Exploring treatment aspects of men with long-term anabolic-androgenic steroid use:

A dual perspective on health service engagement and the safety and feasibility of endocrine therapy for anabolic-androgenic steroid induced hypogonadism

Dissertation for the Degree of PhD

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Oslo, Norway

2024

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-348-0446-5

Cover: UiO.
Photo cover: Rune Hammerstad https://fotografoslo.no/
Print production: Graphic center, University of Oslo.

Exploring treatment aspects of men with long-term anabolic-androgenic steroid use: *A dual perspective on health service engagement and the safety and feasibility of endocrine therapy for anabolic-androgenic steroid induced hypogonadism*

Thesis for Doctoral Degree (Ph.D.)

By

Hans Christian August Bordado Henriksen

This thesis will be defended in public in the Round Auditorium, Domus Medica, University of Oslo, Sognsvannsveien 9, Oslo, Norway.

Time: Friday 21 June, 2024, trial lecture 10:15 AM and public defense 1:15 PM.

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To my parents

Acknowledgements

The completion of this thesis owes much to the invaluable support provided by several individuals. To everyone mentioned here and to those I might unintentionally have forgotten to mention, please know that I am grateful for each and every contribution.

Above all, I would like to express my heartfelt gratitude to my main supervisor, Ingrid Amalia Havnes, whose guidance, expertise, and encouragement have been essential throughout my PhD work. I feel very privileged to have been under your excellent mentorship during these three years, both in research and in life. I want to especially thank you for bringing the CloTASH project to life, and for inviting me to be a small part of your persistent dedication to research.

I am deeply thankful to my co-supervisors for their unique qualities that have not only enriched my academic experience but also enhanced the quality of the two studies in this thesis. To Anders Palmstrøm Jørgensen, your expertise in interpreting hormone analyses and treating hypogonadism have been essential to the treatment outcome for the participants involved in the CloTASH study, as well as to my personal evolvement in the field of endocrinology. To Astrid Bjørnebekk, for your knowledge of and commitment to AAS research – I consider myself very fortunate to have been given the possibility to delve further into your valuable AAS data, and to be a part of your incredible research group. To Sudan Prasad Neupane, your generous spirit and quick constructive feedback have contributed to the depth of this thesis, as well as the papers included in it.

I want to recognize the South-Eastern Norway Health Authority for generously funding this PhD project, Oslo University Hospital for conducting the two studies involved in it, and University of Oslo for admitting me to the PhD program; thereby granting me the opportunity to pursue a doctoral degree. I wish to express sincere gratitude to Espen Ajo Arnevik and to the whole RusForsk research group, for your camaraderie and shared passion for science, and to Marianne Riksheim Stavseth for solid statistical advice. A special heartfelt acknowledgment goes to the National Steroid Project represented by Christine Wisløff, Marie Lindvik Jørstad and Ann-Kristin Selmer, whose dedication and hard efforts also played a crucial role in the recruitment of participants to the CloTASH study. To Morgan Scarth, who embarked on this academic journey alongside me and with whom I have shared the delightful Peisstua, for the past three years: Thank you for being a great colleague and friend. To Ansgar Heck for graciously welcoming me into the research environment at the Section for Specialized Endocrinology. To SERAF for organizing crash courses and journal clubs that have been of great value to the progression of my PhD. To ProCardio Center for Research Based Innovation and Vibeke Marie Almaas, who generously provided the cardiovascular data used in the second paper of this thesis. To the remaining co-authors on the five papers included in this thesis: Thank you for every valuable contribution and for the collaborations on each paper. Thanks to Anders Grøndahl, and to

Anders Juul and all my former colleagues at the Department of Growth and Reproduction at Rigshospitalet in Copenhagen, for their collective influence on my recent career choices, including my decision to apply for this PhD project. Lastly, I need to mention the Mind the Graph platform for serving as a valuable tool in developing visual content for this thesis.

The CloTASH study would not have been achievable without the contributions of the following people and institutions mentioned in the following section. I am thankful to the user representatives, who took part in the planning, recruitment and dissemination of the study. To the Department of Medical Biochemistry and the Hormone Laboratory for analyzing all blood samples. To Jonny Hisdal and Helene Støle Melsom at Section of Vascular Investigations, for investigating vascular morphology and function. To Ingebjørg Seljeflot, Sissel Åkra and Sheryl Palmero, at Oslo Center for Clinical Heart Research, responsible for collecting and biobanking fat and blood samples. To the Section for Specialized Endocrinology, and in particular the nurses for their efforts in coordinating and conducting the DXA and ECG investigations. To Lillian Robin Guardian at Department of Medical Biochemistry, and Ingeborg Amundsen at Senter for laboratoriemedisin, Sykehuset Østfold, for dispatching and analyzing urine samples. To the Andrology Lab and Reproductive Medicine Group, for their dedicated efforts in analyzing semen samples. To Sykehusapoteket Rikshospitalet, and specifically, Laila Ichoutene and Oda Opdahl Nordland, for your excellent handling of the study medications employed in the intervention. To the SUD outpatient clinic, and in particular Kim Amundsen, who provided essential psychosocial support: Your commitment to the well-being of the participants did not only improve the quality of the CloTASH study but also shows a deep dedication to individuals with AAS use. Finally, I express gratitude to every study participant involved, for dedicating your time and effort to contribute to the advancement of future treatment methods for people with AAS use.

This thesis would not be possible without the love and support of my family and close friends. To my dear friends, Camilla, Camilla and Julie, for your committed friendship during a period of significant transitions – relocating to Oslo, adapting to a new city and job, and navigating the challenges brought about by the COVID-19 pandemic: Your friendship has always been a source of love and belonging. I also want to give a shout out to my faithful furry friend, Pelle, whose company brought me happiness and comfort during long research hours. To my Swedish family, thank you for welcoming into your family and making my recent transition to Stockholm much smoother. To my three older sisters, Cecilie, Margrethe, and Kristine, your ambitions and unmatched loyalty, from my upbringing until now, have consistently been a source of inspiration. To Fred, I extend my deepest appreciation and love for your endless patience and devotion: Your support, cheerleading and love is and always will be my main anchor in life. Finally, I want to acknowledge and thank my parents, Asteria Cecilia and Per Arne. Their lifelong dedication to education, their unwavering belief in the value of academics and the example they set in terms of persistence and resilience, laid the foundation for my academic pursuits in life including this doctoral degree.

General summary

The use of anabolic-androgenic steroids (AAS) have several documented adverse effects on both physical and mental health, including dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis, and the subsequent decrease in endogenous testosterone production. This condition following AAS cessation, termed AAS-induced hypogonadism (ASIH), manifests as symptoms often referred to as "AAS withdrawal symptoms", and include fatigue, depression, anxiety and sexual dysfunction. Although the HPG axis typically recovers within 1.5 years after ceasing use, suboptimal levels of testosterone and/or associated symptoms may persist for longer. Despite experiencing ASIH or other side effects from use, individuals using AAS often exhibit reluctance to seek treatment.

There is limited knowledge about health service engagement and potential barriers to seek treatment among people who use AAS. Reluctance to seek health services is largely attributed to the absence of treatment guidelines and clinicians' lack of confidence in addressing ASIH. Consequently, many resort to post cycle therapy (PCT), a self-initiated treatment approach designed to treat symptoms of ASIH. Despite PCT being a common practice, there is a scientific knowledge gap in how to address ASIH, as no previous experimental study has assessed PCT. This thesis aims to enhance treatment knowledge for men using AAS by a two-fold approach: First, by examining the association between health service engagement and AAS-related health issues, and second, by assessing the safety and feasibility of an off-label hormone intervention with clomiphene citrate (CC) for men struggling with ASIH and AAS dependence aiming to discontinue long-term AAS use.

Paper I investigates AAS use characteristics, treatment-seeking behavior, side effects, and health concerns among men with a history of AAS use. The study is based on self-report data from 90 Norwegian men with current or former AAS use exceeding 12 months, whereas 45.6% of the men had sought treatment at least once during life-time, while 54.4% had not. The findings revealed that treatment seekers were younger and experienced more side effects from AAS use, including gynecomastia, excessive sweating, fatigue, depression, and anxiety. However, these group differences did not remain significant following post-hoc multiple comparison tests. The treatment seekers also expressed greater concern about endogenous testosterone deficiency. The most common reason for seeking treatment was preventive health check-ups. In meetings with health care providers, the majority of patients were transparent about AAS use. Reasons for not engaging health services included the belief that the experienced side effect did not warrant treatment or that healthcare professionals lacked sufficient knowledge about AAS use. The findings emphasize the importance of educating treatment providers to effectively meet the needs of this specific patient group to avoid continued health risks associated with AAS use.

Paper II investigates the associations between AAS use, related objective health issues, and the utilization of health services. The study involved 90 men with a minimum of 12 months of

cumulative current or past AAS use. Participants reported AAS characteristics through an online questionnaire, and clinical interviews, blood samples, blood pressure measurements and transthoracic echocardiography, were conducted. The treatment-seeking group with current AAS use exhibited a higher prevalence of dyspnea and established cardiovascular disease (CVD), such as combined reduced left ventricular ejection fraction, left ventricular hypertrophy and high blood pressure compared to the men who had not engaged health services. The findings also showed how the majority had never sought treatment for AAS related issues, despite signs and symptoms indicative of on-going CVD. The results suggest a potential lack of awareness about the cardiovascular risks associated with AAS among those who use, and a lacking knowledge among healthcare providers on how to diagnose and follow-up on this issue. In conclusion, underlying cardiovascular issues linked to AAS use may not show symptoms and may go undetected by certain screening tools. Thus, echocardiography is crucial for detecting some AAS-related CVD, especially in those with long-term use.

Paper III is the protocol paper of a non-randomized proof-of-concept pilot study investigating the safety of off-label CC therapy in males with continuous long-term AAS dependence looking to discontinue AAS use. The paper describes the planned 16-week long intervention, during which CC is administered to stimulate endogenous testosterone production and alleviate symptoms of androgen deficiency among AAS dependent males enrolled in substance use disorder (SUD) treatment.

Paper IV presents the challenges encountered in recruiting participants for the pilot study delineated in Paper III. The paper depicts the recruitment process, with particular focus on barriers to participation among people who use AAS. The study faced several challenges in recruitment, due to strict exclusion criteria that included residency outside the study area, concurrent illicit substance use, or severe medical conditions. Findings from an online AAS community forum also revealed a fear of legal consequences and a general disapproval of the chosen study methodology and of the concurrent SUD treatment. In the end, it resulted in the inclusion of 12 out of 81 potential participants; which was fewer than the initially intended 25-30 participants.

Paper V explores the safety and feasibility of an endocrine therapy approach in AAS dependent on AAS, as outlined in the protocol (Paper III). In this pilot study, participants aiming to permanently discontinue AAS use, were administered 25 mg CC every other day for 16 weeks. Ten participants completed the intervention, experiencing only mild adverse events such as headaches, dizziness, and mood swings. In the total sample, a decrease was seen in hemoglobin, and in hematocrit, the percentage of red blood cells found in the blood. Alanine aminotransferase (ALT), reflecting damage to cells of the liver, also decreased. There was an overall increase in levels of the pituitary signaling hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that are crucial for sperm and testosterone production in men, as well as sex hormone-binding globulin (SHBG), an important binding protein to testosterone. Although this could indicate a positive HPG axis response, only half of the participants achieved normal total testosterone levels during the 16

weeks. Moreover, the endogenous testosterone did not align with the severity of withdrawal symptoms. The research suggests that CC may be considered safe for men withdrawing from AAS, although it is only partially feasible in addressing ASIH.

In summary, the findings of this thesis highlight how individuals who use AAS form a diverse and complex patient population. They exhibit varied perspectives and needs within the healthcare system, which in turn influence their treatment-seeking behavior. Moreover, the findings delineate the intricate nature of ASIH and emphasize the importance of understanding how hormonal and psychological mechanisms can impact the treatment outcomes of AAS dependence. The study's limitations include reliance on cross-sectional data (Paper I and II) where causal relationships cannot be established, and assessing outcomes from a proof-of-concept study (Paper III-V) with a small sample that cannot ascertain a treatment's efficacy. Nevertheless, there are clear indications that treatment with CC may be both safe and feasible in addressing ASIH. Furthermore, insights gained from the recruitment process could provide the foundation for conducting future randomized controlled trials investigating efficacies of similar interventions with use of control groups. Ultimately, this may contribute to the development of new treatment guidelines for individuals seeking to cease AAS use but facing challenges. New guidelines may in turn increase health service engagement among people with AAS use and reduce the AAS associated risks of physical and mental harm.

Summary in Norwegian

Bruk av anabole-androgene steroider (AAS) har flere dokumenterte uønskede effekter både på fysisk og mental helse, inklusive påvirkning av hypothalamus-hypofyse-gonade(HPG)-aksen, og den påfølgende nedsatte produksjonen av testosteron fra testiklene. Denne tilstanden etter avsluttet AAS-bruk, kalt AAS-indusert hypogonadisme (ASIH), fører til symptomer som økt tretthet, depresjon, angst, redusert libido og potensproblemer. Selv om HPG-aksen vanligvis normaliseres innen 1,5 år etter at AAS-bruk er avsluttet, kan lave testosteronnivåer og/eller tilhørende symptomer vedvare lenger enn dette. Til tross for disse og andre fysiske og psykiske bivirkninger fra bruk, viser personer som bruker AAS ofte motvilje for å søke behandling eller la seg rekruttere til behandlingsforskning. Det er begrenset kunnskap om behandlingssøkende adferd og potensielle barrierer for å søke behandling blant personer som bruker AAS, spesielt med hensyn til sammenhengen med underliggende helserisiko. Motvilje blant personer som bruker AAS til å søke helsetjenester kan i stor grad tilskrives mangelen på behandlingsretningslinjer og legers tvil om hvordan ASIH skal håndteres. Som et resultat benyttes ofte post-syklus terapi (PCT) etter AAS-bruk, en selvpåført behandlingsmetode ment for å minske symptomene på testosteronmangel knyttet til avsluttet AAS-bruk. Til tross for at PCT er en vanlig praksis blant de som bruker AAS, finnes det lite evidens for at dette er en sikker og effektiv behandling. Denne PhD-avhandlingen har som mål å styrke kunnskapen om behandling av menn som bruker AAS ved en todelt tilnærming: Først ved å undersøke sammenhengen mellom behandlingssøkende adferd og AAS-relaterte helseproblemer. Deretter å vurdere sikkerheten og gjennomførbarheten av hormonstimulerende behandling til menn som sliter med AAS-indusert hypogonadisme og AAS-avhengighet, og som har et mål om å avslutte langvarig AAS-bruk.

Artikkel I undersøker brukskarakteristikker relatert til AAS, behandlingssøkende adferd, bivirkninger og helsebekymringer blant menn som bruker AAS. Funnene er basert på selvrapporterte data fra 90 norske menn med nåværende eller tidligere akkumulert AAS-bruk på over 12 måneder, der 45,6% av mennene hadde søkt behandling minst en gang i løpet av livet, mens 54,4% ikke hadde det. Resultatene viste at de som søkte behandling opplevde flere bivirkninger, inkludert gynekomasti, økt svetting, tretthet, depresjon og angst, selv om forskjellene ikke forble signifikante etter korrigering for multippel testing. Samtidig uttrykte de også større bekymring for manglende testosteronproduksjon. Den vanligste årsaken til å søke behandling var forebyggende helsekontroller. I møter med helsepersonell var flertallet av pasientene åpne om at de brukte AAS. Årsaker til ikke å henvende seg til helsevesenet var at de ikke opplevde bivirkningene som alvorlige nok, eller at helsepersonell manglet tilstrekkelig kunnskap om AAS-bruk og behandling. Resultatene understreker hvor viktig det er å utdanne klinikere som kan møte behovene til denne spesifikke pasientgruppen, slik at man unngår økt helserisiko tilknyttet kontinuerlig AAS-bruk.

