN 978-91-554-7270-2.

The use of anabolic androgenic steroids (AAS) has been associated with use of illegal or unprescribed prescription drugs, as well as different adverse psychiatric effects, such as ma-ania, psychosis and hostility. Further, there is an association between use of AAS and other different risk behaviours, including carrying guns and reckless driving. Taken together, these data suggest that there is a group of AAS users that are not elite athletes, but rather young men at risk for psychiatric illness and criminality, and who use AAS primarily for their aes-thetic effects and possibly for their psychoactive effects. The aim of this thesis is to investi-gate further the connection between use of AAS and use of other drugs, and to investigate whether the proposed side effects of AAS cause an increase in morbidity and mortality.

The first study (Paper I) investigates morbidity and mortality in persons testing positive for AAS compared to persons testing negative for AAS at a doping laboratory. Paper II of this thesis studies the presence of psychoactive drugs in diseased men who tested positive for AAS upon autopsy and whether there is any difference between deceased users of AAS and deceased users of heroin or amphetamine (control group). The third article (Paper III) dis-cusses a surprising finding in paper I of increased seizures NOS in users of AAS. Paper IV and V are interview studies from an out-patient substance abuse clinic.

The main findings in Paper I was that the majority of deceased users of AAS were also positive for other drugs and/or alcohol on autopsy, and that users of AAS more often than the control group had died from intentional death (suicide or homicide). The main finding of Paper II was that users of AAS were severely at risk for premature death compared to both the control group and the general population. Paper III concluded that the high prevalence of Convulsion NOS in users of AAS most likely was the result of concomitant substance abuse and withdrawal from such use. Paper IV concluded that twelve percent of the patients at the substance abuse clinic had used AAS for at least one cycle. Users of AAS had a higher risk of having been convicted of a violent offence, and users of AAS more often reported having been physically abused. In Paper V, long-terme users of AAS were found to have an increased risk for developing depression in connection with cessation of AAS use. AAS was also re-ported to be used in preparation for crime.

In summary, this thesis concludes that there is a solid association between use of AAS and use of other psychotropic drugs in certain subpopulations, and that users of AAS are at risk for premature death due to unnatural causes that may be secondary to use of AAS.

Keywords: Anabolic steroids, Crime, morbidity, mortality, substance abuse

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ISSN 1651-6206

ISBN 978-91-554-7270-2

urn:nbn:se:uu:diva-9261 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-9261>)

*To my parents for all their support.
And to Walter, for just being there.*

“After enlightenment, the laundry.”

(Zen proverb)

List of papers

Paper I: **Petersson A**, Garle M, Holmgren P, Druid H, Krantz P, Thiblin I. Toxicological findings and manner of death in autopsied users of anabolic androgenic steroids. *Drug Alcohol Depend.* 2006 Feb 28;81(3):241-9

Paper II: **Petersson A**, Garle M, Granath F, Thiblin I. Morbidity and mortality in patients testing positively for the presence of anabolic androgenic steroids in connection with receiving medical care. A controlled retrospective cohort study. *Drug Alcohol Depend.* 2006 Feb 28;81(3):215-20

Paper III: **Petersson A**, Garle M, Granath F, Thiblin I. Convulsions in users of anabolic androgenic steroids: possible explanations. *J Clin Psychopharmacol.* 2007 Dec; 27 (6):723-5

Paper IV: **Petersson A**, Klötz F, Voltaire-Carlsson A, Bengtsson J, Granath F, Thiblin I. Use of anabolic androgenic steroids at an outpatient substance abuse clinic in Stockholm, Sweden. *Manuscript.*

Paper V: **Petersson A**, Klötz F, Bengtsson J, Voltaire-Carlsson A, Thiblin I. The significance of anabolic androgenic steroid use by patients seeking health care for alcohol or drug abuse. *Manuscript.*

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Abbreviations

AAS	Anabolic Androgenic Steroids
AASpos-subst neg	AAS-positive, but negative for illegal drugs on autopsy
AASpos-subst pos	AAS-positive, and positive for illegal drugs on autopsy. May be positive for alcohol or prescription drugs.
ACEs	Adverse Childhood Experiences
AR	Androgen Receptor
ASI	Addiction Severity Index
BDD	Body Dysmorphic Disorder
BZ	Benzodiazepines
BMI	Body Mass Index
CI	Confidence Interval
CNS	Central Nervous System
CRF	Corticotrophin-Releasing Factor
CS	Central Stimulants
DDR	Deutsche Demokratische Republik
DHT	Dihydrotestosterone
DSM III	Diagnostic and Statistical Manual of Mental Disorder, third Edition
DSM IV	Diagnostic and Statistical Manual of Mental Disorder, 4 th Edition
GH	Growth Hormone
GnRH	Gonadotropin Releasing Hormone
HPG-axis	Hypothalamic-pituitary-gonadal axis
IOC	International Olympics Committee
MD	Muscle Dysmorphia
NA	Nucleus Accumbens
NOS	Not Other ways Specified
SMR	Standardized Mortality Ratio
SSRI	Selective Serotonin Reuptake Inhibitors
Substpos-AASneg	Positive for illegal drugs on autopsy, but negative for AAS
THC	Tetrahydrocannabinol (cannabis)
VTA	Ventral Tegmental area
WADA	World Anti-Doping Agency

Introduction

Definitions of Anabolic Androgenic Steroids

Anabolic Androgenic Steroids (AAS) are chemically modified molecules of the primarily male endogenous sex hormone testosterone. Like testosterone, AAS have anabolic, tissue (muscle)-building properties, and like testosterone, AAS also have androgenic (development and sustenance of secondary male characteristics such as hair growth and deepening of the voice) properties. Much effort has been spent on trying to develop an AAS that is devoid of androgenic properties (and thus reducing many of the side effects of AAS), but this has not succeeded. Therefore, the term AAS is more accurate than the more commonly used term Anabolic Steroids (AS), and will consistently be used throughout this thesis (Marshall, 1988).

Background

Man has yearned for superhuman strength and stamina for centuries. Gods or humans endowed with these gifts have been described as early as 3000 years B.C, in the Epic of Gilgamesh. The Old Testament (as exemplified by Hercules and the frightening Goliath), Greek, Roman and Nordic mythology were also laden with these “super heroes”. The Greek and Roman mythologies were also promoting a male *physical* ideal, as depicted in Myron’s muscular statue Discobolus, which would ironically later appear as the opening shot in Lene Riefenstahl’s propaganda film about the Olympic Games in Berlin in 1936.

To gain this desirable strength and stamina, man has not hesitated to use primarily centrally stimulating substances throughout history. For example, coca leaves were chewed by the Andean Indians, and Saharan African Cafre dipped bread into a herbal brew to endure long wanderings. The word doping is derived from the Boer-Dutch language *dopen* from this custom. However, the previously used centrally stimulating substances have been devoid of *anabolic* (tissue building) properties. Only with modern science has this been possible.

The history of testosterone

Substances with anabolic properties were not discovered until the 19th century, when John Hunter, a Scottish physician developed methods to transplant testicular tissue into foreign tissue. His work inspired another physician, Berthold of Göttingen, to experiment with castrated roosters. In 1849, Berthold concluded, from observations of roosters, that the testes contained a substance that was secreted into the blood and which maintained secondary sexual characteristics (i.e. a hormone). When the castrated roosters were given a testicular implant into the abdomen the male characteristics (e.g. regrowth of the comb and social dominance) of the rooster reappeared. (However, when reproducing these experiments, researchers have modified the importance of testosterone in the importance of its development of aggression; only rats who were “socially naïve” would significantly reduce their level of aggression in the absence of testosterone, thus suggesting that the aggressive behaviour first needs to be learned in order to be reinforced by testosterone (Mizcek and DeBold, 1983)).

In 1889, French physiologist Brown-Sequard rather boldly injected himself with extracts from the testes of animals (however, this project was probably more reasonable than his former experiments where he proposed to inject animal sperm into elderly men’s blood). He claimed that the extract was rejuvenating both physically and mentally, starting a turn of the century surge of crude hormonal replacement therapy for a general sense of “well being” in the Western World (Hoberman, 2005).

In the United States, executed San Quentin prisoners would “donate” their testicles to have them implanted in fellow inmates under the supervision of Dr. L.L. Stanley. In Europe, Paris surgeon Dr. Voronoff, implanted monkey testicles into men with great (monetary) success (Hoberman, 2005).

However, the exact basis for the perceived effects of these extracts was not isolated until 15 mg of a pro-hormone of testosterone, androsterone, was purified from vast amounts of human urine by Adolf Butenandt in 1935.

These discoveries lead at least two different research groups to a frantic attempt to identify the primary human male hormone. In 1935, the two major research groups (lead by former colleagues Butenandt and Ruzsica, respectively) simultaneously identified testosterone, and were awarded the Nobel Prize in Chemistry in 1939 (Kochakian 1993).

Since the 1940s chemists have attempted to modify the testosterone molecule to minimize its androgenic effects and maximize its anabolic effects, but to this day no purely anabolic substance has been produced (Dotson and Brown 2007). Interestingly, former DDR and Soviet physicians are in great demand in the development of new and modified testosterone molecules (Hoberman, 2005).

Therapeutic use of testosterone and AAS

Initially, the discovery of testosterone was hailed as a panacea for many illnesses; “neurasthenia”, anaemias, osteoporosis, mammary carcinoma and catabolic states such as cachexia (e.g. survivors from concentrations camps), burns and trauma. Psychiatry was also quick to adopt testosterone as a cure-all; depression, psychosis and neurosis were all treated with testosterone, with varying results (Dotson and Brown 2007).

Today, the only medical indication for use of AAS (Nandrolone decanoate) in Sweden is uremic anaemia and osteoporosis in senior citizens. Testosterone and testosterone undecanoate are used to treat hypogonadism. The therapeutic doses are much lower than the doses used non-medically (www.fass.se).

However, just like at the turn of the 19th century, all over the Western world but particularly in the United States, there is increasing demand from senior male *and* female patients (i.e. aging, affluent “baby boomers”) to be prescribed testosterone (as well as growth hormone, GH) as “hormonal replacement therapy” for a sense of rejuvenation (compare to the turn of the century surge for crude “rejuvenating” testes extracts) when hormone levels decline with biological age (Hoberman, 2005). Some physicians, testifying to the norms of “libertarian patient-centred medicine” (Hoberman, 2005) where the patient him or herself defines their own “treatment”, readily prescribe AAS and Growth Hormone (GH) to these patients, who grew up with a sense of entitlement from living in a flowering economy with many opportunities for vertical social mobility.

Thus; testosterone is viewed by the public in many, paradoxical ways: as a “fountain of youth”, yet a horrifying threat to “fair sportsmanship”.

AAS in elite athletes

Anecdotal data claim that modified versions of testosterone were used by German Storm Troopers as early as during World War II; the testosterone was given in order to increase aggressiveness. However, the Soviet Union’s weight-lifting team at the World Weightlifting Championship in Vienna in 1954 is considered the first group to take steroids systematically (Wright 1980).

Performers of many other sports adopted use of AAS when this was revealed. There was an outcry of public opinion, though, when the stigmata of AAS became more and more obvious, especially in Soviet Union (and satellite states) women. The notion of “fair sportsmanship” was considered to no longer have any meaning, and the International Olympics Committee (IOC) was forced to face and consider the use of AAS. In 1975, the use of AAS was no longer permitted in competitive sports (Hoberman, 2005). In 1991, the Swedish doping law was established and it was enforced in 1992. In the US, AAS was criminalized in 1990 as a schedule III controlled substance

schedule III substances include opiates, amphetamines and barbiturates (Lukas 1993). The precursor androstenedione was also listed as a schedule III controlled substance in the U.S. in 2004 (Smurawa and Congeni 2007).

However, the nature of use of AAS (e.g. “cycling”, where AAS is used for a period of time with intense training and a strict food regimen, and a “clean” period, almost always during competition) debilitates the control of use of AAS in elite sports, even though measures are taken to avoid this problem through testing during practice periods and not only at competitions. For example, in 2006, 2941 out-of-competition urine samples covering 41 sports were tested by the World Anti-Doping Agency, WADA, but only 12 steroid-users, four refusals to participate and two manipulations of samples were detected (http://www.wada-ama.org/rtecontent/document/DOPINGCONTROL_2006_OOCT_Stats_EN.pdf). Interestingly, American football did not adopt the WADA-code until 2008 (<http://www.usafootball.com/articles/displayArticle/5511/4743>).

There are suggestions from writers and philosophers that the use of AAS should be allowed in elite athletes. The arguments proposed are crudely from three different perspectives; those who think that illicit compounds always will be used in order to secure good athletic results, so that illegalization will forever be moot, and athletes will therefore never compete fairly unless doping is allowed. The second argument is concerned with the fact that we are living in a modernized and medicalized world, where liberal patient-centred medicine must allow prescription of AAS to athletes merely because they are *available* (Hoberman, 2005). The third, more theoretical argument is represented by practical philosophy professor Torbjörn Tännsjö, who thinks it is *unstoppable* that mankind will use the techniques available to transgress the genetic possibilities of the biological body. Tännsjö also parallels the athlete to the musician, who is allowed to take beta-blockers before a demanding concert since the music rather than the performer is the focus; in sports, the effort is closely linked to the athlete himself (e.g. one can enjoy Chopin without having Chopin himself play the piano, but it is difficult to enjoy Ben Johnson’s efforts without Ben Johnson) but should rather be linked to the effort. He claims further that with new technology, genetic predisposition will no longer determine who performs better in sports, and envisions a future where the athlete utilizes his or her body to represent different pharmaceutical companies; much like Formel 1-racers represent different car companies (Tännsjö, 2005). Philosopher Peter Singer (2007) argues that already the genetic disposition as such opposes the notion of “fair sportsmanship”, and suggests that only drugs that can seriously damage a person’s health should be banned. A similar proposition is offered by Italian bioethics professor Julian Savulescu; athletes should be allowed to consume whatever they want, as long as it is safe for them to do so. Exclusion from competitions would be based on variables such as dangerously high blood counts or arrhythmias (Savulescu et al. 2004). Concerning AAS, philosophers seem little aware of the short-term and long-time cardiovascular and/or psychiatric changes that AAS-use may induce, and to legalize AAS on the premises of

whether they are damaging or not would thus be impossible, since it is impossible to predict who will suffer the long-term side effects.

In addition, philosophical debate takes no stand at all on the illegal use of AAS outside of sports; this use may very well be more of an issue to the utilitarian, since such users lack the socially accepted borders of elite sports, and has entered a subculture where the bonding agent is an illegal substance (Maycock and Howat 2007).

Prevalence studies

In the general population, the estimated life time prevalence of AAS use is 1-6 % (Buckley et al. 1988; Handelsman and Gupta 1997; Kersey 1996; Melia et al. 1996; Nilsson et al. 2001; Rachon et al. 2006; Radakovich et al. 1993; Schweltnus et al. 1992; Tanner et al. 1995; Wanjek et al. 2007; Whitehead et al. 1992), though a recent study found that in non-athlete college students the male AAS life time prevalence rate was as high as 9 % (Berning et al. 2008).

The gym culture (amateur body builders, fitness competitors) is known to be a haven for use of AAS, though few body builders admit such use, and drop-out rates are high in most studies, yet the use of AAS in gym populations is estimated to be 10-20 times higher than that of the general population (Lindstrom et al. 1990; Simon et al. 2006; Striegel et al. 2006).

AAS and substance abuse

A growing body of evidence has established that use of AAS is associated with use of other psycho-active substances (Bahrke et al. 1998; DuRant et al. 1993; Kindlundh et al. 1999; Middleman and DuRant 1996; Miller et al. 2002; Nilsson et al. 2004b; Whitehead et al. 1992; Wichstrom and Pedersen 2001), demonstrating that AAS is not a concern only in the world of sports.

Substances associated with use of AAS in case reports and survey studies are cocaine (Elliot et al. 2007; Meilman et al. 1995; Roccella et al. 2005; Simon et al. 2006; Striegel et al. 2006; Welder and Melchert 1993), cannabis (Durant et al. 1994; DuRant et al. 1993; Elliot et al. 2007; Kindlundh et al. 1999; Wichstrom and Pedersen 2001), LSD (Kindlundh et al. 1999; Roccella et al. 2005), amphetamines (Kindlundh et al. 1999), alcohol (DuRant et al. 1993; McCabe et al. 2007; Meilman et al. 1995; Nilsson et al. 2004a; Pallesen et al. 2006; Radakovich et al. 1993), opiates (Kanayama et al. 2003; Roccella et al. 2005), ephedrine (Clark and Schofield 2005; Dumestre-Toulet et al. 2002; Mark et al. 2005). Also, insulin (Konrad et al. 1998; Skarberg and Engstrom 2007) and clenbuterol (Delbeke et al. 1995; Dumestre-Toulet

et al. 2002; Goldstein et al. 1998) are sometimes used concomitantly for their anabolic properties.

The survey studies have also shown a link between use of AAS and anti-social or risk-taking behaviour such as truancy and petty theft (Kindlundh et al. 1999), drunk or reckless driving (McCabe et al. 2007; Middleman et al. 1995), suicidal ideation (Miller et al. 2002), carrying a gun (Elliot et al. 2007; Middleman et al. 1995) and sexual risk taking (Holmberg and Berg-Kelly 2002; Middleman et al. 1995; Midgley et al. 2000; Miller et al. 2002). Immigrant status has also been associated with use of AAS (Kindlundh et al. 1999; Nilsson et al. 2004a).

In one study, the use of AAS was examined among a group of patients who received care for drug dependence. 13 % admitted AAS use among all the patients, but in the subgroup of opioid dependent patients in the same study the prevalence was 25 % (Arvary and Pope 2000). Another study of U.S. college students revealed that 70% of recreational AAS-users met the criteria for a DSM IV alcohol use disorder (McCabe et al. 2007).

The temporal relationship of AAS to use of other drugs in Arvary and Pope's study suggested that AAS may serve as a gateway to use of other illicit drugs. Kanayama (Kanayama et al. 2003) also proposes that former use of AAS needs to be assessed in substance abusers in order to fully comprehend a persons abuse history. Another interesting study presents three cases of nalbuphine (an opioid analgesic) dependence in users of AAS, and reports that users of AAS claim that nalbuphine is very common in gymnasiums (Wines et al. 1999).

The use of AAS has also been suggested to cause symptoms of abuse and dependence according to the DSM IV criteria and elsewhere (Arvary and Pope 2000; Brower et al. 1989a; Corcoran and Longo 1992; Wood 2008). In one study as many as 48 % of users exhibited such symptoms (Copeland et al., 1999) and in another study 21% of the group of AAS-users who were treated for other forms of drug dependence reported a history of dependence of AAS (Kanayama et al. 2003).

However, the exact mechanisms by which the symptoms of abuse or dependence appear, or the temporal influence of AAS in a generalized substance abuse syndrome, are not fully understood. AAS are, like other drugs of abuse, likely to influence the sensitivity of brain reward systems such as dopaminergic pathways in the mesocorticolimbic and venterotegmental areas (Clark et al. 2006; Kindlundh et al. 2001). Animal experiments have demonstrated conditioned place preference and self-administration of AAS, thus further strengthening the possibility of a psychoactive effect, especially when animals are exposed to injectable AAS (Ballard and Wood 2005; Wood 2008).

There is some evidence that AAS, Stanozolol in particular, interact with benzodiazepine receptors in the brain (Masonis and McCarthy 1996), thus possibly rendering the same anxiolytic but also withdrawal symptoms as

benzodiazepines. Other theories imply that AAS modulate endogenous opiate receptors in the central nervous system, making the brain more sensitive to subsequent opiate administration as well as predisposing for withdrawal symptoms (Célérier et al. 2003), though another study contradicts these results (Negus et al, 2001). An animal study has shown that rats pretreated with AAS have an enhanced intake of alcohol and altered levels of endogenous opioids compared to controls (Johansson et al. 2000). It has also been established that the GABA_A-receptor of the brain, is acutely affected by androgens due to an allosteric binding of androgens to the receptor, thus influencing this important inhibitory receptor (Bitran et al. 1996; Bitran et al. 1993; Jorge-Rivera et al. 2000; Yang et al. 2002), contributing to the psychoactive potential of AAS. Also, testosterone enhanced cocaine-induced hyperactivity in animals (Martinez-Sanchis et al. 2002).

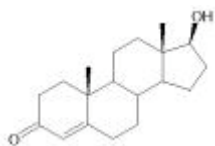
Additionally, animal experiments have shown that AAS also can induce gene-transcription alterations of other receptors in the rat brain than the androgen receptor, like the dopamine receptors of the nucleus accumbens (NA) (Kindlundh et al. 2003b) possibly contributing to the brain rewarding aspects of AAS use that may lead to abuse, and actual dopamine levels have been demonstrated to increase after chronic administration of supraphysiological doses of Nandrolone decanoate (Kurling et al. 2005); however, another study saw no alterations in actual dopamine levels after chronic administration of testosterone (Triemstra et al. 2008). A higher density of dopamine transporters have been demonstrated in the rat brain after chronic administration with Nandrolone (Kindlundh et al. 2004).

Statistics from Swedish police and Swedish customs imply that the use of AAS has increased since the mid 1990s. Unlike other countries such as Germany (Striegel et al. 2006), physicians are implicated in very few prescriptions of AAS for illicit use in Sweden (Gunnar Hermansson, personal communication), and further, users of AAS show little trust in the skills or opinions on AAS by physicians (Pope et al. 2004). In 1993, "Dopingjouren" (a telephone help-line for AAS users and their relatives) was established in connection to the Doping Laboratory at Huddinge Hospital in Stockholm, and this facility has also noticed an increase in AAS-users (Eklof et al. 2003).

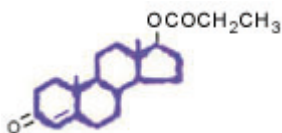
Chemical structure of AAS

AAS are synthetic derivatives of testosterone, the steroid hormone that endogenously is biosynthesized from cholesterol in the adrenal and gonadal/placental glands. Testosterone is a four-ringed compound with 19 carbon atoms. Testosterone is transported in blood bound to the sex-steroid-binding globulin and is rapidly metabolized by the liver if given orally.

There are approximately 60 different AAS identified today, and they can roughly be divided into three categories:

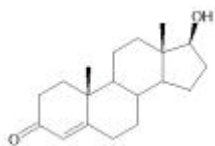


Testosterone

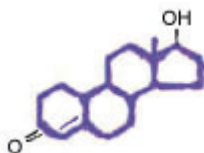


Testosterone propionate

A. **Testosterone esters** such as testosterone propionate and testosterone cyprionate. They are esterified at the 17th carbon and as such highly solvable in lipids. They are administered by intramuscular injection and are often subject to aromatization to estradiol in the body, an oestrogen metabolite often implicated in many of the side effects of AAS, or by 5 α -reductas to dihydrotestosterone (DHT), a metabolite with higher activity at the androgen receptor than testosterone itself.

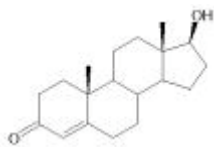


Testosterone

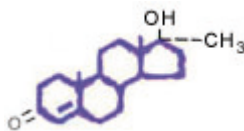


Nandrolone

B. **19-nortestosterone AAS**, that have a modified ring structure and includes the widely used Nandrolone decanoate. These steroids are injected intramuscularly and subject to aromatization to estradiol, but are not metabolized to DHT. Nandrolone have a higher affinity for the androgen receptor than testosterone, but less than DHT.



Testosterone



Methandienone

C. **17- α alkyated AAS**, including Stanozolol (“winstrol”) and Metandienone (“ryssfemmor”). The alkylation decreases hepatic metabolism and are thus orally active. These steroids do not seem to be converted to estradiol or DHT in the body.

Mechanism of action

The effects of AAS are mediated by binding to the androgen receptor (AR). This receptor is a protein consisting of approximately 919 amino acids. The androgen receptor is expressed in many areas of the brain (forebrain, mid-brain, lower brainstem, ventromedial hypothalamus) and in the presence of androgens the receptor is upregulated in these areas, as well as in areas that normally do not express substantial amounts of androgen receptors. One such non-classical androgen-receptor area is the ventral tegmental area (VTA), which is implicated in the patterns of addictive behaviour.