Artikkel II undersøker sammenhengene mellom AAS-bruk, relaterte objektive helseproblemer og bruk av helsevesenet. Studien inkluderte 90 menn med minimum 12 måneders samlet nåværende eller tidligere AAS-bruk. Deltakerne rapporterte brukskarakteristikker relatert til AAS og behandlingssøkende adferd gjennom et spørreskjema på nett, og møtte opp fysisk til et klinisk intervju, blodprøve, blodtrykksmåling og ekkokardiografi (ultralyd av hjertet). Gruppen som hadde søkt behandling og med nåværende AAS-bruk, viste en høyere forekomst av dyspné og etablert hjertepatologi på undersøkelsene, sammenlignet med gruppen som ikke hadde benyttet seg av helsevesenet. Dette inkluderte blant annet en kombinasjon av redusert pumpefunksjon i venstre hjertekammer (nedsatt ejeksjonsfraksjon), forstørret hjertemuskel (myokardhypertrofi) og forhøyet blodtrykk. Resultatene viste likevel at flertallet av deltakerne aldri hadde søkt behandling for AAS-relaterte bivirkninger, til tross for at mange av dem hadde symptomer og tegn på mulig hjertesykdom. Mange som bruker AAS ser ikke ut til å kunne være i stand til å tolke symptomer på hjertekarsykdom, og helsearbeidere kan samtidig være usikre på hvordan dette skal utredes og følges opp. Noen hjerteproblemer knyttet til AAS-bruk kan forekomme uten symptomer og blir heller ikke fanget opp av generelle screeningverktøy som elektrokardiogram. Konklusjonen er derfor at regelmessig overvåking av blodtrykk og ekkokardiografi er avgjørende for tidlig diagnostikk av hjerte- og karsykdom, spesielt hos dem med langvarige AAS-bruk.

Artikkel III er protokollartikkelen for en ikke-randomisert intervensjon-pilotstudie som undersøker sikkerheten og gjennomførbarheten av terapi med klomifensitrat hos menn med kontinuerlig langvarig AAS-avhengighet, men som ønsker å avslutte AAS-bruk permanent. Artikkelen beskriver den planlagte 16 ukers intervensjonen, der klomifensitrat ble administrert til deltakerne for å stimulere naturlig testosteronproduksjon og lindre symptomer på testosteronmangel. Deltakerne følger samtidig et parallelt poliklinisk behandlingsforløp for rus- og avhengighet.

Artikkel IV presenterer utfordringene som ble møtt under rekruttering av deltakere til pilotstudien med hormonbehandling beskrevet i Artikkel III. De største utfordringene ved rekrutteringen til studien var de strenge eksklusjonskriteriene, som inkluderte bosted utenfor studieområdet, samtidig bruk av ulovlige stoffer og alvorlig underliggende sykdom. I et AAS-nettforum kom det også frem at mange mulige studiedeltagere var bekymret for juridiske konsekvenser eller viste generell skepsis til studiemetodologien og den obligatoriske oppfølgingen ved poliklinikk for rus og avhengighet. Dette resulterte i at kun 12 av 81 potensielle deltakere kunne inkluderes, noe som var færre enn de opprinnelig tiltenkte 25-30 deltakerne.

Artikkel V utforsker sikkerheten og gjennomførbarheten til en hormonterapimodell som er designet for å normalisere egenproduksjonen av testosteron og lindre testosteronmangelsymptomer hos AAS-avhengige menn som ønsker å avslutte AAS-bruk permanent. Under intervensjonen fikk de inkluderte ti deltakerne 25 mg klomifensitrat annenhver dag i 16 uker. Kun milde bivirkninger ble rapportert, inklusive hodepine, svimmelhet og humørsvingninger. I gruppen ble det observert en nedgang både i hemoglobin og i hematokrit (prosentandelen av røde blodlegemer i blodet). Nivået av

alanin aminotransferase (ALT), som er en viktig markør for skade på leverceller, gikk også ned. Det var en generell økning i nivåene av signalhormonene follikkelstimulerende hormon (FSH) og luteiniserende hormon (LH), som er avgjørende for produksjon av sæd og testosteron hos menn, samt kjønnshormonbindende globulin (SHBG), et viktig bindeprotein for testosteron. Selv om dette kunne indikere en positiv stimulering av hypofysen, oppnådde bare halvparten av deltakerne normale totale testosteronnivåer i løpet av de 16 ukene. Basert på selvrapporterte data som ble samlet inn under intervensjonen, var det ikke god overensstemmelse mellom testosteronnivåene og de subjektive testosteronmangelsymptomene. Studien indikerer at behandlingsmodellen generelt kan anses som trygg blant menn som avslutter AAS, selv om ikke alle merker en subjektiv bedring.

Samlet sett fremhever disse resultatene at personer som bruker AAS utgjør en mangfoldig og kompleks pasientpopulasjon, med varierende behov innenfor helsesystemet som til slutt påvirker deres behandlingssøkende adferd. Den intrikate naturen av ASIH som beskrives i avhandlingen understreker viktigheten av å forstå hvordan hormonelle og psykologiske mekanismer kan påvirke behandlingsresultatene av AAS-avhengighet. Det er avgjørende å anerkjenne studiens begrensninger: Bruk av tverrsnittsdata kan ikke forklare årsakssammenhenger (artikkel I-II). Videre kan resultater fra en proof-of-concept-studie med få studiedeltakere ikke fastslå at en behandling er effektiv (artikkel III-V). Med hensyn til resultatene fra intervensjonen beskrevet i denne avhandlingen, er det indikasjoner på at behandling med CC kan være en trygg og gjennomførbar måte å håndtere ASIH på. Videre kan erfaringene fra rekrutteringsprosessen være nyttige ved gjennomføring av fremtidige kliniske studier i feltet. Funnene som presenteres i denne avhandlingen understreker behovet for fremtidige randomiserte kontrollerte studier for å befeste og fremme konseptet. Til syvende og sist kan dette bidra til utviklingen av nye retningslinjer for behandling for personer som ønsker å avslutte AAS-bruk. Dette kan igjen potensielt øke engasjementet for å søke hjelp i helsevesenet blant mennesker med AAS-bruk og redusere risikoen for ytterligere fysisk og mental skade forbundet med bruk.

List of papers

I **Health service engagement, side effects and concerns among men with anabolic-androgenic steroid use: a cross-sectional Norwegian study**

Henriksen HCB, Havnes IA, Jørstad ML, Bjørnebekk A.

Substance Abuse Treatment, Prevention, and Policy, Published 2023 Apr 3;18(1):19 doi: 10.1186/s13011-023-00528-z.

II **Treatment-seeking behaviour and cardiovascular morbidity among men with anabolic-androgenic steroid use: A cross-sectional study**

Henriksen HCB, Havnes IA, Jørstad ML, Abdullah R, Thorsby PM, Hauger LE, Edvardsen T, Haugaa KH, Almaas VM, Bjørnebekk A.

Scandinavian Journal of Medicine & Science in Sports. First published: 04 Jan 2024 doi: https://doi.org/10.1111/sms.14554

III **Off-label use of Clomiphene citrate to Treat Anabolic-androgenic Steroid induced Hypogonadism upon cessation among men (CloTASH) - a pilot study protocol**

Havnes IA, **Henriksen HCB**, Johansen PW, Bjørnebekk A, Neupane SP, Hisdal J, Seljeflot I, Wisløff C, Jørstad ML, McVeigh J, & Jørgensen AP

Submitted to Contemporary Clinical Trials 29 Nov 2023.

IV **Challenges recruiting men with a desire to cease anabolic-androgenic steroid use to a pilot involving hormone therapy intervention**

Henriksen HCB, Palmstrøm AJ, Wisløff C, Havnes IA.

Drugs: Education, Prevention and Policy.1-13. Published online: 11 Aug 2023. doi: 10.1080/09687637.2023.2244655

V **Clomiphene citrate for treating male hypogonadism arising from long-term anabolic-androgenic steroid use – a pilot study**

Henriksen HCB, Jørgensen AP, Bjørnebekk A, Neupane SP, & Havnes IA

Submitted to Endocrinology, Diabetes & Metabolism 30 Jan 2024

Table of Contents

List of abbreviations

Abbreviation	Definition
AAS	Anabolic-androgenic steroids
AI	Aromatase inhibitors
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ASIH	AAS induced hypogonadism
AST	Aspartate aminotransferase
AU	Alcohol unit
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body mass index
BSA	Body surface area
CC	Clomiphene citrate
CV	Cardiovascular
CVD	Cardiovascular disease
DHT	Dihydrotestosterone
dl	Deciliter
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DUDIT	Drug Use Disorders Identification Test
EACVI	European Association of Cardiovascular Imaging
EAPC	European Association of Preventive Cardiology
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
FAI	Free androgen index
FDR	False discovery rate
FSH	Follicle-stimulating hormone
fT4	Free thyroxine
FTI	Free testosterone index
g	Gram
GFR	Glomerular filtration rate
GnRH	Gonadotropin hormone-releasing hormone
GP	General practitioner
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPG	Hypothalamic-pituitary-gonadal
HSCL-10	Hopkins Symptom Checklist-10
IPED	Image and performance-enhancing drugs
IQR	Interquartile range
ISO	International Organization for Standardization
IU	International unit
kg	Kilogram

L	Liter
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricle mass
LVMI	Left ventricular mass index
m	Metre
mg	Milligram
n	Number
nmol	Nanomol
NOK	Norwegian krone
Non-TSG	Non-treatment-seeking group
OUH	Oslo University Hospital
P	Plasma
PCT	Post cycle therapy
RCT	Randomized controlled trial
REC	Regional Committees for Medical and Health Research Ethics
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SFQ	Shortened Fatigue Questionnaire
SHBG	Sex hormone binding globulin
SUD	Substance use disorder
TRT	Testosterone replacement therapy
TSG	Treatment-seeking group
TSH	Thyroid-stimulating hormone
TT	Total testosterone
U	Unit
WHO-5	World Health Organisation - Five Well-Being Index

1 Introduction

1.1 Anabolic-androgenic steroids - properties and non-prescribed use

Anabolic-androgenic steroids (AAS) consist of testosterone and synthetic derivatives, which is predominantly used to enhance lean muscle mass and strength (1, 2). AAS shares structural biochemical similarities with testosterone and exhibit comparable effects when administered at appropriate doses (3). Various AAS compounds exist, with slight chemical variations between them. The term 'anabolic' denotes the muscle-building property, whereas 'androgenic' depicts the virilizing effects, leading to beard growth, deepening of voice, and development of masculine secondary sexual traits (4, 5). Although the term 'AAS' has been widely utilized since its development, some critics argue that the term is now outdated (6). Their argument is that all compounds in this category bind and activate the androgen receptor, and thus, they all function as *androgens*, inherently possessing both a muscle building *and* a virilizing effect (7). Nevertheless, in our study, we have retained the term 'anabolic-androgenic steroid' acknowledging the definition's historical, sociocultural, and scientific importance.

1.1.1 Testosterone – an overview

Testosterone, the primary male hormone or androgen, is a natural steroid that binds to androgen receptors (8). It plays a crucial role in sex differentiation, the development of male sex characteristics, spermatogenesis, fertility, as well as the regulation of secondary male sex traits, including patterns of male hair, voice deepening, and anabolic effects on skeletal muscle growth (8). Additionally, testosterone stimulates erythropoiesis, leading to subsequent higher hematocrit levels in men compared to women (9). In males, testosterone is primarily made in the testes, which is also responsible for normal spermatogenesis (10). Of note, intratesticular testosterone concentrations are about 30-fold higher than serum testosterone concentrations, creating an optimal environment for spermatogenesis (11, 12). The majority of testosterone in the blood is bound to binding-proteins in plasma, such as sex hormone binding globulin (SHBG) and albumin, acting as a hormone surplus for the body (13). About 1-3% of testosterone in the body is unbound (14), also known as free testosterone. Free testosterone interacts with the androgen receptor, regulates gene transcription and protein synthesis, and ultimately exerts its effects on androgen sensitive tissues (15).

In the cells, the enzyme aromatase converts some fractions of testosterone into 17 β-estradiol, a process known as aromatization (16). Estradiol plays a crucial role in regulating libido, erectile function, and spermatogenesis in men (17). Simultaneously, another portion of testosterone is transformed into dihydrotestosterone (DHT) by 5α-reductase (18). DHT is known to be a more potent androgen than testosterone, with a threefold higher affinity for the androgen receptor, despite having weak anabolic effects (19). The HPG axis is the key regulator of reproductive axis, testosterone levels and testicular function in the body (20), see Figure 1. The hypothalamus secretes gonadotropin

hormone-releasing hormone (GnRH) through pulsation every 1 to 3 hours (21). GnRH descends the hypothalamo-hypophyseal portal system, and stimulates the anterior pituitary to release FSH and LH, two hormones often collectively referred to as *gonadotropins* (22). The gonadotropins travel through the blood and act on receptors in the testicles: While LH stimulates testosterone production in the Leydig cells, FSH acts on Sertoli cells, promoting spermatogenesis (23). Testosterone secretion and gonadal function is highly regulated by its own negative feedback mechanism on the HPG-axis (20).

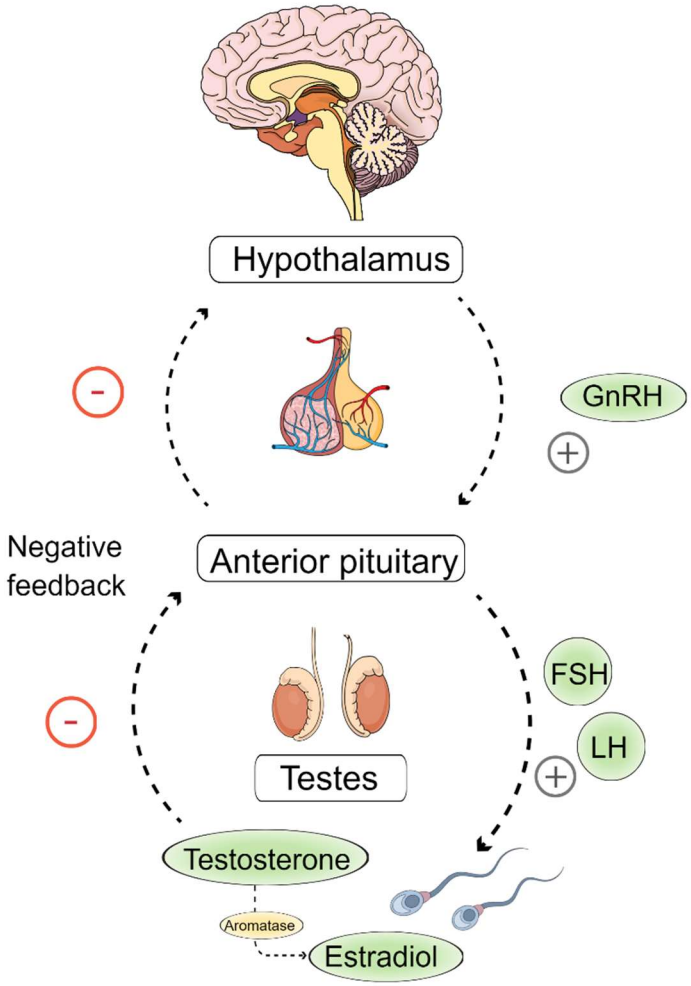

Figure 1: Normal physiology of the hypothalamic–pituitary–gonadal axis, with the hypothalamus depicted in purple. Testicular testosterone and sperm production is regulated by negative feedback from testosterone and estradiol on the anterior pituitary and hypothalamus. GnRH = gonadotropin-releasing hormone, FSH = follicle-stimulating hormone and LH = luteinizing hormone. Figure created in the Mind the Graph platform. Copyright Henriksen, HCB.

Today, prescribed exogenous testosterone or *testosterone replacement therapy* (TRT), is used in a few medical settings including delayed puberty, gender dysphoria, HIV-associated weight loss, and some cases of osteoporosis (24, 25). However, its main application is in treating men with pathologically low testosterone levels, a condition known as *hypogonadism* (26). Hypogonadism may be classified as either primary (hypergonadotropic) or secondary (hypogonadotropic), depending on whether the disorder is located in the testicles or in the anterior pituitary or hypothalamus, respectively (20). In addition, late-onset hypogonadism, also known as age-related hypogonadism, refers to a condition in which there is a natural decline in testosterone levels in middle-aged and elderly men (27). More recently, TRT has proven effective in improving mood and energy levels in men with late-onset hypogonadism (28), with low risk of adverse events, even among older men with established cardiovascular disease (CVD) (29). According to Norwegian guidelines, patients diagnosed by an endocrinologist with evident *primary or secondary* hypogonadism are entitled to receive testosterone through a reimbursable prescription (in Norwegian "blå resept"). In this scenario, the government may subsidize a portion of the costs associated with medications and medical supplies (30). In contrast, men with late-onset hypogonadism and testosterone levels within the lower normal range, are generally not deemed eligible for TRT in Norway.