The main effects of all steroid receptors are exerted in the nucleus of the cell, where the receptor/ligand-complex binds to strands of DNA and bring about changes in gene transcription such as enhanced muscle protein synthesis and inhibition of the catabolic effects of stress hormones. These changes take hours to days to accomplish (Choong et al.).

There is however data suggesting that AAS also bind to allosteric binding sites on the GABA_A-receptors of the brain, causing a more acute response to AAS, which may explain the sense of well-being that some users experience acutely. Changes in membrane fluidity are likely to bring about some of these acute changes as well (Clark, 2003).

Additionally, animal experiments have shown that AAS also can induce gene-transcription alterations of other receptors in the rat brain than the androgen receptor, like the dopamine receptors of the nucleus accumbens (NA), possibly contributing to the brain rewarding aspects of AAS use that may lead to abuse (Kindlundh et al. 2003b). In a similar fashion, serotonin receptors as well as serotonin levels and 5-hydroxytryptophan (5-HT) me-

tabolism in the brain have been shown to be altered (lower levels of serotonin and receptor density, higher turnover of 5-HT) after AAS-administration in rats, suggesting a mechanism whereby the commonly reported depressions after prolonged use of AAS may be explained (Kindlundh et al. 2003a; Lindqvist et al. 2002; Ricci et al. 2006; Thiblin et al. 1999a).

Patterns of use

AAS may be administered by injection (most often intramuscularly) for a slow release from tissues and to avoid first pass liver metabolism. The compounds used by injection are the testosterone esters and the 19-nortestosterone AAS. AAS may also be taken orally, which requires that the compound has been alkylated at the 17 α -carbon, thus reducing hepatic metabolism. Even with these modifications, orally administered AAS are cleared more quickly from the body. The orally active AAS are more hepatotoxic than other AAS. Substances produced for sublingual, nasal and cutaneous (Wollina et al. 2007) administration have been developed.

The illicit use of AAS for non-medical purposes differs from therapeutic use in many aspects. The doses that are employed are much higher (6 - 100 times that of therapeutic use). Also, several compounds are often used simultaneously in a pattern that is known as *stacking* (Hall 2005; Trenton and Currier 2005). This pattern of use is thought by users to diminish androgenic side effects that one compound may cause in large doses. Another method supposed to diminish side effects is *pyramiding*, i.e. starting with a low dose and gradually increasing the dose during the cycle. The use of AAS is commonly sustained in patterns of *cycling* (Hall 2005), where the user alternates between periods of AAS use, heavy training combined with a strict dietary regimen and periods of AAS abstinence. One common pattern of use for beginners is called the 10/30, and means that the users take 10 mg of Metandienone orally daily for thirty days.

Screening for AAS

Screening for AAS is performed on urine by mass spectrophotometry (Hatton and Catlin 1987). Huddinge Doping Laboratory was established in 1985 and performs all AAS-tests on living individuals in Sweden. Additionally, the forensic chemistry laboratory in Linköping performs AAS-tests on deceased individuals in connection with forensic autopsy, if the forensic pathologist requires this. In cases where there is no urine present on autopsy, it is possible, though costly, to perform hair analyses (Hold et al. 1999),

though single doses of AAS may not be detected through hair analysis (Segura et al. 2000).

Side effects

Users of AAS use supratherepautical doses of AAS (Alen and Hakkinen 1985; Alen et al. 1984; Froehner et al. 1999; Karila et al. 2003), and the possibility of performing controlled human studies are thus limited for obvious ethical reasons. However, case reports, a few controlled studies (Table 1), retrospective studies, self-administration studies, cross sectional studies on AAS using populations, e.g. body builders, and animal experimental data have given a lucid picture of the side effects associated with use of AAS.

1. Overdose potential

There is no classical “overdose” associated with use of AAS, even though one rodent study resulted in the death of 10 % of mice when allowed self administration and controlled intermittent doses of AAS. However, none of these deaths occurred acutely in connection with administration of AAS, though the deaths *were* related to the levels of AAS detected post-mortem. Unfortunately, there is no account for the *nature* of the rodent deaths (Peters and Wood 2005). Therefore one can still conclude that long-term changes in the cardiovascular system, reproductive system or the liver as well as development of behavioural disorders may cause morbidity and mortality in AAS users.

2. Physical side effects

Users of AAS may exhibit a wide variety of physical stigmas after commencing use. The most commonly occurring side effects are striae (stretch marks in the anterior shoulder-chest region) or linear keloids (Scott et al. 1994), male pattern baldness, acne (Kiralý et al. 1987; Melnik et al. 2007), gynecomastia (Pope and Katz 1994), muscular hypertrophy, hyperlididemia (Cohen et al. 1996; Hurley et al. 1984; Pope and Katz 1994; Webb et al. 1984) and testicular atrophy (Alen and Hakkinen 1985; Boyadjiev et al. 2000; Pope and Katz 1994).

In adulthood, endogenous testosterone is necessary to maintain spermatogenesis (and thus male fertility). Exogenously administered AAS inhibits the release of GnRH and subsequent release of LH from the anterior pituitary, thus inhibiting endogenous testosterone production in the Leydig cells of the testes (Dohle et al. 2003), which may cause impotence and infertility (Boyadjiev et al. 2000; Daly et al. 2003; Dohle et al. 2003; Gazvani et al. 1997; Moss et al. 1993). Users of AAS often try to stimulate endogenous testosterone production by self-medication with human Coronic Gonadotrophic Hormone. At least one human study confirms that hCGH does increase endogenous testosterone production (Martikainen et al. 1986). Even in the

absence of stimulatory pharmacological agents, suppressed spermatogenesis seems to be reversible when AAS-use is ceased, but exceptions are described (van Breda et al. 2003). Some studies suggest that altered spermatozoa are caused by AAS; one study noted normal sperm in only 17% of AAS users (Torres-Calleja et al. 2001) and another study presents the possibility of altered meiotic segregation after recovery (Moretti et al. 2007).

Closure of the epiphyses of the long bones is stimulated by testosterone and its derivatives, leading to stunted stature if distributed to prepubescent boys or girls.

The tendons of the muscles are not susceptible to the effects of AAS, which sometimes causes ruptures of tendons since they are not adapted to the large muscular mass developed (Visuri and Lindholm 1994).

Less common, but often more serious, side effects include abscesses at injection sites (Al-Ismael et al. 2002; Rich et al. 1999b), viral infections due to unsafe injection techniques (needle sharing) (Bolding et al. 1999; Rich et al. 1999a), rhabdomyolysis (Adamson et al. 2005; Braseth et al. 2001), cardiovascular events such as ventricular hypertrophy (D'Andrea et al. 2007), dilated cardiomyopathy (Ferrera et al. 1997), acute myocardial ischemia (AMI) (Fineschi et al. 2001; Fineschi et al. 2007; Halvorsen et al. 2004; Huie 1994; Santamarina et al. 2008a), CVL (Akhter et al. 1994; Frankle et al. 1988; Santamarina et al. 2008b) myocardial morphologic changes (Di Bello et al. 1999), disturbances of blood coagulation (Ferenchick et al. 1992; Graham et al. 2006; Kahn et al. 2006), vessel dilation (Ebenbichler et al. 2001), thrombosis (Alvarado et al. 2001), pulmonary embolism (Liljeqvist et al. 2008) and increased blood pressure (Grace et al. 2003), all of which may cause premature death. For a review of the cardiovascular effects of AAS see (Melchert and Welder 1995). Some cardiovascular changes, i.e. left ventricular hypertrophy seem to remain after cessation of use of AAS (Urhausen et al. 2004). There are, however, human studies that are inconclusive regarding the cardiotoxic effect of AAS (Hartgens et al. 2003), and one other study noted that three months after cessation of AAS use, no cardiovascular changes were found (Hartgens et al. 1996). One study concluded that both hepatic and cardiovascular markers were reversible in two HIV-positive men who used AAS illicitly (Abra and Lonergan 2006).

Peliosis hepatitis (blood filled cysts of the liver), which may lead to rupture of the liver (Bagia et al. 2000; Carrasco et al. 1985; Hernandez-Nieto et al. 1977) has been reported (1975) as well as other hepatotoxic reactions (Daneshmend and Bradfield 1979; Falk et al. 1979; Ishak and Zimmerman 1987; Johnson et al. 1972; Kafrouni et al. 2007) and acute pancreatitis (Balasch et al. 1994). Thyroid impairment has been observed (Alen et al. 1987; Deyssig and Weissel 1993) as have disturbances of sleep pattern (Bahrke et al. 1992; Venancio et al. 2008). One case of intratesticular leiomyosarcoma is described (Froehner et al. 1999).

Excessive use of AAS leads to increased levels of oestradiol in the body (Hartgens and Kuipers 2004), which may contribute to many of the side effects. Endogenously, estrogens (oestradiol being the most potent, oestrone and oestriol less so) are implicated in salt and water retention and increased

levels of triglycerides, though HDL is simultaneously raised. Blood coagulability is increased by estrogens. In males, estrogens additionally induce feminization - gynecomastia (“bitch tits”) (Visuri and Lindholm 1994) is one of the more noteworthy side effects in AAS users. Users of AAS often self-medicate with anti-oestrogen such as Tamoxifen and Clomiphene to diminish side effects caused by aromatization of AAS to oestradiol (Handelsman 2008).

All of these side effects are accounted for in the literature, yet AAS continues to be used. This may be because of poor knowledge of the risks associated with AAS (Anshel and Russell 1997), or it may be a deliberate risk-taking depending on personality profile, environmental and social factors (Chittester 2007).

3. Psychiatric side effects

The controlled studies on psychiatric effects of AAS are accounted for in Table 1. As mentioned before, doses are most often not nearly as high as those used “on the street” (or rather, “in the gyms”), which debilitates the interpretation of the findings.

When first initiating use of AAS, it is often reported that users feel vigorous (Humbert 1990), energetic, enthusiastic, potent and self-confident (Bahrke et al. 1992). Hypomania and increased aggression and irritability (Bahrke et al. 1992; Midgley et al. 2001) may also appear during use. One study has shown that 2 out of 20 volunteers in a study of the effects on mood by suprathreshold doses of testosterone developed manic or hypomanic episodes according to DSM III criteria in two weeks (Daly et al. 2003). One-dose administration of AAS seems however to be devoid of psychoactive effects (Fingerhood et al. 1997).

As the endogenous production of testosterone wanes, and as neurobiological changes take place, more adverse effects are appearing. Loss of impulse control (Galligani et al. 1996), aggression (Galligani et al. 1996; Wilson-Fearon and Parrott 1999), hostility (Choi et al. 1990; Galligani et al. 1996; Humbert 1990; Pagonis et al. 2006b), dependence of AAS (Brower 2002; Brower et al. 1989a; Brower et al. 1991), depression (Perry et al. 1990), exacerbation of tics (Leckman and Scahill 1990), psychosis (Teuber et al. 2003a), mood disorders (Bond et al. 1995; Papazisis et al. 2007; Perry et al. 1990; Pope and Katz 1994), Cluster B personality disorder (Boydjiev et al. 2000; Cooper et al. 1996; Perry et al. 2003; Porcerelli and Sandler 1995), mania or hypomania (Peet and Peters 1995; Pope and Katz 1994), paranoia (Teuber et al. 2003a; Teuber et al. 2003b), sexual molestation of children (Driessen et al. 1996), domestic violence (Choi and Pope 1994), acute onset of a schizophrenic episode (Annitto and Layman 1980) and even homicide (Kleinman 1990; Pope et al. 1996) have been described. There are other researchers who suggest that although AAS invariably is a component in compulsive weight training, it is a form of manic behaviour sustained rather than caused by AAS (Tereshchenko 2007).

However, there is little research on the temporal relationship between for example cluster B personality disorder and the onset of use of AAS. One study notes, however, that users of AAS whose personality profiles were assessed retrospectively to illuminate the effect of AAS on personality traits, concluded that the onset of use of AAS significantly increased the likelihood of being diagnosed with a personality disorder (Cooper et al. 1996).