1.1.2 A brief history of recreational AAS use

Testosterone was first isolated and described by German and Dutch chemists in the 1930s (31). Its initial medical purpose was to treat melancholia and depression in males, as well as "male climacteric" (32). In the 1940-50s, variations of testosterone, so-called “anabolic-androgenic steroids” were developed and found its way into various medical contexts, including the treatment of hypogonadism and aplastic anemia (7, 33). At the same time, professional athletes began using AAS to gain performance advantages (34). The use of AAS spread among athletes and bodybuilders from the 1950s to the 1970s (35), culminating in the development of international antidoping agencies and the banning of AAS use in the Olympics in 1967 (36). However, the public and much of the medical community remained largely uninformed about these drugs and their effects until the 1980s when AAS use became more widespread in the general population (37). By the late 1980s, AAS use shifted from elite athletes to local gym-goers seeking strength and muscle enhancement. In recent decades, AAS proliferation among young men has partly been fueled by the increased emphasis on the muscular male body in Western societies, with advertisements and social media targeting men's physique and aesthetic appearances (38, 39).

1.1.3 Biochemical properties and administration

AAS are mostly consumed orally or via injections (40). Injectable AAS, typically in the form of testosterone esters, are commonly used due to their ability to bypass first-pass metabolism in the liver (19). However, in their unmodified state, AAS quickly enter the bloodstream, leading to elevated peak levels and a brief plasma half-life (41). To enhance pharmacokinetics and prolong the half-life, a fatty

acid chain is usually attached to the steroid, determining the release rate from the injected depot (2). Other AAS, 17α-alkylated steroids, have undergone alkylation to resist liver metabolization, making them suitable for oral consumption (42), although this process also makes them hepatotoxic (43). AAS use regimens usually include one or more compounds taken at *supraphysiological doses*, meaning they surpass the physiological endogenous testosterone levels (2, 44). It has long been established that testosterone administration increases muscle mass and strength in a dose-dependent manner (45), with strength training amplifying the effects of AAS considerably (19, 46). According to a survey, more than 50% of those who use AAS consume doses exceeding 1000 mg weekly (47), a quantity that is tenfold higher than physiologic levels of endogenous testosterone synthesis or prescribed dosages used for TRT. In fact, prescribed treatment of male hypogonadism of other causes than AAS, usually involves 1000 mg of exogenous testosterone every *10–14 weeks* (25).

1.1.4 Patterns of use

AAS administration can occur through various methods, each associated with specific terminology (24). *Stacking* is the practice of combining multiple AAS and/or other image and performance enhancing drugs (IPEDs) into a single regimen to be taken concurrently, and often involves mixing oral and injectable types. *Tapering* involves the gradual reduction of AAS over time, to avoid sudden disruptions in sex hormone balance, and allowing the body to enhance its endogenous testosterone production. *Cycling* involves using one or more AAS for a predetermined period, typically ranging between 6-16 weeks, followed by a comparable duration of abstinence. *Blast and cruise* describes the alternating but continuous pattern of high and low doses of AAS without complete discontinuation of AAS use, where high-dose phases are referred to as *blast*, and low-dose phases are termed *cruise*. Finally, many tend to self-initiate post-cycle therapy (PCT) or TRT at the end of a cure or after AAS cessation (48, 49). The aim of these self-medicating procedures is to achieve serum testosterone levels within the physiological range and alleviate symptoms associated with testosterone deficiency after AAS withdrawal, such as reduced libido, erectile dysfunction, depression, and loss of muscle mass (44, 50).

1.1.5 Epidemiology

Today, the use of AAS and other IPEDs is predominantly found in Western Europe, the United States, Australia, Brazil and the Middle East (35, 51-57). Although global prevalence studies on AAS are lacking, a meta-analysis estimated that approximately 3.3 % engage in AAS use at least once during their lifetime with higher prevalence among males (6.4%), athletes (13.4%) and recreational athletes (18.4%) (51). In a more recent population-based study from Iceland, 1.6% of adolescents (78% male) reported AAS use (58); a finding that aligns with previous Nordic prevalence studies on AAS use (59) and a recent study among Canadian adolescents and young adults (60). However, the exact global prevalence might be challenging to predict, as lifetime prevalence does not depict current AAS use, and many prior studies are based on groups with notably higher AAS prevalence when compared to

the general population such as male athletes, people with a prison sentence or patients receiving treatment for substance use disorders (61-63). In a study from Norway, 28% of individuals undergoing SUD treatment reported lifetime AAS use, partly attributed to many resorting to AAS as a means to address the adverse effects of opiate dependence (62). Moreover, many individuals who use AAS engage in high risk sexual activity, leading to a higher prevalence of HIV and hepatitis C compared to the general population (64). The rising prevalence of online platforms enabling the acquisition of both pharmacological and psychoactive substances (65, 66), coupled with the escalating impact of the movie industry and social media on male body aesthetics and performance (67), suggests AAS use may further increase among the general population in the coming years (68).

1.2 AAS related health risks

AAS use is associated with various physical and mental side effects, including dependence (5). The occurrence and severity of side effects associated with AAS use have been shown to depend on the type of combinations used, the amount and duration of use, concurrent polysubstance use, age and individual variations including psychological and genetic factors (5, 69, 70).

1.2.1 Physical health risks

1.2.1.1 Cardiovascular risk

In terms of the cardiovascular (CV) system, AAS may cause several adverse effects. CV effects include increased blood pressure, fluid retention, platelet aggregation and hematocrit levels (secondary polycythemia), as well as a decrease in high-density lipoprotein (HDL) and an increase in low-density lipoprotein (LDL) (69, 71-76). These changes, accentuated at high AAS doses, have been associated with increased risk of reduced arterial elasticity, atherosclerosis and blood clot formation, predisposing individuals to a heightened risk of thromboembolic events such as myocardial infarctions, deep vein thrombosis or cerebral strokes (77-81). AAS use has also been associated with an increased risk of cardiac arrhythmias, cardiomyopathy, reduced left ventricular ejection fraction, heart failure and sudden death (71, 82-86). Although hypertension and left ventricular hypertrophy from cycling or short-term AAS use have been found to be reversible (87), other studies have reported cardiovascular adverse effects still present years after AAS cessation, such as biventricular cardiomyopathy, cardiac systolic dysfunction, and heart failure (83, 85, 88).

1.2.1.1 Anabolic steroid-induced hypogonadism

AAS may lead to harm to sexual and reproductive organs resulting in infertility, hypogonadism, and sexual dysfunction (75, 89, 90). In fact, the administration of high, supraphysiological doses of androgens suppress the release of GnRH, LH and FSH through negative feedback, culminating in impaired spermatogenesis and testosterone production (44). Hence, marked testicular volume reduction, azoospermia and hypogonadism are evident during active AAS consumption (91, 92).

Moreover, the elevated estrogen production through aromatization of exogenous AAS strongly intensifies the negative feedback on the HPG axis, further reducing the synthesis of endogenous testosterone (93, 94). The HPG axis usually recovers within 3-18 months post-discontinuation (92, 95), but suboptimal levels of sperm and testosterone might persist for longer (90, 96, 97). This condition is commonly denoted as *anabolic steroid-induced hypogonadism* (ASIH), resulting in symptoms consistent with hypogonadism often termed "AAS withdrawal symptoms" following AAS cessation (44). Signs and symptoms include fatigue, depression, increased suicidal risk, anxiety, reduced libido, and erectile dysfunction (98-101). See Figure 2 for an illustration of the pathophysiology behind ASIH.

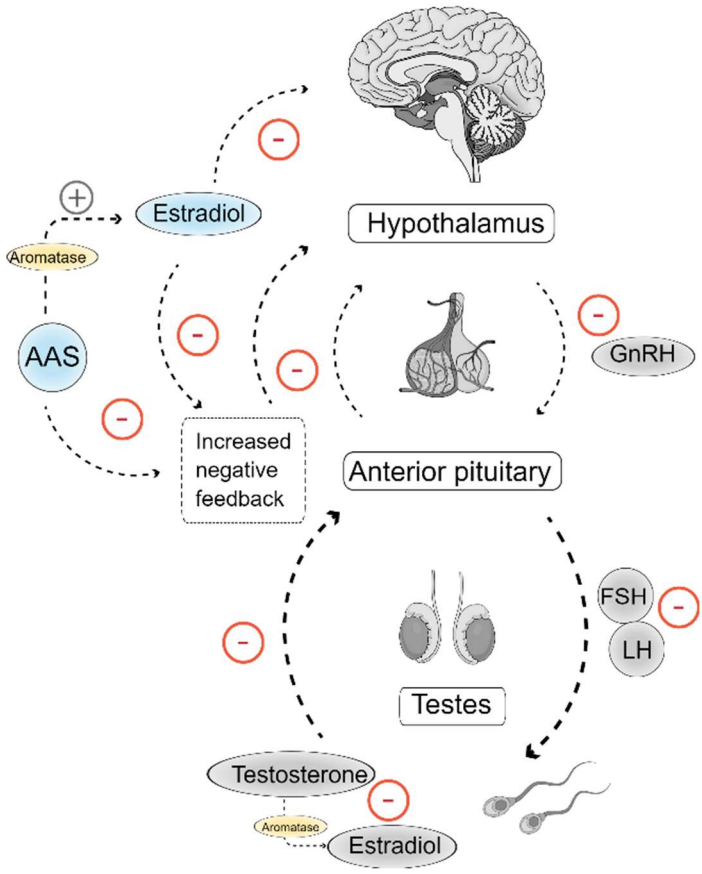

Figure 2: The pathophysiology behind the development of anabolic steroid-induced hypogonadism. Supraphysiological levels of exogenous AAS (anabolic-androgenic steroids) leads to high levels of estradiol in serum through aromatization. Subsequently, negative feedback on the HPG axis increases, which decreases hypothalamic GnRH (gonadotropin-releasing hormone) responsible for the release of pituitary FSH (follicle-stimulating hormone) and LH (luteinizing hormone). Figure created in the Mind the Graph platform. Copyright Henriksen, HCB.

1.2.1.2 AAS dependence

Approximately one third of individuals engaging in AAS use develop dependence, characterized by continued usage despite strenuous effects on physical and mental well-being (102-105). It is important to acknowledge that AAS do not elicit the conventional psychological effects associated with addiction and substance use. This divergence arises, in part, from the fact that AAS are not employed for immediate intoxication or to induce euphoria; rather, their usage is directed towards enhancing physical health, facilitating muscle gain, and improving aesthetic appearance (106, 107).

Kanayama et al. (2010) proposed three etiologic mechanisms leading to AAS dependence that involved anabolic, androgenic, and hedonic factors (108). First, the *anabolic* mechanism involves positive reinforcement arising from the muscle-building effects of AAS, with a dosage escalation driven by concerns related to body image, a condition often referred to as muscle dysmorphia or "megarexia"(107, 109). Second, the *androgenic* mechanism includes distressing symptoms of hypogonadism due to dysregulation of the HPG axis, compelling people who use to resume AAS use to alleviate these symptoms (97, 106). Third, the *hedonic* mechanism highlights the impact on brain reward effects through opioidergic pathways (110).

1.2.1.2.1 Diagnosing AAS dependence

AAS dependence is usually assessed using Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders criteria (SCID II for DSM-IV) (111), which adheres to the standard substance-dependence criteria of DSM–IV (112) but is tailored to address AAS dependence (104). The revised DSM-V (113) use the diagnosis *Substance use disorder*, involving various classes of psychoactive substances, where AAS can be seen as "other substance" and therefore labelled *AAS use disorder* (114). In International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (115), the diagnosis *Substance dependence* involves classes of psychoactive substances, where AAS is not listed. In the still not implemented ICD-11 version (116), AAS is listed as one of the substances under *Disorders due to use of other specified psychoactive substances, including medications.* However, researchers commonly employ the term AAS dependence based on DSM-IV criteria. Hence, the dependence data collected in this thesis conforms to the criteria for substance dependence adapted from the DSM-IV (112) rather than the more recent DSM-V (113), which also accounts for the number and severity levels of present symptoms. In a recent study evaluating AAS dependence using DSM-V criteria for SUD adapted for AAS, it was determined that 24.3% of men using AAS exhibited moderate or severe AAS use disorder (114).

AAS dependence may be distinguished from non-dependence by several factors. A recent meta-analysis (105) revealed that those dependent on AAS are more likely to be older, initiate AAS consumption at a younger age, take higher doses and a wider variety of androgens, have longer cycle durations, and possess limited knowledge of androgen effects. Additionally, they tend to report more physical and mental side effects associated with use, including sexual dysfunction, aggression,

anxiety, and a higher inclination towards substance and polypharmacy use. Lastly, people with AAS dependence exhibit a higher tendency to persist in AAS use compared to those who are not dependent, despite encountering physical and mental issues and elevated concerns about long-term side effects.

The adapted SCID encompasses seven key items where dependence is defined as presence of three or more items classified as severe, occurring within the same 12-month period (111):

1) Tolerance may require higher doses to achieve the same desired outcomes
2) Withdrawal symptoms often follow AAS cessation, resulting from the suppression of the HPG axis and subsequent low endogenous testosterone levels
3) Current use surpasses intended dosages or cycle duration
4) Current desire to reduce usage
5) Significant time spent on either using or recovering from AAS
6) Neglect of social, occupational, or recreational activities due to AAS use
7) Continued use despite potential risks of physical and mental harm health issues

1.2.1.3 Other physical health risks

Other physical side effects include severe acne (117), deviant liver- and kidney parameters (118, 119) and harm to the musculoskeletal system due to the rapid and disproportionate growth of muscles compared to tendons (120). In addition, supraphysiological AAS levels subsequently lead to increased levels of both estradiol through aromatization and DHT through 5α-reduction (121), causing gynecomastia (122) or male alopecia featuring receding hairlines and baldness (91), respectively. Consequently, people who have used AAS tend to use non-prescribed medication targeted to bypass or reduce the unwanted side effects associated with these biochemical pathways (123).

1.2.2 Mental health risks

Besides AAS dependence, AAS use is linked to a range of mental and cognitive effects. These effects can vary depending on the specific stage of AAS use; whether an individual is actively using or in a period of cessation (124, 125). Adverse mental effects can range from mood disturbances such as increased irritability or mood swings to more severe psychiatric manifestations including depression, suicidal ideation, anxiety and heightened levels of psychopathology (58, 98, 102, 125-129). AAS use has also been linked to the onset of manic episodes (130), and the manifestation of psychotic symptoms, such as paranoia or hallucinations (131, 132).

There is a notable prevalence of polypharmacy and simultaneous use of illicit psychoactive substances among people with AAS use (70, 133-135). These may include impotence agents, antidepressants, benzodiazepines and other components, mainly aimed to alleviate distressing symptoms associated with ongoing AAS use or after cessation (48, 136-138). In a large cohort of men who had previously tested positive for AAS through anti-doping controls and subsequently faced doping sanction, a higher prevalence of prescribed antidepressants, anxiolytics, and antipsychotics was observed when compared to controls (139). Furthermore, prolonged exposure to high-dose androgens

and AAS dependence have been associated with lower cognitive performance including concentration, memory and decision-making (140), as well as reduced emotion recognition of fearful stimuli (141, 142). Lastly, AAS use has been associated with behavioral changes such as heightened levels of aggression and interpersonal violence, in particular among men with AAS dependence (102, 143). Although this should be considered a public health concern, the precise association between AAS use and violent behavioral traits remains unclear (144).

1.3 Post-cycle therapy

PCT is a common self-therapeutic practice among those who use AAS, aimed at restoring HPG axis after a period of AAS use (44, 145). While there can be considerable variations in the pharmacological agents, dosages, and duration of use among individuals, the PCT approach generally involves the use of medications designed to sustain and stimulate the endogenous production of testosterone after a cycle (146). Hence, the purpose of PCT is to assist in ensuring a seamless transition from the on-cycle to the off-cycle phase and relieve symptoms of ASIH (48). Indeed, although lacking formal scientific validation, recent observational studies have demonstrated the potential of PCT to accelerate the recovery of endogenous testosterone production and alleviate withdrawal symptoms following AAS cessation (49, 50).

Drugs that are commonly associated with PCT protocols include selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and human chorionic gonadotropin (hCG) (147). Clomiphene citrate (CC, explained in more detail below) and tamoxifen are examples of SERMs, used to block the effects of estrogen on the hypothalamus and on the anterior pituitary. SERMs work by stimulating the production of GnRH and gonadotropins, which in turn promote natural testosterone production and spermatogenesis (44). AIs, such as anastrozole and letrozole, block the activity of the enzyme aromatase, which converts androgens into estrogens, and thus control excessive estrogen levels that may cause gynecomastia or hinder the recovery of endogenous testosterone production through estrogenic negative feedback on the HPG axis (147). hCG is commonly used as part of a PCT protocol or during AAS cycles to mimic the action of LH, and thus maintaining normal testicular function and endogenous testosterone production (148).

Finally, allowing the HPG axis sufficient time to recover and resume natural hormonal homeostasis is an integral aspect of PCT (149), The duration of this period with no use or low-dose-use may vary depending on the specific AAS cycle and individual factors (49, 150). See Figure 3 for the pharmacological mechanisms of CC and hCG in men.

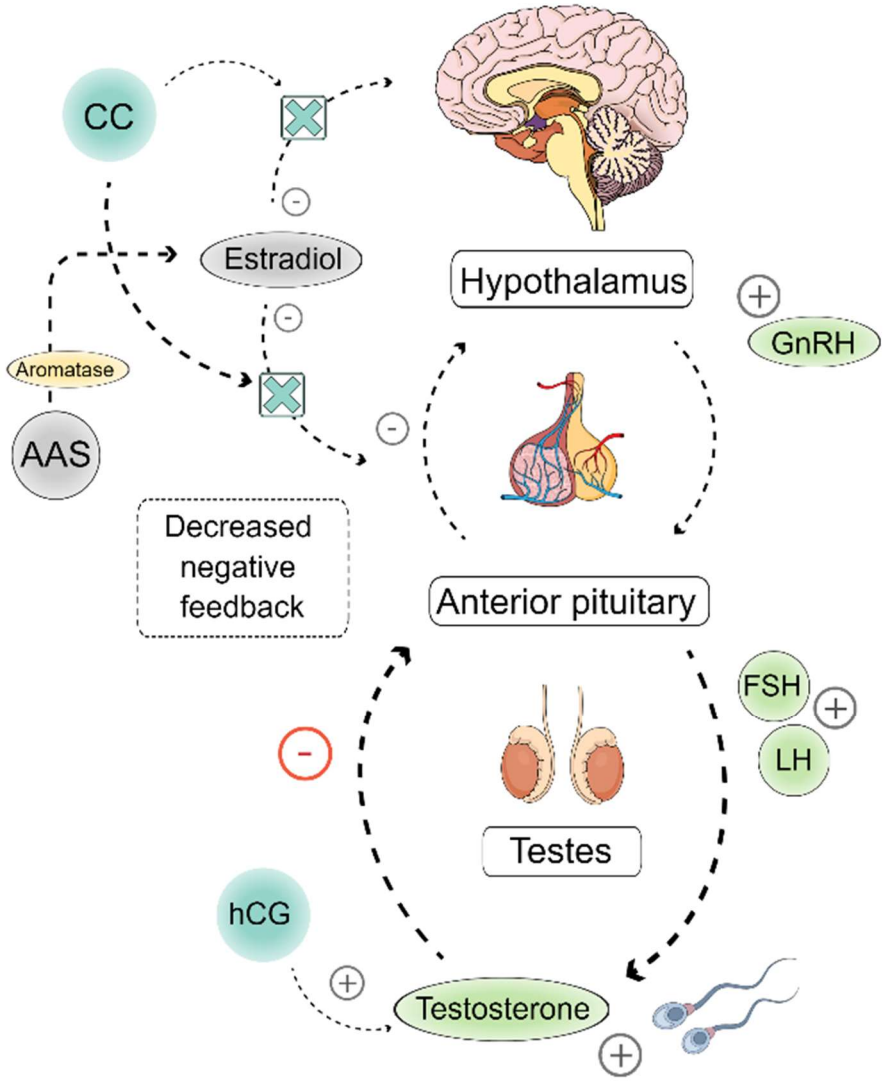

Figure 3: The mechanism behind CC (clomiphene citrate) and hCG (human chorionic gonadotropin). As an antagonist on estrogen receptors in the hypothalamus and anterior pituitary, CC blocks the inhibitory feedback of estrogens caused by the aromatization of AAS (anabolic-androgenic steroids) on the HPG axis. This prompts a decreased negative feedback, a rise in GnRH (gonadotropin-releasing hormone) secretion, subsequently stimulating the pituitary gland to release higher levels of FSH (follicle-stimulating hormone) and LH (luteinizing hormone). Also illustrated to the lower left is hCG, which acts as an analog of LH, to preserve testicular function. Figure created in the Mind the Graph platform. Copyright Henriksen, HCB.

1.3.1 Clomiphene citrate – an overview

CC is classified as a SERM, and acts as an antagonist on hypothalamic and pituitary estrogen receptors, inhibiting the negative feedback of estrogen on the HPG axis (151). Subsequently, CC leads to an increased secretion of GnRH, which in turn, stimulates the pituitary gland to release increased amounts of gonadotropins. The drug was approved by the U.S. Food and Drug Administration for the

use in infertile women in the late 1960s (152). In women, CC stimulates the release of eggs during the process of ovulation, and it is still predominantly prescribed for this purpose today (153). In men, CC has been used off-label to treat hypogonadism and suboptimal spermatogenesis unrelated to AAS use for decades (154, 155). In the same way as in women, its mode of action is to stimulate the release of pituitary FSH and LH, thereby reinstating and maintaining physiological testicular testosterone production and spermatogenesis without suppressing the HPG axis (152). Additionally, the clomiphene stimulation test has historically been utilized to assess the function of HPG axis (156) and has also been tested briefly on men with prolonged AAS use (157). Frequently reported adverse effects of CC encompass headache, dizziness, flushing, mood swings, nausea, abdominal discomfort, breast tenderness and gynecomastia (152, 154, 158). A few more severe adverse effects have previously been described in literature including psychotic episodes with suicidal behavior (159), thromboembolic events (160), liver affection (161), and visual disturbances (162).

1.4 Treatment and information seeking

1.4.1 Health service engagement

Despite the potential health risks and the associated concerns linked to the use of AAS, individuals who use AAS often exhibit a reluctance to engage with health services (163, 164). There are likely several factors contributing to the avoidance of medical support. The widespread access to information and the sale of non-prescribed and self-initiated PCT and TRT, primarily through online AAS forums, causes some men who use AAS to perceive health services as redundant, given their belief that doctors would not prescribe such treatments regardless (145, 163, 165). For instance, commonly cited reasons for not engaging health services or disclosing use include the perception that physicians may either lack sufficient understanding of AAS or capabilities to provide effective treatment (134, 145, 163, 166). Furthermore, people who use AAS tend to believe that their AAS-related side effects or concerns may not be substantial enough to warrant seeking healthcare support (64, 167). Instead, many attempt to manage potential side effects or complications themselves rather than seeking professional medical guidance (166). This includes the employment of non-prescribed medications to self-assess symptoms linked to ongoing AAS use or those emerging shortly after discontinuation (50), such as medications intended to treat depressive symptoms, anxiety, erectile dysfunction, muscle ache, acne, or gynecomastia (138, 147).

In addition to the scarcity of treatment guidelines for individuals using AAS, recent evidence has also indicated that only a small fraction of clinicians (168), including endocrinologists specializing in the treatment of male hypogonadism, feel competent in addressing AAS related issues, particularly in the management of testosterone deficiency in ASIH (169). However, there is also reason to believe

that AAS knowledge levels may also vary among people who use AAS, and that many only base their knowledge from their own or peers' previous experiences of AAS use (170).

AAS use tends to be associated with stigma (171), and people who use may be hesitant to seek treatment due to fear of judgement or legal consequences (52, 163, 172). Lastly, accessibility to healthcare services due to geographical residency, the availability of syringe programs or specialized healthcare providers, and economic disadvantages, are all factors that may impact treatment-seeking behavior (40, 125, 164, 172).

1.4.2 Norwegian context

The healthcare system in Norway functions on a publicly funded basis, ensuring that all residents have access to public healthcare through the National Insurance Scheme (173). In Norway, residents are assigned a publicly funded general practitioners (GPs) who can provide treatment or refer patients to specialized somatic or psychiatric health services at publicly funded hospitals. While most costs for public health services are covered, patients typically pay a small user fee for each healthcare visit. Once a maximum user fee threshold is reached per year, patients receive a healthcare exemption card (30). Patients can also seek care from private GPs or private specialists without a referral, but they would be responsible for the associated costs.

In 2013, Norway implemented a legislative change through an amendment to the Norwegian Drug Act making the use and possession of AAS and other IPEDs illegal (62). Around the same time, individuals engaging in AAS use were granted the right to substance use disorder (SUD) treatment within the public healthcare system. SUD treatment involves a psychosocial approach for those with an established SUD or for those with current, past, or withdrawing AAS use (125). More specifically, the therapy aims to offer people who use AAS essential medical assessments, supportive psychotherapy and prescription medicines to mitigate challenging withdrawal symptoms such as depression, anxiety and sleep disturbances that may arise after discontinuing AAS use (174). However, SUD treatment does not involve initiation of testosterone substitution to treat AAS withdrawal. As of today, there are no official established national or international guidelines specifying whether or how endocrine therapy should be integrated into the treatment regimen for AAS cessation.

In 2014, Oslo University Hospital (OUH) created the National Steroid Project, featuring a cost-free and anonymous helpline aiming to assist individuals with AAS use and their families, as well as educating healthcare professionals and the public about the side effects, and legal and socioeconomic consequences connected to AAS use (125).

1.4.3 Online communities

Online communities play a crucial role in the utilization and administration of AAS, serving as a readily accessible platform for community members to disseminate and acquire information on AAS use (145, 175). Shared AAS-related beliefs and practices are commonly exchanged through informal

channels such as online forums, gyms, or social circles (176). The exchanged advice usually involves various aspects of AAS use, including dosages, cycles, and potential side effects, predominantly based on personal experiences and subjective observations rather than scientific evidence (177, 178). Consequently, as this sharing culture fundamentally lacks a foundation in scientifically validated information, it may contribute to potentially unsafe practices (165, 179). Moreover, information about AAS access and distribution is usually shared on the same internet sites, with numerous websites offering global sales, even in countries where AAS are prohibited (175, 180). Nevertheless, the unregulated nature of these online markets can result in the distribution and consumption of contaminated or counterfeit products with inaccurately labeled doses, and potentially hazardous substances or dosages (165).

1.5 Knowledge gap

Individuals who use AAS may be viewed as a hard-to-reach group, both in regards to health service engagement and for the recruitment and participation in health research (145, 163, 181). As AAS constitute a relatively recent form of substance use among the general population (35), there is a foreseeable increase in individuals experiencing health issues linked to prolonged AAS use, who will be approaching health services for treatment, in the forthcoming decades. It is therefore crucial to understand the type of support they desire and find beneficial, and to customize health services, as prolonged reluctance to seek treatment could pose a substantial health risk. Previous research on AAS-related side effects, concerns and health service experiences have been accustomed to considerable disparities between countries in how the healthcare system is organized and funded (163, 177, 182, 183). Consequently, findings in these studies may not be as representative for the setting in Norway or in similar countries, where AAS use is illegal, individuals with current or past AAS use have rights to SUD treatment, and public health services are accessible and funded (125). There is a significant knowledge gap in health service engagement among people who use AAS, and on potential barriers to seek treatment in this particular setting. A notable issue revolves around the lack of research investigating how the current physical health status may impact the decision to seek treatment. It remains uncertain whether individuals using AAS, who abstain from seeking health services, might harbor unnoticed severe physical health issues, including CVD. In addition, there are currently few insights addressing barriers to participation in clinical research that investigates tailored treatment alternatives for people who struggle to withdraw from AAS use due to androgenic AAS dependence (104). While PCT is commonly self-employed by men with AAS use for self-monitoring ASIH symptoms, there exists a significant knowledge gap regarding how to manage ASIH with PCT (49). This gap results from the absence of previous intervention studies assessing the safety and feasibility profile of PCT. Acquiring this knowledge has the potential to encourage heightened treatment-seeking behavior in this group of patients, to enable effective health monitoring within regulated medical environments, and to address ASIH in an appropriate manner.

2 Aims of the Study

The overarching objective of this thesis is to gain new treatment knowledge that can optimize future healthcare approaches for men who use AAS through 1) investigating the relationship between health service engagement and AAS-related adverse effects and health concerns in a cross sectional study, and 2) testing an off-label hormone intervention upon AAS cessation among men with ASIH and dependence, who struggle to cease use, in a non-randomized proof-of-concept study.

The specific aims for Substudy 1 are to:

- compare occurrences of self-reported side effects and health concerns between individuals who proactively seek treatment for AAS-related issues during their lifetime with those who do not, and to explore reasons behind seeking treatment, experiences with the healthcare system, and factors influencing the decision not to engage with health services (Paper I), and to
- present associations between health service engagement and physical health measures among men with ongoing or prior AAS use, and to highlight how many with long-term AAS use who refrain from seeking health services, display signs of pathology, including CVD, endocrine disturbances, or harms to the liver or kidneys (Paper II)

The specific aims for Substudy 2 are to:

- describe a proof-of-concept pilot study with a 16 week off-label intervention with clomiphene citrate to treat ASIH among AAS-dependent men withdrawing from long-term AAS use, with safety and health risk assessments before, during and after the intervention (Paper III),
- uncover recruitment challenges to the pilot study, possible reasons for not wanting participation, describe ethical considerations and lessons learned during planning and recruitment (Paper IV), and to
- present safety measures of the endocrine intervention, and determine its feasibility in restoration of endogenous testosterone levels and alleviation of ASIH symptoms after AAS cessation (Paper V).

3 Materials and Methods

This thesis incorporates data from two distinct interdisciplinary studies focused on men with experience using AAS, at Oslo University Hospital, Norway. Substudy 1 utilizes cross-sectional data from a research project on long-term AAS effects on cognition, brain and cardiovascular health (77, 83, 102, 184), and investigates associations with treatment-seeking behavior among 90 male weightlifters with former or current AAS use. Substudy 2 involves a proof-of-concept pilot intervention study that investigates challenges of recruitment and safety and feasibility of an endocrine therapy model on AAS dependent men withdrawing from long-term use. Hence, to optimize readability, the two discrete sub-studies are individually presented.

3.1 Substudy 1 (Paper I-II)

The main aims of Substudy 1 were to investigate treatment-seeking behavior among people with AAS use, and to compare health concerns, and subjective and objective side effects, between men who had engaged health services for AAS related issues with those who had not.

3.1.1 Study design

Data from this cross-sectional study at Oslo University Hospital (*Anabolic steroid effects on brain morphology, cognitive functioning, and emotional processing: a follow-up of long-term steroid users*) were collected in 2017-2019. Participants were recruited through social media platforms and other relevant online forums, as well as posters and flyers distributed at selected gyms in Oslo. A self-administered web questionnaire was employed to gather information on socio-economic demographics, AAS use history and characteristics, and treatment-seeking behavior for AAS-related issues (n = 90). For Paper II, physical assessment data were also included, such as clinical interviews, cardiovascular health evaluations, and analysis of blood samples. Clinical interviews and assessments of CVD including blood pressure measurements and transthoracic echocardiographic examinations were performed at the Department of Cardiology at OUH.

3.1.2 Study population

All 90 participants were men >18 years of age, capable of giving consent, with a current or former cumulative AAS use of at least one year. The categorization of current AAS use was determined by participants' answers to the query "Are you presently using AAS?" coupled with a follow-up question regarding the duration since discontinuation if applicable. Former use was defined as having ceased AAS consumption for at least one year. Participants were categorized into a treatment-seeking group (TSG, n = 41) or a non-treatment-seeking group (non-TSG, n = 49) based on their responses in the web questionnaire. Those classified as treatment seekers had engaged healthcare providers for AAS-related side effects at least once during or after AAS use. These healthcare providers included their public assigned GP, a public specialist referred by their GP, and/or a private healthcare provider that

could involve either a private GP or a private specialist in diverse somatic health disciplines. In Substudy 1, the central focus was the investigation of lifelong trends of treatment-seeking behavior, with the classification into current or former AAS use regarded as a secondary consideration. Still, due to current AAS' confounding effect on objective measures, a clear distinction was made between current and former use in Paper II, evaluating each group independently for all objective measures.

3.1.3 Measures

A self-report web questionnaire was used to gather information on socioeconomic demographics, such as age, education, work status, parenthood, alcohol and tobacco consumption, the use of prescribed psychopharmacological medication, AAS use history and characteristics, side effects, and treatment-seeking patterns for AAS-related concerns. The lifetime AAS dose was approximated by computing the average weekly dose reported throughout their lifetime and multiplying it by the total number of weeks of AAS exposure.