Individual vulnerability seems to play a large part in who develops these side effects (as well as some of the physical side effects), but who exhibits this vulnerability is virtually impossible to predict. The dosage and severity of AAS-use have been implicated in psychiatric side effects (Choi et al. 1990; Pagonis et al. 2006a).

The cessation of AAS-use is associated with development of depression (Allnutt and Chaimowitz 1994; Brower et al. 1990; Cowan 1994) and anxiety, and suicide may occur (Brower et al. 1989b; Thiblin et al. 1999b). Addiction to AAS has been described as early as 1964 (Kelly 1964; Kelly 1965) and as defined by the DSM III and DSM IV, and treatment has been suggested (Brower et al. 1989a; Corcoran and Longo 1992; Medras and Tworowska 2001). Also, AAS have been suggested as a gate-way to abuse of other drugs (Arvary and Pope 2000), though it is yet to discern whether this is caused by the neurobiological alterations that AAS induce, or if certain personality types are attracted to AAS. Most likely, combinations of both factors are involved. Also, the concomitant use of other drugs with AAS often limits the conclusion that can be made about the effects of AAS on the human psyche.

Table 1. Controlled studies on the psychiatric effects of AAS in human subjects

<u>Reference</u>	<u>Parameters examined</u>	<u>Study design</u>	<u>Study group(s)</u>	<u>Control group(s)</u>	<u>Methodology</u>	<u>Findings</u>
Perry P et al., 2003	Effects of AAS on aggression and mood changes	Cross-sectional exposed/non-exposed study	Male weightlifters admitting to current use of AAS (n=10)	Male weightlifters not using AAS (n=18)	<p><i>Personality inventories:</i> --</p> <ul style="list-style-type: none"> -Buss-Durkee Hostility Inventory (BDHI) -Point Subtraction Aggression Paradigm (PSAP) -Hamilton Rating Scale of Depression (HAM-D) -Modified Mania Rating Scale (MMRS) -Personality Disorder Questionnaire (PDQ) <p><i>Blood parameters:</i> total, free and weakly bound testosterone</p>	Enhanced aggression (as assessed by BDHI and PSAP) among the AAS users was correlated with attenuated concentrations of endogenous testosterone.. The AAS users also demonstrated Cluster B personality disorder traits for antisocial, borderline and histrionic personality disorder.
Tricker R et al., 1989	Effects of supra-physiological doses of testosterone on angry behavior in healthy eugonadal men	Double-blind, placebo-controlled study	43 healthy men (aged 19 randomly into 4 groups: placebo and did not receive testosterone per week) without received a placebo and (strength-training received TE and	-40 years) were divided Group 1 received exercise. Group 2 enanthate (TE; 600 mg exercise. Group 3 performed exercise times a week). Group 4 exercised.	<ul style="list-style-type: none"> -Mood inventory (MI) -Multi-Dimensional Anger Inventory (MAI) - Observer Mood Inventory (OMI) (completed by spouse) 	No significant differences or changes in MAI or OMI were observed within or between any of the groups.

Su T et al., 1993	Acute effects of anabolic steroids on mood and behavior	Double-blind, fixed-order, placebo-controlled crossover study	20 healthy male of age and without a psychiatric illness or abuse of AAS or other for consecutive 3-day (baseline), 40 mg methyl 240 mg methyl/testosterone placebo again.	volunteers 18-42 years history of previous or current substances were treated periods with a placebo testosterone per day and, finally,	The following personality inventories were applied: - Visual Analog Scale (VAS) of mood, behavioural and cognitive symptoms - the Beck Depression Inventory (BDI) - Spielberger State Trait Anxiety Inventory (STAI) state form - Brief Psychiatric Rating Scale (BPRS) - Hamilton Depression Rating Scale (HAM-D) - Mini-Mental State Examination (MMSE)	During high-dose administration of methyl testosterone, there were significant increases in symptom scores with respect to euphoria, energy, sexual arousal, irritability, mood swings, violent feelings, hostility, distractibility, forgetfulness and confusion. One subject developed an acute manic episode and another became hypomanic.
Porcerelli J.H. & Sandler, 1995	Effects of AAS on narcissism and empathy	Cross-sectional exposed/non-exposed study	Body-builders who admitted using AAS during the past year (n=16)	Bodybuilders who reportedly had never used AAS (n=20)	The Narcissistic Personality Inventory (NPI), together with clinical ratings of empathy	Steroid users demonstrated significantly lower ratings with respect to empathy and higher scores on the exploitativeness and exhibitionism factors of the NPI.

<p>Pope H et al., 2000</p>	<p>Effects of supra-physiological doses of testosterone on mood and aggression</p>	<p>Randomized, double-blind placebo-controlled crossover study</p>	<p>Participants were recruited from three groups (all 20-50 years of age): men with no history of weightlifting or AAS use; men with a history of weightlifting, but not of AAS use; and men who had formerly used AAS (total n=50). These subjects received testosterone in doses up to 600 mg/week for six weeks.</p>	<p>Matched individuals received a placebo for six weeks.</p>	<p>Young Mania Rating Scale (YMRS), Point Subtraction Aggression Paradigm (PSAP), the Aggression Questionnaire of Buss and Perry, Symptom Checklist-90-R and daily diaries of psychiatric symptoms kept by both the participants and their significant others</p>	<p>Testosterone-treated individuals had significantly higher manic scores as assessed by the YMRS, as well as on the basis of the daily diaries, in addition to significantly increased aggressive responses as assessed by the PSAP. Major interindividual variability in the effects of testosterone on mood and aggression were observed: 8 subjects were "responders" in this respect, whereas 42 were "non-responders". Responders and non-responders did not differ significantly with respect to their demographic and psychological characteristics or laboratory and physiological values</p>
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Daly R et al., 2001	Effects of methyltestosterone on the composition of the cerebrospinal fluid (CSF) and on behaviour	Randomized, double-blind placebo-controlled study	Healthy men 18-42 years of age (n=20) and with no history of psychiatric illness received methyltestosterone (40 mg/day for three days, followed by 240 mg/day for 3 days).	A similar group of men (n=20) were administered a placebo.	Levels of monoamine metabolites, neurohormones and neuropeptides in CSF were examined. Behavioural changes were assessed using a visual analogue scale (VAS).	Increased levels of 5-HIAA were present in the CSF following short-term administration of AAS. These increases were correlated with the development of VAS activation symptoms (i.e., diminished sleep time, increased energy, increased libido).
Daly R et al., 2003	Neuroendocrine and behavioural effects of high-doses of AAS	Randomized, double-blind, placebo-controlled study	Healthy men 18-42 years of age (n=20) and with no history of psychiatric illness received methyltestosterone (40 mg/day for three days, followed by 240 mg/day for 3 days).	A similar group of men (n=20) were administered a placebo.	Behavioural symptoms were rated using a visual analogue scale (VAS) and laboratory measurements of neuroendocrine parameters were performed.	The aggressiveness symptom-cluster assessed by the VAS was significantly increased during the high-dose phase of methyltestosterone administration compared to baseline. This increase was significantly correlated with increases in the level of FT4 and decreases in total testosterone, suggesting that the behavioural effects of AAS were secondary to changes in endogenous hormonal levels

Kouri E et al., 1995	Effects of supraphysiological and gradually increasing doses of testosterone on aggressive behaviour	Double-blind, randomized cross-over study	Healthy men 20 – 39 of whom lifted weights Three of these men had AAS use. These subjects to one of two regimens: testosterone cypionate increasing doses (from treatment, treatment treatment again; or treatment, injections of and then no treatment lasting six weeks.	years of age (n=8), five regularly, were studied. a previous history of were assigned randomly either injections of (TC) in gradually 150 – 600 mg/week), no with placebo, and no injection of placebo, no increasing doses of TC, again, with each period	Aggression was assessed using the Point Subtraction Aggression Paradigm (PSAP) and the Aggression Questionnaire. In addition, the Young Manic Rating Scale (MRS) was used to assess manic states.	Aggressive responses as assessed by the PSAP were significantly higher following testosterone administration in comparison to both the placebo and baseline periods. Furthermore, the scores on the Aggression Questionnaire were significantly higher after testosterone administration than during the baseline period. The MRS scores were also elevated following testosterone administration, although this change was not statistically significant.
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<p>Yates W et al., 1999</p>	<p>Psychosexual effects of testosterone</p>	<p>Randomized, controlled, double-blind study</p>	<p>Healthy men 21 – 40 previous history of use or current illicit drug completed the study). injections were randomly assigned testosterone cypionate (mg).</p>	<p>years of age with no psychiatric illness, AAS use (n=42, 31 of whom Two weeks of placebo followed by three weekly doses of (TSC; 100, 250 or 500</p>	<p>Psychosexual effects were assessed using the Buss-Durkee Hostility Inventory (BDHI), Brief Psychiatric Rating Scale (BPRS), Modified Mania Rating Scale (MMRS) and Hamilton Depression Rating Scale (HDRS). In addition, the subjects kept a diary of sexual interest and frequency of orgasm.</p>	<p>Only minimal effects on mood and behaviour during the acute and withdrawal phases of TSC were observed in the subjects who completed the study. However, one individual was withdrawn from the study due to the development of an agitated and irritable mania-like syndrome. No effects on psychosexual function were observed.</p>
<p>Bagatell C et al., 1994</p>	<p>Metabolic and behavioural effects of exogenous testosterone</p>	<p>Longitudinal baseline – treatment -- follow-up study</p>	<p>After a three-month pre-menstrual period received 200 mg testosterone for 20 weeks and were followed-up for 4-6 months of recovery.</p>	<p>treatment period, 19 testosterone/week for 20 followed-up during 4-6</p>	<p>Self-reporting of sexual and aggressive behaviour</p>	<p>Only minimal effects of exogenous testosterone on behavioural parameters were noted.</p>

Anderson RA et al., 1992	Effects of supra-physiological levels of testosterone (used for male contraception) on sexual behaviour and mood	Single-blind, placebo-controlled study	31 healthy men were two groups, one of testosterone enanthate once weekly for 8 weeks (Group). The other group injections once weekly followed by 200 mg TE subsequent 4 weeks (Group).	divided randomly into which received 200 mg (TE) by i.m. injection (Testosterone Only received placebo for the first 4 weeks weekly for the, (Placebo/Testosterone	Various aspects of sexuality were assessed using questionnaires involving sexuality experience scales (SES) at the end of each 4-week period. In addition, sexual activity and mood states were recorded in dairies and employing self-rating scales.	The Placebo/Testosterone group demonstrated an increase in self-reported interest in sex during testosterone treatment, but not during treatment with the placebo. There was no evidence to suggest an alteration in any of the mood states examined, including those associated with aggression.
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Other perspectives

AAS and the media

The obsession with male muscular tone and the stamina and will power it implies has lingered throughout the popular culture and elite athletics of the 20th century. As Pope, Philips and Olivardia have shown in *The Adonis Complex* (2000), popular culture such as the toy industry has adopted a muscular ideal that is virtually impossible to obtain through weight lifting alone.

This muscular ideal has, not surprisingly, led to psychological conflicts between what is perceived as the ideal body and boys' and men's actual bodies, which is illustrated by a number of studies that conclude that male concern and malcontent with their bodies has increased in the latter decade (Cafri et al. 2006; Labre 2002; Peters and Phelps 2001; Stout and Frame 2004; Wooten 2007). In Wooten's words "the images produced and circulated by media become an idealized standard of behaviour and body type by which consumers should live their lives". Description of severe body dissatisfaction in body builders have been published earlier (Blouin and Goldfield 1995).

Pope et al suggests that there is a "reversed" form of anorexia in some AAS-user, and have coined the term Muscle Dysmorphia (MD) to describe this condition, where a person no longer is able to see how muscular they are, but instead feel that they are inappropriately thin and amuscular (Blouin and Goldfield 1995; Kanayama et al. 2006). This condition is likely to share mechanisms with both *anorexia nervosa* and body dysmorphic disorder (BDD) as defined by the DSM IV (Pope et al, 1997, (Wroblewska 1997).