Specifically for Paper I, the assessment of AAS dependence utilized a modified version of the SCID II for DSM-IV, tailored for AAS dependence criteria (104, 111). Three or more severe items occurring within the same 12-month period defined AAS dependence. Alcohol consumption was evaluated using the Alcohol Use Disorders Identification Test (AUDIT) (185, 186), and illicit non-prescribed drug use was assessed with the Drug Use Disorders Identification Test (DUDIT) (187, 188). Regular illicit substance use was defined as monthly use of substance. Concerns about AAS related side effects, reasons for seeking or not seeking treatment, health service experiences, AAS use transparency and satisfaction levels were measured, with participants providing feedback on healthcare workers' knowledge about AAS. Satisfaction levels were categorized as satisfied or unsatisfied.

Specifically for Paper II, an evaluation of symptoms suggestive of cardiovascular disease, such as dyspnea, chest pain, palpitations, dizziness, and syncope, was conducted through a semi-structured clinical interview. Signs of hypertension was defined as systolic blood pressure ≥140 and/or diastolic pressure ≥90 mmHg, while signs of prehypertension was defined as systolic blood pressure ≥130 and ≤139 and/or diastolic pressure ≥80 and ≤89 mmHg. Due to the likely influence of current AAS use on clinical outcomes (122), a distinction was made between current and former use (AAS cessation ≥ 1 year). Thus, data were presented in two separate tables for all clinical measurements including echocardiography and blood analyses, which will be described in further detail below. Echocardiographic measurements were conducted by one investigator using Vivid E95 (GE Vingmed Ultrasound, Horten, Norway). Data analysis was carried out offline by another investigator, who was blinded to AAS use status, utilizing the EchoPAC v203 software (GE, Horten, Norway). Left ventricular mass was estimated from parasternal views using the formula by Devereux et al. (189), customized for body surface area with the Du Bois' formula (190). Left ventricular hypertrophy (LVH) was characterized as an left ventricular (LV) mass/body surface area (BSA) exceeding 115

g/m2 in alignment with the guidelines from EAPC and EACVI for assessing the athlete's heart (191). Left ventricular mass index (LVMI) was not calculated in instances of suboptimal image quality or insufficient image alignment. The left ventricular ejection fraction (LVEF) was determined using the modified Simpson's biplane method and classified into three ranges: ≥50% (considered normal), 41-49% (indicating reduced function), and ≤40% (signifying severely reduced function) (192). Blood samples that were analyzed at the routine laboratory at the Department of Medical Biochemistry, OUH, included hematocrit, hemoglobin, ALT, aspartate aminotransferase (AST), creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). An eGFR of less than 30 mL/min/1.73m2 was defined as severely reduced kidney function (193). Blood samples that were analyzed at the hormone laboratory, OUH included FSH, LH, SHBG, total testosterone (TT), free androgen index (FAI) or *free testosterone index* (FTI), estradiol, TSH and free thyroxine (fT4).

3.1.4 Statistical analyses

The assessment of normality was conducted through visual examination with histograms. For numerical variables conforming to a normal distribution, variables were expressed as mean ± standard deviation (SD), and two-sample t-tests were employed to compare differences between the TSG and the non-TSG groups. For numerical data not adhering to a normal distribution, medians with interquartile ranges (IQR, 25th-75th percentiles) were presented, and non-parametric tests, such as the Wilcoxon rank-sum tests (Mann-Whitney), were utilized for between-group comparisons. Chi-square tests were used for comparisons involving categorical and/or dichotomous variables, with Fisher's exact test applied when expected numbers were less than five. A two-sided p-value of <0.05 was considered statistically significant. For Paper II, to address for multiple testing, false discovery rate (FDR, Benjamini-Hochberg) corrected P-values were applied. All statistical calculations and analyses were conducted using STATA (version 17.0, StataCorp LLC, Texas, USA).

3.1.5 Ethics

The study adhered to the principles of the Declaration of Helsinki. The Regional Committees for Medical and Health Research Ethics South East Norway (REC) granted approval for the study (2013/601). Before participating, all individuals received both verbal and written information about the study, and written informed consent was obtained. Participants were reimbursed with NOK 500 for their involvement in the study. Participants retained the right to withdraw from the study at any point. A physician evaluated all pathological findings, and further investigations were conducted when deemed necessary.

3.2 Substudy 2 (Paper III-V)

The main aims of Substudy 2 were to outline an off-label intervention with CC to address ASIH from prolonged AAS use, describe challenges in recruitment, analyze reasons for non-participation, and to evaluate the intervention's safety and feasibility in restoring endogenous testosterone levels and alleviating withdrawal symptoms after AAS cessation.

3.2.1 Study design

Paper III-V comprise the design of the CloTASH-study (*Health risks and off-label use of clomiphene citrate to Treat Anabolic-androgenic Steroid (AAS) induced Hypogonadism upon cessation among men – a pilot study)*; a single-site, single-group, open, proof-of-concept, longitudinal pilot study including AAS dependent men that engage in continuous AAS use but aim to discontinue usage permanently. The pilot study investigates a) health risks associated with AAS use and b) the safety and feasibility of a 16-week endocrine intervention with the SERM clomiphene citrate on ASIH and AAS withdrawal,

3.2.1.1 The intervention

The endocrine therapy layout was based on a modified version of a 16-week hormone therapy model, originally proposed by Rahnema et al. (2014) (44). In this adapted approach, participants received 25 mg of CC every other day continuously for 16 weeks, alongside the application of 50 mg transdermal testosterone daily during the initial four weeks prior to the start of the hypothesized CC response. Additionally, participants with an inadequate endogenous testosterone response below 10 nmol/l were treated with rescue medication in the form of hCG injections for a maximum of eight consecutive weeks. If indicated, participants were given an initial dose of 1500 IU hCG administered twice per week during weeks 4-8, and if an insufficient testicular response was still persistent at week eight, the dosages were increased to 1500 IU three times per week during weeks 8-12. The target set for total testosterone (TT) levels was ≥ 20 nmol/l during or at the end of the intervention, see Figure 4. A successful treatment response was defined as TT levels exceeding 20 nmol/l during the intervention or falling within the normal reference range for TT according to OUH reference standards at the end of the intervention (i.e. ≥ 9-30 nmol/l). Consequently, participants demonstrating a response to treatment could conclude the intervention before week 16. Cases with TT levels below 9 nmol/l by week 16 were considered non-responsive to the intervention.

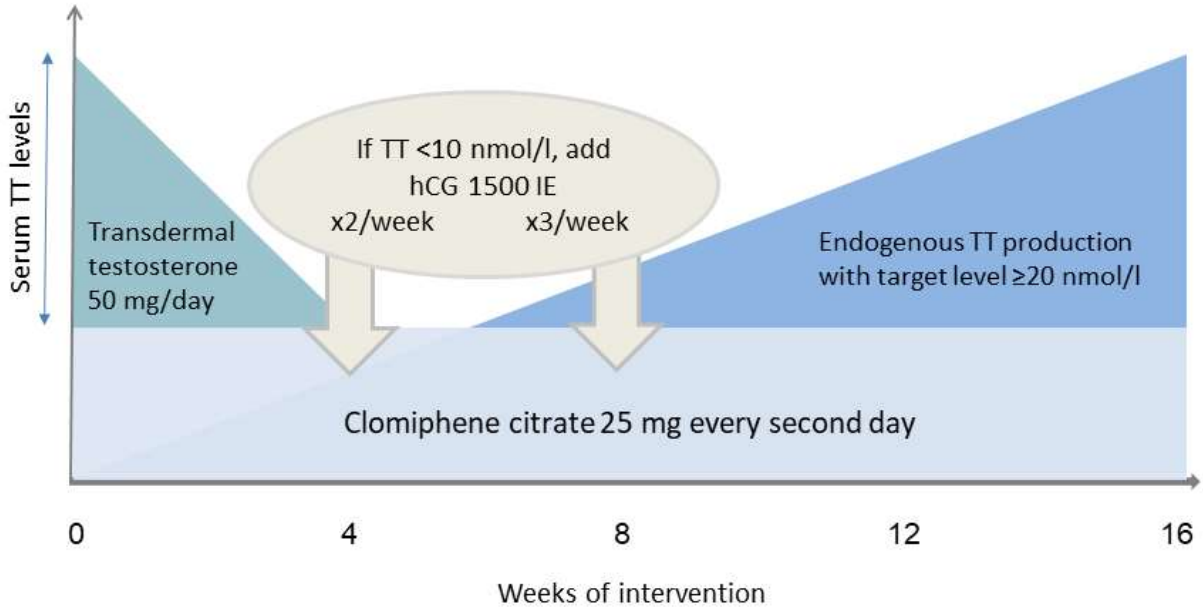

Figure 4: The modified endocrine intervention model for treating anabolic-androgenic steroid induced hypogonadism. TT = total testosterone, hCG = human chorionic gonadotropin.

3.2.1.2 Study period

The inclusion phase and data collection spanned from January 1, 2022, to December 31, 2023. Men with AAS dependence meeting eligibility criteria were recruited for the 16-week hormone therapy intervention, and exclusion reasons were recorded and discussed. Physical and mental health parameters were measured and analyzed through within-subjects repeated measures design during ongoing AAS use (i.e. at inclusion, before starting intervention), throughout the 16 weeks of intervention, and at follow-up at 6 and 12 months. Participants underwent physical examinations and blood collection every 4th week and reported self-report withdrawal symptoms and other subjective health measures through web-based questionnaires during on-going AAS use, every two weeks throughout intervention period (during cessation) and after cessation. However, only the measures that are included in the articles (Paper IV and V) will be described, reported and discussed in this thesis.

Paper III is a protocol paper that in addition to describing the 16-week hormonal intervention, health examinations and self-report data during the intervention also describes the secondary aims of the original pilot in detail. See Figure 5 for an illustration of the all data that were collected in the pilot study. Hence, data regarding the following will not be included in this thesis; health risk investigations

at 0, 6 and 12 months, and comparison data with participants from another study investigating men that cease cycling AAS use temporarily without any intervention.

Paper IV follows a methodological approach, describing the recruitment process for the CloTASH-study, and also includes qualitative data from an online discussion thread on an AAS forum, which was initially used to recruit participants. To explore potential barriers to participation, an observational netnography was used to thematically analyze the content of the online forum thread.

Paper V outlines the data from the CloTASH-study that included the safety and feasibility assessment among men who received the 16-week endocrine intervention upon AAS cessation.

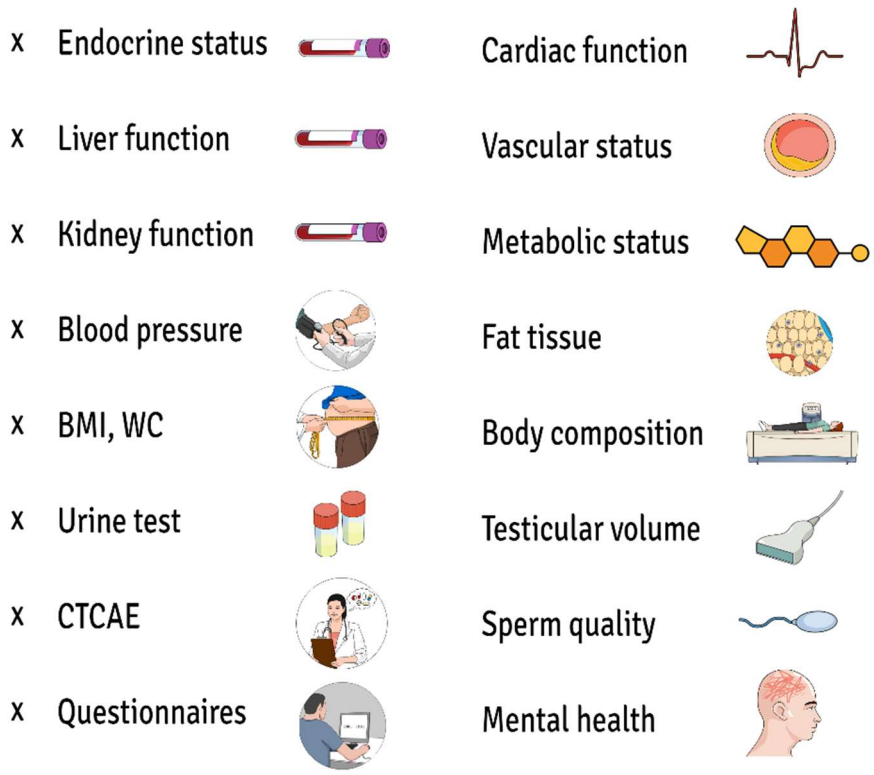

Figure 5: An illustration of the data collected in the pilot study at Oslo University Hospital during the years 2022-2023. On the left side, the investigations that were included in the papers for this thesis are presented and marked with X. BMI = body mass index, WC = waist circumference, CTCAE = Common Terminology Criteria for Adverse Events. Figure created in the Mind the Graph platform. Copyright HCB Henriksen.

3.2.2 Study population

All ten participants that completed the 16-week intervention in the CloTASH-study were males >18 years of age, residents of or near Oslo, having engaged in a minimum of 6 months of continuous AAS use, fulfilling DSM-IV criteria for AAS dependence (104). They were either currently using AAS or having ceased AAS use within the last four weeks before study inclusion, with a simultaneous strong

desire to permanently discontinue AAS use. Before starting intervention, all participants had to be enrolled into SUD treatment at OUH, and present with a serum testosterone levels of ≤ 25 nmol/l (normal reference 9-30), hemoglobin levels below <18 g/dl (13.4–17), ALT levels below <210 U/L (10–70) and AST levels below <135 U/L (15–45). Every four weeks throughout the 16-week intervention, participants underwent physical examinations, assessment of adverse events and blood and urine collection, alongside completing online questionnaires every two weeks. Paper III also briefly describes the study population for the comparison study: Men ≥18 years, using AAS in a cycling matter with a ≥400 mg weekly dose and ≥6weeks breaks between cycles.

3.2.3 Measures

Questionnaire data: Background data and AAS use characteristics were collected at inclusion point. Self-reported questionnaires were conducted every two weeks during intervention, and covered symptoms related to hypogonadism and mental health, such as fatigue, depression, suicidal thoughts, anxiety, general well-being, sexual dysfunction, sleep quality, aggression, and body dysmorphia. Paper V specifically explores the questionnaire data on ASIH-symptoms to assess the subjective efficacy of the intervention: Fatigue levels were evaluated using the Shortened Fatigue Questionnaire (SFQ) (194), which employs a 7-point Likert Scale across four items. Depression and anxiety symptoms were measured by the Hopkins Symptom Checklist-10 (HSCL-10) (195, 196), and well-being was assessed through the WHO-5 (197), providing a percentage score reflecting mental well-being. Sexual function assessment relied on a questionnaire adapted from Cleary et al. (1995) (198) utilizing a 5-item scale across four questions to measure sexual interest and functioning.

Physical assessments: Adverse events were closely monitored through a combination of self-report questionnaires administered biweekly and comprehensive physical examinations and clinical interviews conducted every four weeks for the 16-week long intervention. The physical examinations included measurements of weight, height, and waist circumference, as well as auscultation of the heart and lungs, assessment of gynecomastia, evaluation of edema, and blood pressure measurements. Additionally, clinical interviews, blood tests, and urine screenings for AAS and psychoactive substance use, were conducted together with the physical examinations. Safety-related blood assessments included hematocrit, hemoglobin, ALT, AST, alkaline phosphatase (ALP), calcium, creatinine, eGFR, and prolactin. The sex hormone panel comprised FSH, LH, estradiol, SHBG, TT and FAI. FAI was computed using the formula: (testosterone in nmol/l) × 10 / (SHBG in nmol/l).

Of note, Paper III (protocol paper) describes the secondary objectives for the pilot study that include assessment of changes in physical health indicators from baseline to follow-up 6 and 12 months after AAS cessation in the intervention group. Paper IV also presents a qualitative four-step netnography approach, based on an online forum thread discussion used for recruitment, exploring potential participation barriers in the CloTASH-study.

3.2.4 Analyses

Paper III outlines the pilot protocol; hence, no analyses were performed for this specific paper. The initial power estimation detailed in Paper III will not be further described or discussed, as data from the between-group comparison were not utilized in this thesis.

Paper IV: In this methodological paper, potential barriers to participation in the CloTASH-study from the content of the online forum thread used for recruitment were thematically analyzed using an observational netnography approach. Netnography involves four steps as illustrated in Kozinets 2020 (199): (1) research inquiry (exploring potential barriers to participation), (2) data collection (a single forum thread), (3) data analysis, and (4) research communication. In step 3, thematic analysis involved individual coding of posts focused on potential barriers, resulting in three main themes: (I) Suggesting modifications to the intervention, (II) Fear of negative outcomes and (III) Proposed alternatives. For step 4 (research communication), ethical considerations were addressed in detail, and relevant quotes were selected to illustrate the identified themes and sub-themes.

Paper V: Safety evaluation data from physical examinations, including laboratory measures, are depicted in frequency distribution tables for the entire sample for each intervention time point. Normal distribution in the dataset was assessed using Shapiro-Wilk tests and histograms.

Means and standard deviations (SD) are utilized to present normally distributed data. Changes in blood measures during the intervention are portrayed through one-way repeated measures analysis of variance (ANOVA), with the effect size reported as adjusted R^2. Subsequent to identifying significant differences between time points, Bonferroni post hoc tests were employed. Before conducting ANOVA, sphericity was assessed using Mauchly's W tests. In cases where the assumption of sphericity was violated, the Greenhouse-Geisser estimate of sphericity was utilized for correction.

Non-normally distributed numerical data are presented as medians and IQR (25th-75th percentiles). To evaluate potential changes in blood measure levels during the intervention, Friedman tests (Chi2) with Kendall's W (effect size) were utilized. Post-hoc Wilcoxon signed-rank tests were subsequently conducted to identify significant differences between specific time points. The significance level was set at $p < 0.05$.

In addition, Paper V follows a descriptive statistical approach, providing a detailed and clinically focused overview of each participant's ASIH status from the start of AAS cessation to the end of the 16-week long intervention. To achieve this, the hormone panels for individual participants are graphically presented together with each participant's questionnaire responses for each time point (week 0-16). All statistical analyses and graphs were conducted using STATA (version 17.0, StataCorp LLC, Texas, USA).

3.2.5 Ethics

The study adhered to the principles defined in Declaration of Helsinki. Ethical clearance was granted by the Norwegian Regional Committees for Medical Research Ethics (33872), the Norwegian Medicines Agency (21/18081-9), and the Data Protection Officer at Oslo University Hospital (20/27593). Prior to joining the intervention, eligible participants were provided with thorough verbal and written details about the study, and written informed consent was acquired. All assessments, medications, and study-related follow-ups were provided at no cost, though travel expenses were not covered. Finally, participants retained the right to withdraw at any point before data publication without losing access to SUD treatment. Participants were provided with unrestricted access to research physicians through a 24-hour direct line via phone or email for emergencies related to the intervention. Moreover, all participants were insured against adverse events linked to the study drug, both during and after participation, facilitated through the Project Leader's affiliation with the Norwegian Drug Liability Association. The research physicians evaluated any identified pathological findings associated with AAS use. If such findings were present, participants were either directly referred to specialist health services or advised to consult their publicly assigned GP for further follow-up.

4 Results

4.1 Substudy 1

4.1.1 Paper I

In the complete sample (n = 90) of men with prior or current AAS use for more than 12 months, the average age (mean±SD) was 38.9±10.6, AAS debut age was 22.6±7.8 years, with an average accumulated AAS usage of 11.9±8.5 years. The TSG included 41 males (45.6%) who had sought treatment at least once during their lifetime due to AAS related adverse effects, while the 49 males (54.4%) had not and comprised the non-TSG. Preventive health check-ups were the primary reason for seeking treatment (n = 22, 53.7%), and 38 men (93%) in the TSG were open about their AAS use during consultations with health professionals. The TSG were about five years younger and reported more side effects, including gynecomastia, excessive sweating, fatigue, depression, and anxiety, and expressed greater concern about testosterone deficiency than the non-TSG. However, following the Benjamini–Hochberg FDR correction that was implemented post-hoc, only the latter measure remained a significant finding. The main reasons for not seeking healthcare services included the belief that the experienced side effects did not warrant treatment (n = 39, 79.6%) and the perception that healthcare providers lacked sufficient knowledge about AAS use and its health effects (n = 12, 24.5%).

4.1.2 Paper II

Data were collected from a self-report questionnaire, clinical interview, blood sample and a physical exam of the same 90 men as described in Paper I; with a TSG (n = 41, 45.6%) and a non-TSG (n = 49, 54.4%). To account for associations between current AAS use on physical examination measures, the groups were secondarily also subdivided according to current or former AAS use. Fifty-nine (66%) men reported current AAS use, and among those with former AAS use (n=31, 34%), a median duration of two years (IQR 1-4.5 years) was reported since AAS cessation. Among men with current AAS use, there was a greater occurrence in the TSG compared to the non-TSG of dyspnea (50% vs. 7%, p=0.000) and reduced LVEF in combination with LVH (36% vs. 9%, p = 0.017), and/or sign of hypertension (32% vs 6%, p=0.015) / (55% vs. 19%, p = 0.041). The findings remained significant after conducting multiple comparison tests (FDR). The findings also illustrated that a large proportion in the non-TSG exhibited potential symptoms and signs of CVD. Among men in the non-TSG with *current* AAS use, 47% had one or more symptoms potentially related to the heart, 34% had reduced LV systolic function, 28% showed signs of LV hypertrophy, and 48% had elevated blood pressure. Among men with *former AAS use* in the non-TSG, as much as 77% had one or more cardiac-related symptoms, 38% had reduced LVEF, 15% showed signs of LVH, and 36% had high blood pressure. See Figure 6 for an illustration of selected CVD findings in the different groups. Abnormal liver and

kidney parameters were noted in several participants in the overall sample, but no significant differences were observed between the TSG and the non-TSG.

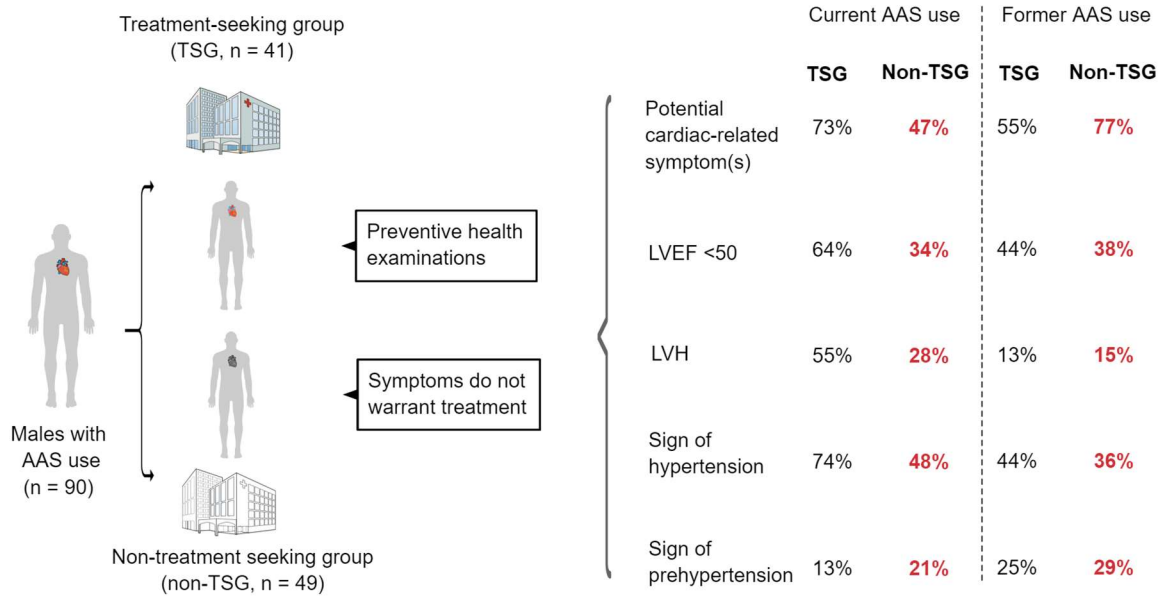

Figure 6: Selected key findings from Substudy 1. Pathological cardiovascular observations in the non-TSG are highlighted in red to underscore the seriousness of underlying health risks in the men who had not sought health services. AAS = anabolic-androgenic steroids, TSG = treatment-seeking group, non-TSG = non-treatment seeking group, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy. Figure created in the Mind the Graph platform. Copyright HCB Henriksen.

4.2 Substudy 2

As Paper III serves as a protocol paper delineating the objectives and methodology of the main pilot intervention study (CloTASH), it does not include a data and a results section. Paper III should therefore be seen as a supplement to the methods section, where it describes the different data that were collected during the PhD-work, and of which some is presented in this thesis. Consequently, further elaboration on Paper III will not be provided in this segment.

4.2.1 Paper IV

Out of 81 potential participants, only twelve were deemed eligible, eleven started and ten successfully completed the intervention. Reasons for exclusion included residing outside of Oslo where the study was conducted, engaging in illicit substance use, or having severe medical conditions, see Figure 7. Various challenges in the recruitment process were identified and included study postponements due to the COVID-19 pandemic, funding constraints, and the effectiveness of social media advertisements.

Although social media appeared to be the primary platform for reaching the public and potential study participants, some initial recruitment advertisements were limited due to breaches of community guidelines. Furthermore, financial costs related to transportation to and from the study site, as well as user fee for each visit to the outpatient SUD clinic, likely impacted the study inclusion by dissuading individuals with economic challenges.

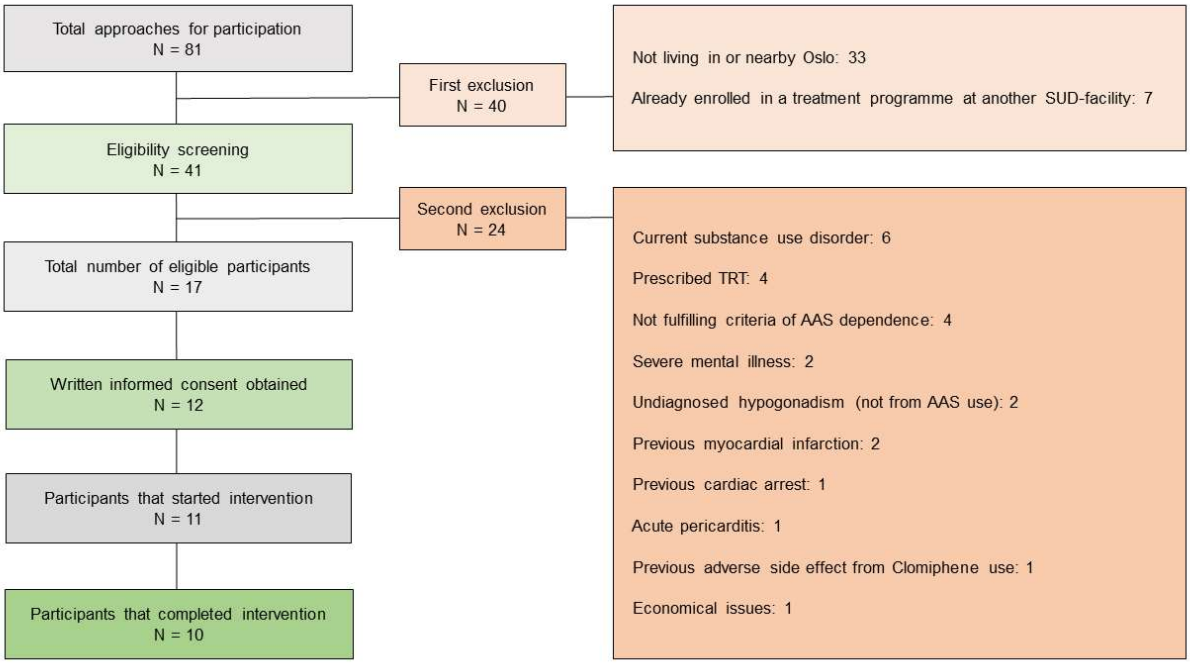

Figure 7: Modified flowchart of the inclusion process for the pilot study, as originally presented in Paper IV.

A thematic analysis of an AAS forum discussion thread that was started by the researchers in an attempt to recruit participants, showed that AAS forum members a) suggested modifications to the intervention such as using higher dose or other substances, b) expressed reservations about the requirement for SUD treatment to participate in the study, c) feared prosecution or other negative outcomes due to health service providers' reporting practices, and/or d) preferred seeking online advice for self-initiated TRT or PCT. Drawing from the insights gained during the recruitment process, recommendations for future studies with similar objectives were provided. These recommendations included user involvement in early study planning, prioritizing safety assessments when conducting off-label intervention studies, implementing parallel, free and optional SUD treatment follow-ups, employing economic incentives for participants due to time consuming investigations, simplifying study examinations with fewer study locations, and utilizing a professional helpline for recruitment.

4.2.2 Paper V

4.2.2.1 Safety measures

Ten participants completed the 16-week intervention, with median age 32 years (IQR 30-45), with a mean±SD accumulated AAS use of 11±4 years. During intervention, seven participants reported at least one adverse event, with headaches, dizziness, and mood swings being the most common, and no serious adverse events occurred. No major abnormal findings were noted on physical exams before or during the intervention, including heart and lung auscultations, edema of lower extremities, gynecomastia and visual exams of eyes. From the start to the end of intervention, there was a significant reduction in hematocrit (0.49±0.04 to 0.46±0.04, p=0.002) and hemoglobin levels 16.4±1.4 to 15.5±1.1, p=0.001). At baseline, seven of ten participants reported reduced life zest, and three reported indifference to death or a recent desire to die. At weeks 8, 12 and 16, no participant showed indifference to death or a recent desire to die, but two still reported reduced life zest at week 16. The findings indicate that the 16-week intervention for men with long term continuous AAS use with CC therapy may be considered safe among participants in our study.

4.2.2.2 Feasibility of intervention

In the total sample, there was an overall increase during intervention in median levels of FSH (0 (IQR 0-1) to 3.2 (IQR 2.7-3-6), p=0.0001) and LH (0.2 (IQR 0-0.5) to 4.9 (IQR 3.6-5.8), p=0.006), as well as an increase in mean±SD SHBG (18±5.6 to 32±14.9, p=0.0003). The individual HPG axis response varied greatly among the participants. Half of the participants (n=5) experienced an endogenous TT response characterized by TT levels reaching ≥ 20 nmol/l during or at the end of the intervention, or ending up within the normal reference range for TT (≥ 9-30 nmol/l) after 16 weeks intervention. These participants were classified as “responders” to intervention. The TT response did not seem to align with the severity of ASIH related withdrawal symptoms. Among the five responders, all expressed intermittent severe fatigue levels, four reported consistently low well-being, three infrequently scored above cut-off for higher mental distress, and two had consistently high levels of sexual dysfunction. Hence, the intervention’s feasibility in addressing ASIH and assisting those struggling to cease years-long AAS use was only partial established.

5 Discussion

5.1 Summary of main findings

This PhD thesis' objective was to contribute to the current research area on treatment aspects for people who use AAS. It was done through a dual design approach comprising two substudies. The interpretation of the results in this thesis requires careful consideration of various limitations and methodological factors, which will be presented in further detail below.

Substudy 1 presents a cross-sectional design aimed to investigate the relationship between treatment-seeking behavior and AAS-related side effects, health concerns, and verifiable physical harms. Our findings suggest that the men who were more inclined to seek treatment presented with elevated levels of self-reported health concerns and side effects, including shortness of breath and established CVD. The results also indicated that, among participants who had never sought treatment for issues related to AAS, 47% with current use and 77% with former use displayed symptoms suggestive of CVD.

Substudy 2 aimed to explore the challenges experienced in recruitment, and the ethical considerations during planning of a non-randomized proof-of-concept pilot intervention study involving men with long-term AAS use struggling to withdraw use. Simultaneously, the study aimed to assess the safety and feasibility of the hormone intervention. We identified recruitment challenges based on online recommendations from peers, criminalization of AAS use, and mandatory concurrent SUD treatment that all negatively affected recruitment, resulting in a limited number of included participants. However, CC treatment was found to be safe in the ten participants who completed the intervention as none developed serious adverse effects. Moreover, half of the participants developed testosterone levels within physiologic range, even though they continued to experience withdrawal symptoms to a large extent. The following section delves into the clinical implications and limitations of these findings.