Adverse childhood experiences

Some studies implicate a "revenge"-motivation for using AAS. Klein suggests, after qualitatively studying body builders, in his ethnography *Little Big Men*, that "men who seek to overcome personal inadequacy, vulnerability, and insecurity by increasing body size and refining musculature" construe the major part of body builders (Boddy, 1993). One consistent finding from survey studies of users of AAS is in deed that low self-esteem to some extent is a predictor of use of AAS (Chittester 2007; Kindlundh et al. 1999; Rash 2004). Skårberg and Engström recently found that users of AAS had experienced abuse in childhood more often than controls (Skarberg and Engstrom 2007) as did Meilman (Meilman et al. 1995).

The consequences of adverse childhood experiences (ACEs) have been studied thoroughly from many perspectives. Schilling et al. (2007) found in a prospective study of high school seniors that ACEs were linked to adverse mental effects (depression, drug abuse and antisocial behaviour) in both men and women. However, early antisocial behaviour was more strongly associ-

ated with ACEs in males. Anda et al. studied 17337 adult HMO members and found high risks of developing psychiatric morbidity after ACEs, including sexual, substance abuse and aggression-related disorders. Physical abuse in childhood was directly linked to adult antisocial personality disorder in a study by Bernstein et al. (Bernstein et al. 1998). Numerous studies point to an association between ACEs and both adult substance abuse (Bennett and Kemper 1994; Brems and Namyniuk 2002; Downs and Harrison 1998; Duncan et al. 1996; Lo and Cheng 2007; Makhija 2007; Min et al. 2007; Trifflerman et al. 1995; Westermeyer et al. 2001) and adulthood psychopathology and/or violent behaviour (Cuomo et al. 2008; Duncan et al. 1996; Evren and Evren 2006; Evren et al. 2006; Hill et al. 2000; Makhija 2007).

Experimental studies have suggested possible neurobiological alterations after ACEs. There is for example solid evidence that early life stress induces long-lived hyperreactivity of corticotropin-releasing factor (CRF) which alters the brain's transmitter system chronically (Heim and Nemeroff 2001).

However, there are studies that reversely imply that adult substance abuse is preceded by childhood or adolescent psychopathology, with or without ACEs (Haehsy et al. 2002; King et al. 2004; Ohannessian et al. 1995; Tarter et al. 1995) which must be kept in mind when interpreting findings related to ACEs.

Criminology

One must not forget that use of AAS is criminalized in most countries. Thus, the AAS user transgresses the accepted norms of society and enters a criminal subculture like all other drug users, possibly and paradoxically to achieve the chiselled body of today's media *norm*. One observational study of Australian AAS users concluded that "while the use of anabolic steroids did not define the [whole] subculture the act of purchasing and using an illegal substance acted as a bonding agent" (Maycock and Howat 2007), thereby securing the exclusivity and subversive nature of dealing with AAS. Maycock and Howat (2005) have also investigated the barriers and rationales used to enter this illegal world in connection with AAS. They included coping with potential stigma, gathering of credible information, and developing the skill to administer the drug (and having access to a supply source). Thus, the barriers to using AAS were different than the barriers to using other drugs in some aspects; gathering of information seems not to be a factor in the initiation of other drug use; however, there seem to be similarities in the initiation of use in that it is a social, group-defining event often initiated by others who provide the supply (Kermode et al. 2007; Nyamathi et al. 1999) and in an environment (in this case gyms) where exposure to the drug is frequent (Segal 1991; Sherman et al. 2005; Sherman et al. 2008; Stenbacka 1990).

AAS use may also be an *instrument* in criminality, described to be consumed prior to criminal activities or to maintain an impressive stature in a hypermasculinized, criminality-laden lifestyle as described in Norwegian newspaper Aftenposten (Hoberman, 2005).

Criminology (defined as the social-psychology of criminal behaviour) may offer some explanations as to *why* a person chooses this life-style instead of the life-style that is generally accepted as societal standard. It is, however, beyond the scope of this thesis to account for all theories of criminology that might apply to the motives to or maintenance of AAS-use. Just a brief account for the major theories of criminology will be presented here. The more speculative theories of the 19th and 20th century will not be accounted for.

The Chicago school of social theory, i.e. *strain theory*, is based on Robert Merton's theories on anomie and strain (though anomie is a term coined by Emile Durkheim in 1897 to describe societal chaos and/or an individual's feelings of alienation when individual achievement and self-perception differs from that of general society). The theory, here presented immensely simplified, which has inspired several of the latter theories in criminology, emphasizes the feeling of belonging a person senses when leading a lifestyle that is in accordance with a lifestyle that is presented as the normative one. When one is devoid of this sense of belonging, such as when living in an impoverished area or when psycho-socially challenged to obtain this sense of belonging, a person is more likely to commit crimes in order to obtain this status that one feels entitled to. Thus, the discrepancy between "middle class" values and the realities of certain subpopulations enables criminal activities. In the case of the AAS user, findings of an association between for example immigrant status (Kindlundh et al. 1999) and the low societal status it implies through invisible racist structures, may motivate a person to use AAS in order to receive the "respect" one feels entitled to but does not think one can achieve through legal means (education, work, salaries, administrative power) (Sarnecky, 2003).

One theory that developed within the Chicago school by George Herbert Mead is *symbolic interactionism* (a term that was actually coined by latter scholar Herbert Blumer). The basis for the theory is the notion that a person develops psycho-socially through symbolic interaction with other persons. Through their reactions to our persons, we create a picture of our selves that we thus sustain through acting as expected. A person that has been hyperactive or showing signs of conduct disorder in childhood (and therefore met by adult dismay) may this way view him or her self in adulthood as essentially "bad" and subconsciously or consciously maintaining this non-conformist attitude (Sarnecky, 2003).

Strain theory is in essence similar to *conflict theory*, represented by Marxist Thorsten Sellin, where the subpopulation that does not achieve societal standard is defined as *the working class*. This theory is criticized since it does not account for "blue collar crime" or criminal activities in "respected" citizens (Sarnecky, 2003).

Differential association, as suggested by Sutherland, basically implies that because of an excess of definitions favorable to violation of law (in the case of the AAS-user this may be a narcissistic pleasure of accomplishing a body that is desirable to others, being rewarded by the jealous looks from other men or the perceived attractiveness to possible partners, or to gain a

sense of belonging within the subculture of AAS-users as described by Maycock and Howat (2007) over definitions unfavorable to violation of the law, crime is committed (Sarnecky, 2003). This suggests also that criminality is a *learned* behavior, where the offender initially is taught the criminal behavior by watching and interacting with a criminal subculture. Maycock and Howat's observations of the barriers to AAS-use implies that use of AAS in deed is commenced in an environment where "learning" to use AAS takes place through interactions with peers and gathering of knowledge. Critique has been raised since Sutherland does not include the influence on learned behavior by external factors such as television or advertisements. In the case of commencing use of AAS this exclusion is especially debilitating since the media picture of masculinity most likely influences the desire for a hypermasculinized body.

Queer theory

There is a growing body of literature in the liberal arts that emphasizes the "queer" nature of use of AAS; i.e. the body builder's focus on the body utilizing tools that previously were exclusively feminine; tanning beds, thongs, being the object rather than the spectator; and yet being paradoxically "hypermasculinised" in the unnatural muscular tone and the stamina it implies.

Even more complex is the interpretation of *female* body builders, where the post-modern notion of deconstruction is represented by the female body builder's refusal to oblige to the limitations of the biological sex (here, queer theory does not take into consideration Soviet girls and women who were more or less forced to use AAS in order to succeed in sports (Franke and Berendonk 1997).

Thus, queer theory challenges the generally accepted axiom that "sport symbolically conveys the notion that the natural and the social **construction** of men and women are determined by their bodies' respective biological, physiological and anatomical structures" (Beamish and Ritchie, 2005) and further implies that it is an illusion that "sports and its bodies are transparent, set apart from politics, culture and economy" (Cole, 1994). The axiom of sports set apart from the rest of society is best represented by a statement from WADA-president John Fahey: "Restore the True Spirit of Sports", he states in a filmed speech at WADA's homepage (<http://www.wada-ama.org/en/>).

Therefore, experimenting with AAS in both women and men can be seen as a possibility to transcend the biological sex, or to "deconstruct" the biological sex; the self then reconstructing a postmodern hybrid of what have been considered normative feminine and masculine traits. AAS becomes, in this line of reasoning, a *challenge* to a heteronormative society, in stead of a means to emphasize masculine traits that the natural sciences usually associate AAS with.

Yet another aspect associated with queer theory is the shift in the gay male ideal; from the softer, lankier man of the 1970s to the “buffed”, muscular ideal of today. This ideal is suggested to be linked to the mass media image of males (which applies to *all* males, not only homosexual men), but more interestingly related to the AIDS epidemic, since a well trained, well nourished body signals that one is healthy, with no sign of AIDS-associated wasting. The use of AAS in the gay community may very well be a result of the above mentioned reasoning, and is further strengthened by the fact that AAS is distributed to concur AIDS-induced wasting, thus normalizing the use of AAS in the gay community by the rationale that it is prescribed by physicians to friends and loved ones (Shernoff, 2002(Bolding et al. 2002)).

Still, however fascinating the theories of the liberal arts may be, they are not likely to be very helpful in a clinical setting; rather one is likely to provoke the actual “average” steroid user by implying he is trying to transgress masculinity in order to become “queer”.

Concluding remarks

The illegal and non-medical use of AAS is associated with a variety of physical side effects, most notably those concerning the cardio-vascular system, as well as psychiatric side effects, such as development of mood disorders. The use of AAS is no longer of concern only to the athletic community, since studies reveal that use of AAS is connected to abuse of other drugs and criminality as well as to body building and elite sports. The mechanisms whereby AAS cause the diverse array of primarily behavioural side effects are not fully elucidated but seem to involve an intrinsic system of neurobiological alterations, with the involvement of serotonin, dopamine, GABA and androgen receptors of the nervous system.

Aim of the thesis

The aim of this thesis is to investigate the relationship of use of AAS to abuse of other illicit or unprescribed substances, and how use of AAS in substance abusers may be connected to morbidity and premature death.

Materials and methods

Participants and settings

Paper I

In the first study, the social security numbers of all individuals tested for AAS at the Doping Laboratory, Huddinge University Hospital, Stockholm, Sweden between January 1, 1995 and December 31, 2001 were collected. Division into two groups according to positive test (n=248) or negative test (n=1199) was made and the groups were compared regarding morbidity and mortality. Comparisons were also made where individuals referred to the Doping Laboratory from substance abuse treatment clinics were omitted, in order to evaluate the importance of concomitant drug use in the diagnoses and causes of death.

Paper II

In the second study, comparisons were made between the 52 deceased individuals who had tested positive for AAS upon autopsy, and 68 deceased drug addicts who had tested negative for AAS upon autopsy. The AAS-positive individuals were divided into two subgroups on the basis of whether they tested positive for other *illegal* substances, thus excluding alcohol or prescription drug positive subjects, (AASpos-subst.pos, n= 31) or not (AASpos-subst.neg, n= 21). The AASpos-subst.neg group contained 11 individuals who tested negative for illegal drugs, alcohol and prescription drugs.

Paper III

In the third study, participants were derived from the unexpected finding in Paper I, of a highly elevated incidence of seizures NOS in users of AAS (11 individuals (4.4%) of the 248 AAS users compared to 1 individual (0.08%) in the 1199 individuals who had tested negatively for AAS. When compared

to the national registry of deaths, four of the 11 AAS positive subjects who had experienced seizures NOS were found to be deceased. Case vignettes are presented for the deceased individuals.

Paper IV

The fourth study was conducted in collaboration with an out-patient substance abuse clinic in Stockholm, Sweden. The clinic uses the Addiction Severity Index as an admittance interview, and this structured interview contains data on six different areas: general information, medical status, alcohol/drug use, employment/support, family/social relationships, legal status and psychiatric/psychological health. During the study period, all males below the age of 50 were asked about use of AAS. Those who responded that they had used AAS were given a survey on the motivation and nature of the use of AAS. 175 persons answered the ASI during the study period, and 20 persons (12%) admitted to AAS use. All obliged to participate in the survey on use of AAS. Comparisons were then made concerning all factors investigated in the ASI between those who responded that they had used AAS (n=20) and those who responded that they had not used AAS (n=155). The results of the survey on AAS use rendered an article of its own, i.e. Paper V.