5.1.1 AAS-related side effects and concerns and health service engagement

The findings from Paper I-II revealed that all 90 participants in the study experienced one or more side effect from their AAS use. Despite this, only 46% of the sample reported to have proactively sought any kind of treatment due to AAS-related health problems or concerns during their lifetime. Nonetheless, on a global scale, a health service engagement rate of approximately 50% should be deemed high in this particular population (164). In fact, previous investigations centered on individuals using AAS and experiencing health issues have revealed a much lower rate of treatment-seeking (163, 166, 200). However, different reasons prompt individuals to seek medical attention in the context of AAS use. In our study, the treatment seekers experienced more health concerns and side effects in general compared to the non-treatment seekers, specifically fatigue, depression, anxiety,

gynecomastia and hyperhidrosis. Despite this, motivations to pursue treatment may not necessarily align with existing health concerns or side effects but rather reflect expectations regarding the potential treatments offered by the healthcare system (47, 177, 201-203). In fact, only 27% of the participants recognized androgen deficiency as a reason for seeking health services, despite it being highlighted as a primary health concern in the TSG. The low treatment seeking regarding this issue, might possibly be attributable to the absence of clinical guidelines (204, 205) or clinicians' unwillingness or unfamiliarity to treat ASIH following the discontinuation of AAS use (169, 178). Moreover, as described by members of an online AAS community (Paper IV); trusting the knowledge and advice from experienced forum members and having easy access to non-prescribed PCT, illicit testosterone or other AAS, may also serve as a barrier to seeking treatment as well as to participate in an intervention study investigating this matter. However, in Substudy 2, hormone intervention might have served as an alternative to publicly available treatment, as all participants presented with long-term continuous use with multiple prior unsuccessful attempts to quit use.

Factors attributed to the stigma and criminalization associated with AAS use, as expressed by the online forum members from Paper IV, closely resemble the reasons why people with AAS use avoid seeking health services for treatment (172, 177). Previous findings have emphasized how limited awareness, concerns of stigma, or perceived lack of healthcare professionals' AAS-related knowledge might impact treatment-seeking behavior (134, 145, 163, 166). Since long-term AAS use in particular is associated with adverse health effects of somatic or psychiatric character (5, 89, 98), it raises a concern that such reluctance may contribute to a heightened and prolonged health risk. In fact, more than half of those who refrained from seeking health services in Substudy 1 fulfilled criteria for AAS dependence (DSM-IV), had accumulated AAS use that surpassed ten years, reported ongoing health concerns, and had an average of 13 different experienced side effects related to AAS use. This suggests that individuals with prolonged AAS use exhibit multiple symptoms that could be indicative of potential severe health risks that will remain undiagnosed and untreated.

Nonetheless, preventive health check-ups was identified as the primary motive for seeking health services, in concordance with previous studies (163). In fact, it has previously been revealed that people who use AAS exhibit a higher frequency of hospital contacts compared to general population, mostly due to unspecific examinations (89). Although there is limited research on the efficacy of such interventions, it prompts inquiries about whether they might function as a harm-reduction strategy for severe diseases linked to prolonged AAS use. Previous suggestions of treatments, proposed in response to harms associated with AAS have been recommended to minimize the risks of adverse health outcomes linked to prolonged use (206). However, it is important to note that seeking treatment does not necessarily lead to the identification of health risks or the implementation of harm reduction strategies. Although there is a general lack of research on the effectiveness of harm reduction strategies on AAS, it is likely that these strategies should adopt a more comprehensive approach (207). Firstly, they should encompass the provision of sterile injecting

equipment to prevent blood borne virus transmission; a harm prevention strategy predominantly used in the United Kingdom and Australia (52, 182, 183, 206). Secondly, educational interventions should be implemented to assist individuals in moderating their AAS use, to encourage and support their health post-cessation, and prevent re-initiation (207).

Notably, undiagnosed cardiovascular harm from long-term AAS use is of critical concern, as evidenced both by previous research (69, 83-85) and findings in Paper II, revealing CVD in a large part of the sample that had not sought previous medical assistance. The TSG exhibited significantly higher levels of dyspnea, along with verifiable LVEF, LVH and/or elevated blood pressure in various combinations. It is important to emphasize that dyspnea could be associated with other comorbidities like asthma, allergies, anxiety or anemia (208), and may not necessarily be linked to CVD. Nevertheless, the distinctions were not observed in individual CV parameters, suggesting that presence of more complex CVD may manifest additional symptoms, thereby heightening the likelihood of seeking treatment, similar to the observed pattern of high symptom burden among treatment seekers in Paper I.

In concordance with previous studies (163), concerns about organ health was reported in Substudy 1 as the primary health concern among the total sample (Paper I), and deviant liver- and kidney-related parameters were frequent findings (Paper II). While the latter findings may suggest potential organ-related effects in the general population, caution must be exercised when interpreting these findings in individuals with recent AAS use. In fact, previous research has demonstrated that these changes are to a large extent reversible within this population (24, 122), and that specific parameters like creatinine, eGFR, and AST may deviate not due to organ damage but rather because of increased muscle mass and dietary practices (118, 122). Furthermore, no significant differences were found between the TSG and non-TSG in these parameters, suggesting that its impact is irrespective of treatment-seeking behavior.

5.1.2 Healthcare experiences and AAS disclosure

The level of confidence in the healthcare system's understanding of AAS-related issues might have a crucial impact on treatment-seeking behavior (145). Many people who use AAS perceive that healthcare providers have inadequate knowledge (166, 209), as also illustrated in Paper I. In our study, a substantial majority (93%) of treatment seekers disclosed their AAS use in meetings with physicians, emphasizing higher levels of transparency in patient-provider communication than demonstrated in previous studies (163, 166, 210). This divergence from other studies suggests local variations that could arise from several reasons. For instance, legal implications and concerns about confidentiality are identified as barriers to health service engagement among men who use AAS (52, 134, 172, 177). In nations such as Norway, where use and possession of AAS is against the law (125), it is plausible to anticipate not only a negative outcome on treatment-seeking, but also on the levels of AAS disclosure (177, 181, 202). Moreover, the illegality of AAS may impact the treatment itself, causing healthcare

providers to abstain from prescribing off-label TRT or PCT for addressing low endogenous levels following AAS discontinuation (175). Nevertheless, in concordance with our findings in Norway, Australia also demonstrates a global-high health service engagement among people who use AAS (211, 212), despite the country's illegal status on AAS.

5.1.3 Self-assessment of side effects

Paper I illustrated that in accordance with previous studies (64, 166, 167), the majority of the non-treatment seeking men in our study reported refraining from consulting physicians simply because they perceived no necessity to do so. Furthermore, they demonstrated confidence in their capacity to independently handle ASIH, without resorting to publicly available medical interventions, which they deemed ineffective, as described in both Paper IV and previous literature (183, 204, 209). This is likely due to the widespread reliance on online information sources and peer guidance for monitoring AAS-related side effects such as depression, acne and gynecomastia, or initiating PCT post-cessation to treat ASIH (138, 176). In fact, this practice may serve as an important barrier to engaging public health services (177), including clinical research projects such as our proof-of-concept study. This is particularly the case for men presenting with symptoms of androgen deficiency, struggling to withdraw from use, as there is lack of current clinical guidelines on how to address ASIH (178).

5.1.4 Recruitment to clinical research involving endocrine therapy of AAS dependent men

Paper IV reported the challenges that were encountered in the recruitment of research participants to the pilot study. A significant factor leading to a lower-than-anticipated inclusion number was safety concerns. However, this precaution was deemed necessary as the study tested safety and feasibility of an off-label protocol for a medication that carried potential adverse effects on both physical and mental health. In addition, it had not been tested on AAS dependent men before. The skepticism towards mandatory SUD treatment was highlighted in discussions among forum members addressing the intervention and has also been emphasized in previous studies (125, 134). According to a recent British survey involving 469 men with AAS use, barely half of those asked expressed interest for a potential clinical trial on post-cycle therapy, and a mere 10% of the men believed that conducting a trial through a public service, such as a public endocrinology department, would be the optimal approach (50). Hence, the study's association with a public university hospital linked to public outpatient SUD treatment likely had a negative impact on recruitment. Norway stands out as one of the few countries where AAS use is criminalized under the drug policy and individuals using AAS are eligible for public and reimbursable SUD treatment (125). While this approach has merits, directing attention to people with AAS use and implementing suitable psychosocial treatment strategies, it also has drawbacks, notably in recruiting participants for clinical research, as demonstrated in this study. In fact, concerns about reporting practices among healthcare professionals, as discussed in the thematic analysis in Paper IV, likely contribute to this reluctance.

5.1.5 Online user recommendations

Based on findings from Paper IV, it appears that online advice from peers may be more appealing to people who use AAS than engaging in studies that explore safety and feasibility of PCT protocols. It is important to note that while these forums can be sources of mutual support, respect and camaraderie (164, 179, 213, 214), the reliability and accuracy of the exchanged information is highly variable and often not based on scientific evidence (147). Furthermore, many individuals acquire substances utilized for PCT through these online forums, even though they may be susceptible to counterfeit products (165, 175, 215), potentially leading to health problems (179). Similarly to recent findings (177, 178), forum members aspired future access to legal and prescribed TRT for men with persistent low endogenous testosterone levels, as opposed to resorting to illicit substances, or join a clinical pilot study investigating PCT use. Although prescribed TRT constitute a superior safe option compared to illicit counterfeit products, it is crucial to note that TRT may not necessarily prove effective in treating clinical depressive disorders in men with hypogonadism (28). Hence, the use of TRT for hypogonadism accompanied by significant depressive symptoms should be approached with caution if intended as a viable monotherapy for ASIH, as it only targets the androgenic part of AAS dependence.

5.1.6 The safety profile of post-cycle therapy

While there is an expanding body of literature on the attributes of PCT among people with AAS use (49, 75, 201, 205), there is scarce data examining its safety when used off-label to treat men with AAS dependence. Research in this area is crucial, as previous findings have demonstrated how more than half of the men who use AAS, regularly use non-prescribed PCT between cycles or during AAS discontinuation (145, 146, 216, 217). During the 16-week intervention, as depicted in Paper V, seven out of ten participants encountered at least one adverse event occurrence, but they were all deemed mild and reversible. Moreover, there was an apparent and clinically relevant improvement in zest for life and a reduction in suicidal thoughts. This is in accordance with a recent study from the United Kingdom, which illustrated a 50% lower rate in suicidal thoughts among men who employ PCT, as opposed to those who do not (50). All in all, our findings imply that treatment with CC, combined with hCG, in the given dosages and time period, may be deemed as a safe approach for addressing the androgenic part of AAS dependence. These results align with earlier research on CC (152, 154, 218) and hCG (219, 220) to treat male hypogonadism, with only mild adverse events associated with its use.

5.1.7 Clomiphene citrate to treat AAS-induced hypogonadism

Besides the limited information about CC safety on AAS withdrawing men, there is also insufficient evidence concerning its effect on the recovery of the HPG axis after prolonged AAS use. Despite demonstrating significant effects on endogenous testosterone production in men with hypogonadism unrelated to AAS (154), its specific efficacy in the context of treating ASIH remains poorly documented by the lack of controlled trials. As illustrated in Paper V, a prompted increase in pituitary gonadotropins was seen during intervention, as well as an adequate HPG axis response to produce

endogenous testosterone within the normal range in five of ten participants. The previous limited existing research field on this topic consists solely of observational studies, with two previous studies not finding any associations between PCT and HPG recovery following AAS cessation (92, 95). However, some of the most recent observational research on this matter illustrates how self-treatment with PCT is linked to an accelerated HPG recovery, resulting in notably higher levels of LH and testosterone compared to individuals who do not undergo PCT (49).

The PCT model utilized in the pilot study, as addressed in Paper III, was a modified version of a treatment approach suggested in Rahnema et al. (2014) (44). A noteworthy aspect of the model was the concomitant administration of hCG, which was co-prescribed with CC in seven out of ten participants due to an initially low endogenous TT response. It is probable that the observed positive TT response would be somewhat partly attributable to the inclusion of hCG (175, 219). In fact, previous research has found associations between hCG and the recovery of physiological testosterone and/or sperm levels in men withdrawing from AAS use (149, 221). However, the ideal timing of hCG in connection with CC administration might be subject for debate. Individuals using AAS typically initiate hCG in the initial weeks post-cessation of AAS, followed up by a SERM at a later stage (147). This sequencing is employed because SERMs are anticipated to have diminished effectiveness immediately after AAS cessation when serum levels of GnRH, LH and FSH are fully suppressed (49). Additionally, the therapeutic efficacy of hCG may be compromised in cases of pathologically elevated gonadotropin levels, as observed in patients with primary testis failure and hypergonadotropic hypogonadism (222).

Despite evidence supporting CC and hCG's efficacies in treating *hypogonadotropic* hypogonadism unrelated to AAS use, ASIH could be recognized as a more complex form of hypogonadism. This might explain why only half of the participants achieved gonadal response during the 16-week intervention. ASIH's complexity lies in its association with polysubstance use, often involving high AAS dosages, combined with the use of psychoactive substances and endocrine disruptors, with direct testicular toxicity (44, 97, 138). Consequently, this may lead to a manifestation of combined hyper- and hypogonadotropic hypogonadism, affecting the outcome of endocrine treatment (96).

Regardless of PCT, the HPG axis recovery following AAS use is unique to each individual (44, 123). More accelerated axis response among people with AAS use has been associated with younger age, less time since AAS cessation, lower cumulative lifetime AAS usage, using no more than one type of AAS or low dosages, and having shorter cycle durations (49, 75, 97, 223-225). While the statistical determination of the impact of such factors proved challenging in our study due to the limited number of participants, there was a noticeable negative association observed in individuals of older age or with a longer duration of AAS use.

The achieved TT response in most of the participants did not align closely with the symptoms of hypogonadism. Still, recent findings suggest that men undergoing self-initiated PCT use self-report

60% less withdrawal symptoms than those who does not use PCT (50). This indicates that the level of withdrawal symptoms is likely rooted in various factors. Notably, some men persist in encountering withdrawal symptoms or reduced quality of life even after an extended period of cessation, despite apparent normal HPG axis with recovered physiological levels of testosterone (216). For instance, it is important to note that the participants in Substudy 2 consisted of men with a continuous long-term use with numerous previous unsuccessful efforts to discontinue usage, averaged an AAS duration that exceeded 11 years and fulfilled the DSM-IV criteria for AAS dependence (104). This is in contrast to previous studies investigating PCT, mostly involving men with short-term cycling AAS use with substantially fewer years of accumulated use (49, 95, 122). Moreover, psychological comorbidities and socioeconomic factors might vary considerably among individuals with AAS use, and pre-existing biopsychosocial factors may create differing outcomes (125, 138, 226). For instance, previous research has found associations between AAS use and adverse childhood events such as compromised parent relationships, history of physical or mental abuse, and learning difficulties in school (227). In addition, people with AAS use often has a concurrent use of illicit psychoactive substances (70, 133, 137, 138, 182). Consequently, predicting the cause-and-effect relationship between AAS and psychological symptoms may prove challenging.

Ultimately, the full impact of the hormone therapy on ASIH remains unknown, as the data post-intervention have not been analyzed yet. Nevertheless, data from the 6- and 12-month follow-ups will be analyzed and published in near future.

5.2 Methodological considerations

5.2.1 The choice of study design

5.2.1.1 Substudy 1

In Substudy 1, a cross-sectional design was utilized; a design that may come with inherent biases and limitations, including the issue of causation (228). In an ideal setting, the cross-sectional design could have been replaced by an extensive prospective cohort study on a large scale with thorough follow-up (229). Moreover, a longitudinal assessment over several months could have been used for comparison of study endpoints between treatment seekers and non-treatment seekers; to provide valuable insights into the persistence or resolution of AAS related side effects. However, measurements of life-time treatment seeking still fits with the cross-sectional nature of the study. In addition, cross-sectional studies offer efficiency by being quick and cost-effective, requiring fewer resources due to the absence of follow-ups (230).

5.2.1.2 Substudy 2

5.2.1.2.1 Preliminary studies

In Substudy 2, a single center, open longitudinal, proof-of-concept, pilot intervention study to test safety and feasibility, was presented. It is widely acknowledged that not all research designs are capable of addressing interventions, and that randomized controlled trials (RCTs) serve as the definitive standard for determining the effectiveness of a drug (231). Although randomization is usually the preferred approach, non-randomized designs, such as proof-of-concept studies or pilot interventions, are frequently unavoidable due to practical or ethical constraints (232). Furthermore, non-randomized trials or observational studies of high quality may still have the potential to broaden evidence across a larger population, especially in situations where conducting randomized controlled trials would be considered unethical or unfeasible (233).