Paper V

In the fifth study, the survey on the nature of the use of AAS that was distributed to the same patients as in Paper IV is accounted for. It thus includes data from those who responded that they had used AAS (n=20). The survey included questions on when the use was commenced, the temporal relationship to use of other drugs, motivation for use; self perceived effects and side effects, whether other drugs had been used to counter side effects from AAS and which AAS had been used. All who had admitted to AAS use during the ASI obliged to answer the survey.

Data from both the ASI and the AAS survey and how they are related is presented in the study.

Statistics

The statistical analyses of the papers included in this thesis demanding use of computer software were performed using the GraphPad in Stat® Version 3.05 (all papers), the Stat Soft's® Statistica Version 7 (Paper II) and the Statistical Analysis System (SAS) package, version 9.1 (SAS Institute Inc, Cary, NC) (Paper I and IV).

Paper I

The number of expected deaths was obtained from Statistics Sweden by multiplying the numbers of person-years at risk with the age, gender and calendar year-specific mortality rates.

The statistical comparisons between those who tested positively for AAS and those who tested negatively regarding proportions of diagnoses, referring institutions and SMRs were calculated by the Fischer's exact test. A value of probability less than 0.5 was considered significant. The data was also presented as Relative Risk (RR), and the 95% confidence intervals (CI) for the incidence of each diagnose, referring clinic and SMR (assuming a Poisson or approximation of normal distribution) were determined.

The statistical comparison of age distribution was employed by the Student's t-test.

Paper II

Differences in the continuous variables age and BMI in the four groups (AASposNarcpos, AASposNarcneg, AASnegAmphetaminepos and AASnegHeroinpos) were analyzed for statistical significance by one-way ANOVA followed by the Tukey-Kramer Multiple Comparisons Test. Tests for normality were prior conducted with the Komologorov-Smirnov test.

Differences in the continuous variables of drug concentrations were analyzed by Welch's t-test, since unequal variance was found when analysing the data with the Komologorov-Smirnov and *F*-tests.

Differences in categorical variables (presence of drugs and manner of death) were analyzed employing Fischer's exact test and a p-value <0.05 was considered significant.

Paper III

This letter to the editor is based on the statistical finding in Paper I where the Fischer's exact test revealed an elevated RR of 53.9 (95% CI = 7.0-

415.7) for convulsions NOS in those who had tested positive for AAS at the Doping Laboratory at Huddinge Hospital, Stockholm, Sweden compared to those who had tested negative.

Paper IV

Categorical variables were compared using Fischer's exact test. Continuous variables were checked for normality with the Kolmogorov-Smirnov test and subsequently analyzed by Students' *t*-test (with Welch's correction in the case of unequal standard deviations) or the Mann-Whitney *U* test, as appropriate. Since the age distributions in Paper IV were different for the AAS and Control groups, the ASI summary data, consisting of interviewers' ratings in 7 different problem areas, were analyzed for all ages by Students' *t* test and the Mann-Whitney *U* test, followed by an age-adjusted ANCOVA

Paper V

Categorical variables were analyzed with Fischer's Exact test. Continuous variables were checked for normality with the Kolmogorow-Smirnov test. If found to be normally distributed, they were analyzed further using Student's *t*-test (with Welch's correction in the case of unequal standard deviations). If the data were not normally distributed the Mann-Whitney test was applied. A *p*-value below 0.05 was considered significant.

Instruments

Paper I

In Paper I, the social security numbers of all patients (not connected to elite sports) tested at the Doping Laboratory in Stockholm, Sweden, were used to assess morbidity and mortality by comparing the social security numbers with the Swedish in-patient registry and. The diagnoses in the in-patient registry is submitted in the form of ICD diagnoses at the time of release from the hospital. The in-patient register has been in effect since 1987 and is assumed to cover 99% of all in-patient hospitalizations. In this study, “clusters” of diagnoses similar to each other are accounted for; injury to head and neck, other injury, personality disorder, psychotic disorder, depression, psychiatric disorder NOS including obsessive-compulsive disorder, autism/autism-like disorder, substance abuse, alcohol abuse, intoxications NOS, convulsions NOS, central thoracic pain and conditions without a clear diagnosis. The social security numbers were then processed through the Swedish official archive of causes of death. The deceased individuals found in the official archive of causes of death were then further compared to the National Forensic Board Registry of forensic post-mortem investigations. All of the deceased individuals were also found in the post-mortem investigation register.

The expected standardized mortality rate was calculated based on age-specific mortality data. The standardized mortality rate was then calculated using the SMR (exp)/SMR (actual) quota.

In order to investigate the effects of the referring institution to the Doping Laboratory (and thus, most obvious general problem area in life), SMRs were calculated for each referring institution, i.e. institutions concerned with substance abuse, psychiatric care, somatic care, doping unit, out-patient health centres, occupational health services, private health care, social services, military, customs and police.

Paper II

In the second paper, the National Forensic Board Registry of toxicological findings upon medico-legal autopsy was used to assemble the 52 users of AAS that comprised the study group. The control group was consecutively tested for AAS from regularly stored samples of urine if positive for either heroin (n=68) or amphetamine (n=21) upon autopsy.

The toxicological analyses (excluding the consecutive tests for AAS) were performed at the Department of Forensic Toxicology in Linköping, Sweden. Ethanol analysis and the analysis of approximately 150 pharmaceutical agents were done using gas chromatography. Illicit drugs were analyzed

using immunological techniques on urine. Positive findings from urine were verified by samples of blood. The study group was tested for AAS in urine in the Department of Forensic Toxicology. The consecutive tests for AAS in the control group were performed at the Doping Laboratory at Huddinge Hospital, Stockholm Sweden, from frozen urine samples stored for one year according to routine at the Department of Forensic Toxicology. The testing for AAS was employed by gas chromatographic-mass spectrometric (GC-MS) technique. Urine samples containing AAS are stable for several years.

Paper III

In the third paper, in the form of a letter to the editor, the finding of a much higher incidence of seizures NOS in users of AAS from Paper I is further investigated. The seizures NOS were identified as ICD-codes from the national in-patient register after the social security numbers of those tested for AAS at Huddinge Doping Laboratory had been compared to the register. The social security numbers of those who had been admitted for seizures NOS were then compared to the National Registry of causes of death, and finally to the National Forensic Board's register of deceased individuals. Thus, four of those treated for seizures NOS were found to be deceased, all of whom AAS-positive. The journals from the four patients were apprehended through requests to respective clinic when available, and case vignettes are presented from the journals and medico-legal autopsy protocol.

Study IV and V

In studies IV and V, the Addiction Severity Index (ASI) was used to assess the history of drug abuse among the participants. The ASI is a form for structured interviews, designed to provide diagnostic information on a client prior, during and after treatment for substance use-related problems. The ASI thoroughly covers six different areas of the patient's life: General information, medical status, alcohol/drug use, employment/support, family/social relationships, legal status and psychiatric/psychological status. All participants in both studies were asked whether they ever had used AAS and in paper V those who answered in affirmative were asked in more detail about this use, using an additional structured interview form. In paper IV, comparisons regarding different variables in the ASI were made between those who admitted to use of AAS and those who claimed never to have used AAS.

Main findings and comments

Paper I

Findings

The two study groups were compared regarding in-care hospitalization diagnoses and mortality rates. The two study groups were also compared to the general population regarding mortality rates.

Approximately half of the AAS-positive subjects were represented in the in-care patient archives, and approximately one third of the AAS-negative subjects.

AAS-positive subjects were statistically significant more likely to have been treated for obsessive-compulsive disorder, anxiety disorder and psychiatric disorder NOS, central thoracic pain, and most strikingly, for convulsions ($p=0.0001$, RR 53.9, 95% CI: 7 – 415.7)

Bordering on being statistically significant was having been diagnosed with a personality disorder ($p=0.05$, 95 % CI: 1.1-14.5).

The expected mortality rate among the AAS positive subjects was 0.63. However, 12 patients were found to have been deceased since the test was taken, thus rendering a standardized mortality rate (SMR) of 20.43. A high SMR was found irrespectively of which kind of clinic the patients had been referred from, but the highest SMR was found in those who had been tested in connection with treatment for substance abuse. In the AAS negative subjects the expected mortality rate was 3.7, but in fact 22 persons died after being tested, which results in an SMR of 6.02. In this group, referrals made from substance abuse clinics also rendered the highest SMR.

Thus, both groups had elevated SMRs, but the AAS-positive group's was more pronounced.

Manner of death in the AAS positive group was suicide ($n=3$), accident ($n=5$), undetermined unnatural death due to intoxication with pharmaceuticals (3), and one natural death (aspiration of gastric content following convulsions).

Manner of death in the AAS-negative cases was suicide ($n=9$), accident ($n=6$), undetermined unnatural death due to intoxication ($n=4$), homicide ($n=1$) and natural causes ($n=2$, myocarditis and unspecified cardiac failure). Manner of death did not differ statistically significant between the two groups.

Comments on the findings

Methodological considerations

The study basis consists of persons tested for AAS at the Swedish Doping Laboratory, and are divided into one study group (positive for AAS) and one control group (negative for AAS). This constitutes an obvious limitation, since they were likely to have been tested because of suspicions of AAS use.

The AAS positive and AAS negative (control) groups are thus likely to represent two very similar populations, which would be only an advantage if one assumes that a negative test equals no use of AAS. However, the cyclic nature of AAS use (as well as the possibility of using “false” AAS and the recently discovered enzymatic activity in approximately ten percent of the population that “masks” the presence of AAS (Schultze, JJ. et al, 2008), and the “snap shot” picture a test constitutes, increases the likelihood that several users of AAS are embedded among those who tested negative. Further, Klötz et al found that several of those that had tested negative for AAS at the doping laboratory in Stockholm had been convicted of crimes related to doping.

However, the two groups still differed significantly from each other regarding mortality and morbidity, and one may conclude that a positive test at the Doping Laboratory at least reflects a more frequent and compulsive use of AAS (i.e. not even the threat of AAS testing deters a person from using AAS).

The protocol study of the medico-legal death investigations, of Paper I is limited by the small number of individuals that are included in each group. Few comparisons between those who had tested negative and those who had tested positive have enough power to be conclusive, and no statistically significant findings were found in the protocol part. This may also mirror the similarity of the control group to the study group.

The finding of a highly elevated risk for having been treated for seizures NOS is likewise limited by the actual small number of persons this had affected, making possible that coincidence played a part in the finding. The wide CI (95% CI: 7 – 415.7) reflects this instability of the finding.

Interpretation of the findings

Even with the above mentioned limitations taken in consideration, the SMR (SMR 20.43); in AAS users was highly elevated compared to both controls and the general population further, this association remained no matter what type of institution the test had been initiated by. This suggests that users of AAS are highly at risk for premature death; the association is likely to be to some extent accounted for by concomitant use of other drugs, but this cannot explain this finding fully, since the SMR in the control group (a similar demographic group) was less pronounced (6.02).

The elevated SMR in the control group is likely to be the outcome of being tested for AAS only if exhibiting risk behaviour, connecting AAS to the use of other drugs and a troubled social history.

Paper II

Findings

This study is an autopsy study, comparing 52 subjects who tested positive for AAS in connection with medico-legal death examination with 68 deceased users of amphetamine (n=21) and/or heroin (n=47) who had been tested but found negative for AAS. A further subdivision of the AAS users into two groups was made: AAS-pos-narc-pos: i.e. AAS positive subjects who were also positive for *illegal* psychotropic substances and AAS-pos-narc-neg, i.e. AAS positive subjects who tested negative for *illegal* psychotropic substances but who may have tested positive for benzodiazepines or alcohol. Thus four groups were compared in this study.

A statistically significant difference in age distribution (age at the point of death) was found between the four groups. Both subgroups of AAS-users were significantly younger than users of amphetamine and heroin. Median age at death in the AAS-pos-narcpos group was 24 years and in the AAS-pos-narcneg group 25 years. Median age at death in the amphetamine group was 40 years, and in the heroin group 34 years.

Use of AAS was concomitant with use of other psychotropic substances in 79% of the cases. Use of illegal substances was present in 60% of the AAS cases (n=31, of which 18 mainly used opiates, 11 mainly used amphetamines, 1 used GHB and 1 THC). Most frequently, only one illegal drug was present at the time of death. Eleven individuals (21%) used no other substance than AAS at the time of death.

AAS users died statistically significant more often of intentional death (homicide or suicide) than heroin users and amphetamine users, even in the presence of other drugs.

The AAS-pos-narc-neg subjects exhibited significantly larger BMIs than the AAS-pos-narc-pos subjects according to post hoc tests, and both AAS-groups exhibited larger BMIs than both users of amphetamine and heroin.

Comments on the findings

Methodological considerations

Studies on a medico-legally autopsied group face several limitations, the most obvious being the selection of the material. Persons subjected to forensic autopsy are to begin with a selected group as such, since forensic autopsies are only performed in case of sudden, unexpected death or suspected unnatural death (homicide, suicide or accident). However, in the age category investigated here, Swedish legislation secures that virtually everyone who dies outside of a hospital setting (and in some cases, such deaths too, if they are the result of a prolonged in-care hospitalization due to uncertain circumstances or accidents) are medico-legally investigated.

It is also possible, even likely, that this selection of deceased AAS users is not representative of AAS users at all. In stead, they may comprise a group that is more susceptible to the side effects of AAS due to neurobiological or psychosocial factors. There may very well be a group of AAS users who never are subjected to neither testing for AAS, conviction of crimes related to AAS nor subjected to medico-legal autopsy. Different user internet-forums (such as www.flashback.se) where users of AAS give each other advice on cycling, stacking and purchase of AAS, suggest that this may be the case. However, those involved in such forums may be in a state of denial, or being in the midst of AAS use, not yet having experienced any side effects that would only appear after cessation of use or after prolonged use.

Then arises another problem; testing for AAS is only performed at the forensic pathologist's explicit request which unfortunately leads to "clusters" of testing for AAS where pathologists are more aware of or more interested in the relation of AAS to premature death. Testing for AAS is otherways only performed when there are statements in the police reports about AAS, or if the stigmata of AAS are obvious.

In addition, testing for AAS upon autopsy only gives us a "snap-shot" picture of a person's consumption of AAS (even if some AAS may remain in the body for months), and it is in the nature of AAS use to be intermittent. Therefore, even testing for AAS may probably not correctly mirror the actual use of AAS in a forensic population. This problem is illustrated by the fact that a few of the consecutively tested (and found negative for AAS) substance abusers exhibited obvious AAS stigmata, and the finding by Klötz et al that several of those that had tested negative for AAS at the doping laboratory in Stockholm had been convicted of crimes related to doping.

Another problem with the "snap-shot"-picture of a test for AAS is that it says nothing about the duration of use – it might have been one individuals first cycle (or even pill) and another one's fiftieth. The fact that the cause of deaths among those who were positive for AAS differed significantly from those who were not does however suggest that no matter where a person is situated in his (or her) use of AAS, AAS is associated with risk behaviour and a psychiatric morbidity that differs from that of other drug users. No causal relationship can be established from these findings, though.

All these limitations aside, it is likely that those positive for AAS upon autopsy were more frequent (and compulsive) users, thus gendering a higher chance of detection at the time of an autopsy. With AAS as the least common denominator, conclusions may be drawn from the groups of this study, and it is noteworthy that users of AAS *did* differ from the drug users in several ways, even when concomitant drug use was present at the time of death.

Interpretation of the findings

The main finding in this study was that AAS-positive individuals differed from a control group consisting of deceased drug users, even when concomitant substances in addition to AAS were detected (which they were in 79% of cases). Significant differences were detected regarding age (AAS-users were younger at the time of death), BMI (AAS-users displayed higher BMIs)

and, most strikingly, regarding cause of death; users of AAS died significantly more often from intentional death, i.e. suicide or homicide.

One interpretation of these results are that users of AAS who are medico-legally investigated constitute a sub-group of substance abusers; a subgroup who may be engaged in bodybuilding, but who mainly also lead a life-style and have a psychiatric history that differs from that of other substance abusers, i.e. putting themselves at a higher risk for being subjected to violence and suffering from depression, and at an earlier age.

The users of AAS who were negative for other substances exhibited higher BMIs than the substance positive AAS users, and their deaths were even more pronounced the result of intentional death. This could be interpreted as them having a higher involvement in body building, possibly because they are part of a subversive, sometimes criminal subculture that requires an impressive stature.

Thus, the findings in this study could be interpreted so that medico-legally investigated AAS users may represent two different groups of users; young men at risk for substance abuse and general psychosocial problems, and a group of men who use AAS mainly as a means to build their bodies in order to be affluent in a criminal subculture (putting them selves at risk for being the victims of homicide) and who build their bodies more obsessively and are susceptible to psychiatric side effects of AAS, possibly due to longer and higher dose regimens in their use.

Paper III

Findings

In Paper I, an overrepresentation of Convulsions NOS was detected. Eleven (4.4%) of the 248 AAS users and only one (0.08%) of the 1215 control subjects (1176 males, 39 females) (RR: 53.9) had suffered convulsions NOS during the study period. Further, four individuals who had suffered Convulsions NOS had died during the study period. Paper I presents the findings surrounding these four deaths (autopsy protocols, police reports, previous in-patient hospitalization charts).

Three of the four deceased individuals who had been diagnosed with convulsions NOS had previously obtained in-patient care for substance abuse-related and/or psychiatric illness, and they were positive for either pharmaceuticals or illegal drugs on autopsy. The fourth person had previously sought care for convulsions on three occasions, but the seizures were attributed to misuse of diuretics. This man was the only one who was tested for AAS on autopsy, and he was positive for Stanozolol and Nandrolone.

Cause of death was one suicide, one natural death and two undetermined deaths (it could not be determined whether the intoxications were intentional or accidental). The natural death was due to aspiration of gastric content in connection with a seizure.

Comments on the findings

Methodological considerations

The methodological limitations of this study have already been discussed in detail in Paper I. However, the relatively few actual *numbers* of individuals who had suffered Convulsions NOS does constitute a particular power problem in this study, since there is a risk that the findings are purely incidental. This must be kept in mind when interpreting this finding.

Also, in-patient charts were not possible to obtain in all cases due to hospital administrative policies. It is therefore possible that genuine epilepsy may wrongly have been categorized as Convulsions NOS in some cases. However, only one of the sufferers of Convulsions NOS had additionally been diagnosed with epilepsy in the in-patient register, which makes the influence of genuine epilepsy on the findings not very likely.

Interpretations of the findings

Given the somatic and psychiatric history of the deceased, it seems unlikely that AAS in themselves would have a pro-convulsive effect, even if there are studies that suggest that testosterone lowers the seizure threshold. Rather, the convulsions NOS were most likely related primarily to either abstinence following substance abuse or the use of doping agents other than AAS (i.e. diuretics or insulin). This supports earlier findings that use of AAS may be part of a mixed substance abuse

Paper IV

Findings

The use of illicit drugs was significantly more common in the AAS group, whereas abuse of alcohol was significantly underrepresented. In addition, 15 persons in the AAS Group (75%) used sedatives (predominantly benzodiazepines) either regularly or sporadically, compared to 17 (11%) persons in the control group.

The proportion of individuals that had been prosecuted of violent offences, crime against property, and crime against the law on illicit drugs in this study was significantly higher among the AAS-using individuals than in the control group

The number of individuals that sometime in life had experienced physical abuse was significantly higher among the AAS-using individuals. AAS-users were also more likely to be of immigrant origin and to exhibit suicidal ideation.

Comments on the findings

Methodological considerations

In this paper 175 male patients 50-years-old or younger were asked about use of AAS in connection with their admittance interview at a substance abuse centre. For practical reasons the study period was limited to two months. This ended up with a group of 20 subjects stating experience of AAS and 155 controls without AAS experience. The rather small number of AAS users resulted in weak statistical power. This problem was further complicated by the fact that the age distributions were different in the AAS-group compared with the 155 controls. For these reasons the findings of this paper have to be interpreted with caution.

Interpretations of the findings

The patients in the AAS group were significantly more often convicted of violent and drug offences. At the same time the AAS group significantly more often had drugs other than alcohol as their main drug of abuse, a finding that remained after controlling for age. Thus, it could be that the violence seen among the AAS users in this particular study to some degree was related to abuse of other substances than alcohol.

Another interesting finding was an overrepresentation of having been exposed to physical violence in the AAS group. In the discussion of the original paper the possible importance of so called Adverse Childhood Experiences (ACEs) for violence and drug abuse is discussed in some detail. In a recent Swedish study at another substance abuse centre similar findings were reported (Skarberg and Engstrom 2007). Thus, it could be that individuals who abuse both illicit drugs and doping agents more often are burdened by ACE:s than is usually the case even among drug addicts, which if so, may contribute to the relatively high degree of violent offences seen among AAS using drug addicts.

Paper V

Findings

In Paper IV, nineteen former and one current AAS-users (12%) were identified among 175 persons seeking out-patient care at an addiction treatment facility in Sweden. The twenty persons were given a survey on the nature of

their use of AAS. Based on this survey, the AAS-experienced users could be divided into two distinct groups; those who had used AAS for more than twelve months (n=10, all of whom actually had used AAS for more than 24 months); and those who had used AAS for less than twelve months (n=10). All subjects had completed at least one cycle. Abuse or addiction to substances other than alcohol was the main reason for seeking care in both groups.

The ten more experienced users were significantly younger when commencing their use of AAS, stated in two cases respectively that their motivation for use was to experience the psychoactive effects of AAS or in preparation for committing crime (compared to none among the less experienced users) and reported more side effects when ceasing the use of AAS (most strikingly, several cases of depression and sustained violent behaviour were reported). Two persons reported feeling addicted to AAS between cycles, whereas only one reported feeling addicted after complete cessation.

The ten less experienced users reported “curiosity” as motivation for use more often than the more experienced users.

Comments on the findings

The lifetime prevalence of AAS-use was, in accordance with other studies that link use of AAS to abuse of other substances, higher (12 %) than the prevalence reported in cross-sectional survey studies on non-selected populations, such as high school students. This finding further strengthens the link between use of AAS and substance abuse, and should encourage clinicians and counsellors working with substance abusers to assess previous AAS-use in a patient’s history.

Main drug of abuse was in most cases substances other than alcohol, further strengthening the association between use of AAS and a subculture of illegal drugs and risk-taking behaviour.

Long-term users of AAS reported motives for use that previously have been suspected clinically, but not described in the scientific literature, i.e. to experience the psycho-active effect of AAS and use in preparation for committing crime.

The long-term users also reported experiencing depression perceived to be related to ceasing use of AAS. This could imply both a dose-dependent and time-dependent factor in the development of psychiatric side effects; it could also imply that individuals more prone to experience positive effects of use of AAS (thus using them for long periods of time) also are more susceptible to the side effects of use.

Interpretation of findings

The main findings in this study (a higher prevalence of AAS use than in the general population, that long-term use is associated with withdrawal depression and motives for use were associated with psychoactive effects) should be interpreted cautiously since the actual number of subjects studied here is very small. This means that chance may play a large part in the results; how-

ever the fact that users reported psychoactive effects as motivation *at all* is remarkable, since these effects are subject to some debate. Here, actual users, though few, confirm that psychoactive effects can motivate use of AAS.

Adverse effects, especially after complete cessation of use of AAS, were reported frequently by long-term users. Sustained aggression and many cases of self-reported depression were two remarkable adverse effects in long-term users. As mentioned before, this must be interpreted cautiously because of the low number of actual individuals, but it is still possible to discern a pattern of adverse effects and long-term use. Assessment of previous or current use of AAS may thus be very helpful in obtaining a person's complete somatic and psychiatric history.

General discussion

The widely spread notion that AAS are a problem only in elite sports or in bodybuilders is challenged by a large body of literature that suggest that AAS in stead is strongly associated to high-risk behaviour, e.g. a solid connection to abuse of other substances. This thesis investigates this suggestion further, and also focuses on the morbidity and mortality of AAS-users and how it may be connected to other substance abuse.

The findings in Paper I (morbidity and mortality in users of AAS) suggests that users of AAS lead a risky life-style with a high risk for premature death compared both to the general population and to users of other drugs, even though drugs were involved in the majority of deaths in AAS-users. Also, users of AAS were at greater risk to have suffered convulsions NOS in connection with use of other drugs. Therefore, it should be reasonable to conclude that users of AAS may comprise a subgroup of substance abusers that exhibit a life-style burdened by a complicated psychiatric history, risk-taking behaviour such as involvement in criminal activities and mixed substance abuse. The importance of AAS in the deaths in Paper I is difficult to interpret, but it is possible that the elevated mortality due to intoxications and suicide are secondary to use of AAS.

Paper II further compares the deaths of users of AAS and users of other drugs. The most striking finding was that a majority of deceased AAS-users were young and positive for other psycho-active substances at the time of death, and that their deaths were more likely to be intentional. The finding in paper V that long-term users of AAS reported depression when ceasing to use AAS more frequently suggests that there may be a component of side effects of AAS in the self-inflicted deaths.

These findings further strengthens the possibility of AAS-use as a component in a mixed substance abuse, especially in young, destructive men. The finding that users of AAS are younger than other substance abusers

probably reflects the relative novelty of AAS as a drug of abuse, and therefore it is likely that the younger population of drug users is more prone to use AAS, suggesting an increasing problem with use of AAS in a generalized risk-taking life-style in the future.

Paper III seeks an explanation to the striking finding of a highly elevated risk for convulsions NOS in the cohort study of users of AAS even in comparison with substance abusers who do not use AAS. Once again, the use of other drugs than AAS is implicated in the finding, suggesting that use of other drugs is more severe and compulsive in users of AAS.

Papers IV and V investigate the prevalence, risk factors and self-reported motivation and side effects of AAS in a help seeking drug-using population. Users of AAS were more likely to be younger, of immigrant origin, to use benzodiazepines concomitantly with other drugs, to have experienced adverse childhood experiences, to abuse drugs other than alcohol and to have been convicted of violent or, logically, drug offences compared to non-AAS-using drug addicts. AAS-users reported a desire to become muscular as the most frequent motivation to use of AAS, though reports of use because of the psychoactive properties of AAS occurred also. Persistent violent behaviour and withdrawal depression were reported as side-effects. Taken together, the findings from Paper IV and V further supports the proposition of a subpopulation of younger drug users that also use AAS, and who are more likely to have a complicated psychiatric history and exhibit risk-taking behaviour such as violent crime.

Conclusion

This thesis has investigated the connection between use of AAS and use of other drugs; it has also focused on the morbidity and mortality in AAS-users. In conclusion, this thesis has supported previous studies that point towards the association of use of AAS mixed substance abuse. In addition, a risk behaviour “profile” can be extracted from the studies; users of AAS are likely to lead a life-style that include drugs, loss of impulse control, adverse psychiatric histories and exposure to self inflicted harm, homicide or injurious or lethal intoxication. This picture of the AAS user differs widely from the popular notion that users of AAS are performers of elite sports who are provided AAS by the controlled supervision of a physician.

Future perspectives

The findings in this thesis do support the previously noted association between use of AAS and use of other illicit or unprescribed substances and

other risk behaviours. With this in mind, it is important that clinicians working with substance abusers assess the full abuse history of the patient, especially the young, perhaps criminal, male abuser of several substances concomitantly (the proposed risk profile for use of AAS), since use of AAS may complicate the treatment with their substance specific side effects such as withdrawal depression or sustained loss of impulse control. Thus, effort should be spent on educating those working with patients in substance abuse care in order to reduce the influence of AAS-use in treatment for mixed substance abuse.

Some users of AAS develop symptoms of abuse and/or addiction to AAS. Currently, there is no consensus on how to treat these conditions. It is therefore urgent that treatment programs are developed, since there is no indication that use of AAS is going to decrease in the near future. The treatment programs need to be based on further research on the reversibility of the side effects of AAS, both physical and psychological. Hopefully, further study will elucidate how pharmacological treatment and counselling may increase the likelihood of reversibility of side effects of AAS.

It is also urgent that future research focuses on possibilities to *predict* who will develop physical and/or psychological side effects of AAS in order to target educational programs to those especially vulnerable to the side effects. This may include further retrospective studies of pre-use personality profiles, prospective cohort studies, for example in gym populations or cohorts of youth (though costly, they may reveal many interesting findings about the biological body and psychological profile of those who proceed to use AAS), neurobiological studies on several receptors (i.e. androgen, dopamine, serotonin and cortisol) and transmitter transporters that may be implicated in AAS-induced side effects and studies on physical and psychiatric parameters in self-administrating users. However, controlled double-blind placebo studies may not be very helpful, since the dose regimen for obvious reasons is nowhere close to that used outside a clinical setting.

Sammanfattning av delarbetena i avhandlingen *Characteristics and Consequences of Use of Anabolic Androgenic Steroids in Poly Substance Abuse*

Första delen i avhandlingen behandlar sjuklighet och dödlighet hos personer som testat positivt för anabola androgena steroider (AAS) i samband med öppen eller-slutenvård.

Studien är en kontrollerad retrospektiv registerstudie, publicerad i tidskriften *Drug and Alcohol Dependence*.

I studien jämfördes personer som testat positivt (n=248) med personer som testat negativt (n=1215) för AAS vid Huddinge dopinglaboratorium under 1995-2001. De som var negativa fick tjäna som kontrollgrupp, eftersom de sannolikt tillhör ett gemensamt patientmaterial. Personerna som testades hade remitterats från slutenvård och öppenvård (f f a missbruksrelaterad sådan), socialtjänst, militär, tull och polisen.

Alla testade behandlades i de svenska dödsorsaks och -slutenvårdsregistren.

Hälften av de som testat positivt för AAS och ungefär en tredjedel av de som testat negativt för AAS fanns registrerade i slutenvårdsregistret. AAS-positiva hade signifikant oftare behandlats för OCD, ångestsjukdom eller psykiatrisk sjukdom UNS, samt för drogberoende, centralbröstsmärta och konvulsioner UNS (RR 53.9 (sic!))

12 patienter hade avlidit sedan det positiva AAS-testet. Den förväntade dödligheten i denna grupp var 0.63 personer vilket gav en standardiserad mortalitetsratio (SMR) på ca 20 gentemot normalbefolkningen. Bland de som testat negativt för AAS hade 22 personer avlidit, vilket gav en SMR på ca 6. Dödssättet skiljde sig inte åt mellan de båda grupperna på något statistiskt signifikant sätt.

Andra studien i avhandlingen är en obduktionsstudie, där 52 personer som testat positivt för AAS vid dödsfallet jämfördes med 68 (47 heroinister, 21 amfetaminister) avlidna narkomaner, som testat negativt för AAS vid dödsfallet. Framför allt jämfördes toxikologiska fynd och döds sätt. AAS-gruppen delades även in i två subgrupper: de som var positiva för AAS **OCH** någon annan illegal eller receptförskrivna substans och de som var positiva för AAS men som inte hade någon illegal eller receptförskrivna substans i blod eller urin vid dödsfallet.

Statistiskt signifikanta fynd gjordes vad gäller ålder; AAS-positiva var signifikant yngre än narkomaner vid dödsfallet; BMI; AAS-positiva

hade högre BMI, i synnerhet de som inte varit positiva för någon annan drog vid dödsfallet; och AAS-gruppen dog i högre utsträckning i "avsiktlig död" (mord eller självmord) än de avlidna narkomanerna, där olycksfall ("överdos") dominerade.

Tredje studien är ett letter som publicerats i Journal of Clinical Psychopharmacology där det oväntade fyndet med konvulsioner UNS som var så slående överrepresenterat hos AAS-gruppen undersöks. Fyra av de 11 personer som diagnostiserats med konvulsioner UNS hade avlidit vid lettrets tillkomst. Deras sjukvårdshistoria och obduktionsprotokoll samt polisrapporter kring dödsfallet diskuteras. Tre av dödsfallen var intoxicationer (varav en ett suicid) och ett av dödsfallen bedömdes som orsakad av aspiration i samband med konvulsioner av okänd etiologi. Den samlade bedömningen i lettret blir att konvulsionerna snarare har att göra med ett avancerat blandmissbruk (och abstinens från detta) snarare än med AAS i sig själva. Diuretika och insulin föreslås som kramptröskelsänkande läkemedel som, förutom illegala droger och alkohol, används i samband med AAS.

Den fjärde studien är ett samarbete med Maria Beroendecentrum AB i Stockholm. De patienter som sökte öppenvård p g a beroendeproblematik (inklusionskriterier: män under 50 år) fick som tillägg till det välvaliderade Addiction Severity Index en direkt fråga om de någon gång använt AAS. De som svarade ja fick svara på en enkät med ett antal frågor om motiv, upplevda effekter/biverkningar samt debutålder och vilka olika AAS som använts.

I studie fyra jämförs dock svaren från ASI hos de som uppgivit användande av AAS (n=21, 12%; dock fick en person exkluderas avseende jämförelser med övriga då det konsekvens saknades ASI-data p g a personens paranoida beteende) med de som uppgivit att de aldrig använt AAS. De som använt AAS skiljde sig signifikant avseende ålder (yngre), huvuddrog (mindre ofta alkohol), tidigare självmordstankar (mer frekvent) samt utsatthet för våld tidigare i livet (oftare); de var också oftare åtalade för vålds- och narkotikabrott. Manuskriptet behandlas för närvarande av peer review vid tidskriften Addiction.

Den femte studien är en fortsättning på samarbetet med Maria Beroendecentrum AB. Även detta manuskript är insänt till tidskriften Addiction. I studie fem närstuderas svaren från enkäten som delades ut i studie fyra till de som uppgivit att de använt AAS någon gång i livet. Debutålder för AAS-bruk var i median 20 åå, och i median hade man använt AAS i sex månader (men det fanns en spridningsbredd mellan 1 till 204 månader). Samtliga hade gått minst en "kur", dvs en cykel på cirka en månad med peroral eller intramuskulär administration av

AAS samt intensiv träning. De 20 personerna som använt AAS delades sedan in i två grupper beroende på användandets längd: ena gruppen bestod av dem som använt AAS 23 månader eller mindre (10 personer), andra gruppen av dem som använt AAS 24 månader eller mer (10 personer).

Det framkom flera statistiskt signifikanta skillnader mellan dem som använt AAS under lång tid jämfört med de mindra aktiva (där majoriteten endast använt AAS i en månads tid). Långtidsanvändarna var yngre vid debutåldern och upplevde oftare depression mellan eller efter helt avslutat användande av AAS. Gemensamt för båda grupperna var att motivet till att man börjat med AAS var en önskan om en "snyggare kropp". Däremot var det endast bland långtidsanvändarna man hittade motiv som antyder att AAS har en psykoaktiv effekt; t.ex. som del av akut förberedelse för att begå brott.

Acknowledgements

I would like to thank:

My supervisor, associate professor Ingemar Thiblin, for his never-ending patience, encouragement of independent thinking and sense of humour.

My co-supervisor, Henrik Druid, for overall support and for boosting my alertness by means of his immensely irritating bird clock during the KI-period.

My gregarious and ever-so-helpful statistician and co-supervisor Fredrik Granath.

Mobiliserings mot narkotika (MOB) and the Swedish National Board of Forensic Medicine, for financial support.

My fellow researcher, Fia Klötz, M.D, Ph. D., for input and, most importantly, for being a role model to a confused and disorganized personality (me).

Mats Garle, head of the Doping Laboratory at Huddinge Hospital in Stockholm, for providing invaluable data for research.

The forensic pathologists at the departments of Forensic Medicine in Sweden, for testing for AAS and thus providing material to this thesis.

Gustaf Holmqvist, for emotional and practical support, making this thesis possible.

My amazing friends Frida Farm and Titti Persson for *dialectics* and reminding me that there is a world outside that of the natural sciences. And for being Bret Michaels and Joey Ramone.

Wendy Soderlund, for input and encouragement.

The friends and loved ones of the deceased persons in study I, II and III.

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