While our proof-of-concept study aimed to explore a previously poorly researched field, there was no immediate intention to conduct a full-scale RCT. Instead, our primary goal was to gather data on the safety and feasibility of CC use among AAS dependent men, present insights gained during planning, recruitment and conducting of the study, and provide guidance for future researchers planning to undertake similar studies or a full-scale RCT. Indeed, feasibility and pilot studies are commonly employed during the initial stages of preparing for a potential RCT, as they may play a crucial role in refining trial interventions or outcome measures, essentially replicating, on a smaller scale, the envisioned aspects of a full RCT (234, 235). Moreover, compared to the standard RCT, feasibility studies are generally more flexible, allowing small modifications to the study design if needed (236). Of note, the different preliminary study designs are not always easily distinguishable (237). In fact, our study should be considered a fusion of various designs of preliminary studies, encompassing the designs of a pilot intervention, a proof-of-concept study, *and* a safety and feasibility investigation.

While RCT's are designed to investigate the efficacy of an intervention relative to a control group (238), preliminary studies typically seek to evaluate the practical aspects of conducting an RCT (234). Consequently, the designs of preliminary studies commonly assume a descriptive nature, as exemplified by the findings presented in Papers IV and V. Thus, in line with the characteristics of preliminary studies, our primary emphasis was placed on practical aspects involved in the study such as the recruitment processes, eligibility screenings, potential barriers to participation, ethical considerations, safety and acceptability of intervention, and participant adherence and retention (234).

Importantly, the findings from preliminary studies must be interpreted with great caution, refraining from implying potential efficacy of an intervention in the absence of a proper control group (237). In addition, they should not be used for the sole purpose of making power calculations (239). As outlined in the protocol (Paper III), the initial intention for the pilot study was to compare questionnaire data on withdrawal symptoms following AAS cessation with another single-center,

single-group study involving men temporarily ceasing an AAS cycle without intervention. However, as of this time point, biobanked blood and questionnaire data have not yet been analyzed and will be presented in future publications. Moreover, despite sharing some similarities in design and setting, the data would represent results from two distinct study populations from two different studies. Given the existing challenge of an already small sample size, any statistical comparison between these groups would potentially be challenging to interpret, or in worst case misleading (239, 240).

5.2.1.2.2 Randomized controlled trial options

In the context of the study design presented in Substudy 2, an optimal approach would involve a double-blinded RCT featuring two groups. In this design, the first group would be subjected to the endocrine intervention outlined in the protocol, while the second group would receive a placebo. Alternatively, another viable option would be to explore different interventions with CC or other SERMs, varying in dosages or durations, and subsequent comparison with a placebo. A third RCT alternative could encompass the randomization of participants into three groups: the first receiving CC, the second solely undergoing TRT and the third receiving a placebo. Nevertheless, the necessary timeframe for such investigations would likely extend over a longer period than 16 weeks to determine any statistical effect.

Cross-over designs can sometimes prove advantageous, wherein each participant undergoes the intervention, but not simultaneously; the two groups switch midway through the study (241). Cross-over designs are known to lead to higher power and statistical efficiency, even with a low number of participants (242). However, they would be considered unsuitable for the non-randomized pilot design used in our study, given that typically, the two groups are randomized. Moreover, considering that the pre-condition for commencing the intervention was that participants either currently used AAS or had ceased usage less than four weeks prior, a crossover design would necessitate half of the participants to engage in illicit AAS use while awaiting the intervention, posing an ethical challenge. In addition, during the execution of the study protocol, several meetings with user representatives were conducted, and they advised against the implementation of a RCT design. This aspect will be discussed later under *Ethical considerations.*

One could postulate that the dosage of CC outlined in the protocol (Paper III) was insufficient or that the intervention duration was too brief. Safety evaluations were employed regarding the choice of SERM, its dosages and intervention duration when used off-label, but the proposed therapy model still received various critique among people who use AAS. However, CC dosages up to 50 mg for several years have been found safe for male patients with hypogonadism stemming from other causes than AAS use (243). Hence, the intervention could potentially have continued after the initial 16 weeks with individual assessments regarding dosage sizes and treatment duration, although this approach would not have been regarded as scientific testing of a therapy model.

Lastly, the extensive and time consuming inclusion assessments were challenging for certain participants, given that the examinations occurred at various clinics and involved multiple examiners. This could have been resolved by reducing the amount of foregoing AAS health risk assessments or by relocating them to the same examination sites.

5.2.2 The choice of analyses

5.2.2.1 Substudy 1

To compare numerical variables following a normal distribution, two sample t-tests were utilized. T-tests are considered simple and straightforward to understand and implement, especially when comparing two groups (244), and are well-suited for small sample sizes. However, T-tests are typically confined to pairwise comparisons to reveal differences (245), and are prone to type I errors when conducting multiple tests (246). Numerical data that were non-parametric were compared with Mann-Whitney U tests (Wilcoxon rank sum tests). The Mann-Whitney U test offers a significant advantage by being applicable to small subject samples, and is recognized as one of the most powerful non-parametric tests, despite its susceptibility to type I errors (247). To minimize the risk of type I errors, multiple comparison tests were used to adjust significance levels in Paper II. In fact, adjustments for multiple comparisons might be important to prevent the erroneous rejection of the null hypothesis when no actual effect exists (248). Nevertheless, adjustment for multiple comparisons might also increase the risk of type II errors, where the null hypothesis is accepted when it should be rejected (248). In Paper II, both corrected and uncorrected p-values were provided, with the Benjamini–Hochberg procedure to control the FDR (249). This particular test was selected for its low susceptibility to type II errors compared to other multiple testing correction methods (250). Unfortunately, Paper I did not include adjusted p-values for multiple comparisons, despite conducting numerous tests, which introduces the risk of type I errors. Therefore, the Benjamini–Hochberg procedure was implemented later, to adjust the original significant p-values (<0.05) from Paper I and to control for the FDR. As depicted in Table 1, “concerns about testosterone deficiency” is the only measure that still indicates a significant difference between the two groups after FDR correction.

Table 1 Characteristics between the TSG and the non-TSG from Paper I with FDR corrected p-values

	TSG (n = 41)	Non-TSG (n = 49)	t or $\chi 2$	p-value	p-FDR
Age (years)	36.3±11.3	41.2±9.5	2.216	0.03	0.12
Anxiolytics, current	8 (20%)	1 (2%)	7.571	0.01	0.17
Fatigue	26 (63%)	17(35%)	7.38	0.007	0.10
Depression	20 (49%)	13(27%)	4.759	0.03	0.14
Anxiety	18 (44%)	11 (22%)	4.704	0.03	0.14
Excessive sweating	33 (81%)	28 (57%)	5.57	0.02	0.12
Gynecomastia	20 (49%)	12 (25%)	5.748	0.02	0.12
AAS-related health concerns	30 (73%)	26 (53%)	3.84	0.05	0.23
Concerns about testosterone deficiency	25 (61%)	15 (31%)	8.335	0.004	**0.04***

TSG = treatment-seeking group, non-TSG = non-treatment-seeking group, AAS = anabolic-androgenic steroids, FDR = false discovery rate (Benjamini-Hochberg) corrected p-values, *significance level $p < 0.05$

For the categorical valuables, Chi-square tests and Fisher exact tests were employed. Their advantages include calculation simplicity, robustness regarding data distribution, and versatility in handling data from studies involving two groups (251). A disadvantage lies in the interpretation challenges in cases of large numbers of categories among independent or dependent variables (252); however, this was not applicable for our study.

For the study described in Paper I, some data were missing for the AAS dependence interview. Furthermore, in Paper II, there was a higher amount of missing data on objective measures, particularly blood sampling, due to participants not attending the physical examination or healthcare providers incorrectly marking the requisition form for the required blood parameters. It remains unknown whether the reasons for not attending investigations were linked to a higher cognitive or psychological burden, or due to practical challenges such as taking time off from work. Detailed patterns of missing data were not investigated in the sample, however, an assumption was made that the data were mostly missing at random (253). While complete case analysis could have been an option to handle with the missing data, it was not employed due to the potential loss of significant amounts of data (254). Furthermore, methods involving single imputation, such as mean imputation, were considered to be susceptible to introducing bias and inaccuracies in standard errors (255). At the same time, multiple imputation would have introduced a potential risk of producing misleading results (256). Due to the relatively modest sample size, various degrees of missing on several measures and the aim of retaining statistical power, a conservative strategy for managing missing data was therefore

implemented. This approach included leaving cells with missing data blank, abstaining from the use of imputation methods.

5.2.2.2 Substudy 2

The original protocol paper (Paper III) presents the initial sample size calculation and a planned analysis plan for the future publications on long-term data including analysis of change in health risks from ongoing AAS use to 6 and 12 months post-cessation. The protocol determined that a sample size of approximately 25-30 participants for both the intervention and comparison group would be sufficient to determine statistical and clinically relevant differences between groups and within groups. Of note, comparisons of data from the intervention group and the comparison group, as described in Paper III, are not included in papers of the thesis and therefore not discussed further here.

Paper IV depicts how recruitment of participants proved more challenging than anticipated, limiting both the statistical power and reliability of the results in Paper V. In fact, Paper V presents with a small sample size of ten participants, and it is important to interpret the findings in consideration of this limitation. Furthermore, the absence of randomization limits the ability of this study to draw definitive conclusions. Despite this, the emphasis of our aim was to direct results towards feasibility rather than statistical significance, which constitutes the primary focus of pilot studies in general. Hence, it was considered plausible that the outcome of each participant would be described according to the nature of feasibility studies (234). Still, changes in blood parameters for both the safety measures and sex hormone levels during intervention were analyzed either through one-way repeated measures ANOVA for numerical data following normal distribution, or with Friedman tests for non-normal numerical data. One-way repeated measures ANOVA is efficient in assessing same subjects under various conditions and enhance analysis sensitivity, providing robust assessment of within-subject changes (257). This proves advantageous in intervention studies that compare changes within the same individuals over time. However, one-way repeated measures ANOVA might be disadvantageous in its assumption of sphericity, which implies that the variances of the differences between all possible pairs of conditions are equal (258). Hence, violations of this assumption can lead to inaccurate results. Nonetheless, before performing ANOVA, assumption of sphericity was tested using Mauchly's W tests (259), and Greenhouse-Geisser estimate was applied to ensure the validity of the analysis and prevent potential inaccuracies in instances where the assumption of sphericity was violated (260). Friedman tests were utilized as the non-parametric alternative to repeated measures ANOVA (261). Its advantage lies in its robustness in the presence of skewed or non-normally distributed data, its ability to detect differences in treatments or conditions, and that it does not rely on the assumption of sphericity (262). Subsequent post-hoc analyses, also known as multiple comparison tests, were utilized to reinterpret findings, addressing the unavoidable risk of type I error associated with some statistical tests (263). Finally, post-hoc analyses, such as the Bonferroni

and Wilcoxon signed-rank tests, were utilized in Paper V to pinpoint the actual group differences, providing a more nuanced understanding of the results (261, 264).

In the context of Paper IV, a small netnography employing qualitative thematic analysis of online discussion among people with AAS use was included. Even though netnographies may be observational or interactive (199), this study was conducted post-hoc as a result of an online discussion of a researcher-initiated informational post originally aimed to recruit participants. Still, a thematic analysis was utilized as it may prove useful for uncovering unexpected insights in small and large samples (265). Despite this, the main limitation lies in the fact that the dataset was derived solely from a singular thread involving 20 active forum members without information about intention to cease AAS use. Moreover, as the netnography was not planned and the analysis was conducted after the discussion had ended, it presented no possibility to interact with potential forum members who intended to cease use (provided ethical approval and consent). Seen in hindsight, if the netnography had been included in the planning of the intervention study, the insights gathered from the online forum might have better equipped us to anticipate some of the challenges that were experienced in the recruitment process. Despite the skepticism among potential participants, largely stemming from the illegal status of AAS in Norway - a factor beyond our control - the researchers could have exerted greater efforts to communicate the anonymity guaranteed to all participants, with the assurance that no information would be reported to the police.

5.2.3 Bias

Numerous measures implemented in this thesis heavily rely on self-reporting, particularly regarding the AAS-related side effects and withdrawal symptoms. The utilization of self-report questionnaires is recognized for its susceptibility to introduce information or recall bias due to challenges in remembering accurate information (266). In addition, cardiovascular symptoms in Paper II and CC adverse events in Paper V, were gathered through clinical interviews that were not blinded, with the possibility that interviewers might unintentionally have prompted inaccurate information from participants (267). In addition, SUD treatment during intervention may have affected the self-report of withdrawal symptoms. Similarly, participants' responses to both questionnaires and interviews may have been influenced by social desirability bias (268). To address these potential biases, validated questionnaires were employed, and interviews were structured prior and conducted by trained personnel.

Selection bias arises when the study sample deviates from accurately reflecting the target population (269). The recruitment of individuals involved in illegal substance use poses several challenges, including skepticism towards researchers or healthcare professionals and the fear of legal consequences for disclosing usage status, which could hinder participation (145, 163). For instance, the study sample from Substudy 1 could potentially comprise a self-selected group consisting of men who are comfortable with research participation, whilst excluding those with the most severe

outcomes of AAS use or those with biggest skepticism to traditional healthcare. In contrast, the sample from Substudy 2 could constitute a self-selected high-risk group due to their long-term AAS use, multiple attempts of cessation and serious symptom burden. In addition, individuals with distressing symptoms could be more prone to seek participation in health-focused research projects (270).

6 Ethical considerations

Of note, in Paper I, IV and V, as well as in this thesis in general, only inclusive and person-first language was utilized, portraying individuals as having an AAS use rather than being "AAS users".

6.1 Describing side effects

In Substudy 1, considerable emphasis was placed on subjective and objective side effects related to long-term AAS use, and the underlying hidden risks in individuals not seeking treatment. However, many people who use AAS believe that researchers tend to overemphasize the link between AAS use and negative outcomes, often highlighting extreme cases of health risks exhibited by those with years-long accumulated use rather than accurately portraying the actual majority (271). In this way, one might argue that the potential self-experienced positive benefits associated with AAS use, such as enhanced muscle growth, as well as improved levels of energy, self-esteem, libido and well-being, (122, 272, 273), have been largely overlooked in previous research. Hence, only giving focus to the high risk-related use of AAS, such as the side effects involved in Paper I and the main focus being CVD in Paper II, might lead to the perception that AAS use is inherently negative (178). Moreover, there have previously been concerns regarding the mainstream scientific and health research approach to AAS use, asserting that it has led to misrepresentation and stigmatization of people who use (178, 274). Ultimately, it could weaken the effectiveness of public health initiatives among those individuals who do not associate their AAS use with risk behaviors (275).

6.2 Before intervention

While planning the study, workshops with a user panel were undertaken, to improve the study methodology, meet the needs of people who use AAS and ultimately the quality of health care (276). The chosen endocrine intervention, clinical assessments and online questionnaires were discussed, approved and supported by the panel both before applying for funding and after funding was secured. When discussing the design in an early phase, numerous individuals within the user panel expressed caution regarding the implementation of a RCT study design. Their reservations centered on the early intervention dropout rates associated with this design, as the randomized placebo group were likely to recognize their assignment as receiving a placebo. Hence, such recognition could precipitate the manifestation of strong ASIH symptoms, leading to subsequent dropout, and a simultaneous return to illicit AAS use. Furthermore, given the elevated risk of suicide during AAS withdrawal, it was deemed unethical to administer a placebo and potentially expose the study population to such risks. This concern was particularly important as the sample was already considered a high-risk group due to their years-long AAS use and substantial symptom burden.

Several potential participants that approached with an intent to participate in the study, and with a concurrent strong desire to quit AAS use, were excluded due to safety concerns. This can present an ethical challenge, as excluding AAS dependent men from a potential effective treatment

would subject them to continued illicit use of potential counterfeit products and continued harm associated with long-term AAS use (5, 165). However, since intervention with CC had not been scientifically tested on men with long-term AAS use, uncertainties existed regarding its safety potential. All participants were enrolled in mandatory SUD treatment at the time of study inclusion. This was mainly due to the heightened risk of severe depression with suicidal ideation after AAS cessation, as experienced by OUH during 15 years of providing SUD treatment to this patient group and also described in previous literature (99, 128, 277). In addition, psychosis with suicidal behavior has been reported as a rare adverse effect of CC use (159). While hormone therapy addresses the endocrine aspect of AAS dependence, SUD treatment aims to address other factors such as body image disorder and reward effects (125). Nevertheless, to recruit more participants, SUD treatment could have been made optional, or limited to participants displaying specific conditions, such as suicidal ideation during AAS withdrawal, body image disorder, or comorbid mental health issues requiring additional psychosocial follow-up.

Concerns about police reports, legal consequences, stigma, or the apprehension of personal information related to AAS use being documented in electronic personal health records could have all affected participation in a clinical study alongside public SUD treatment. In fact, many people who use AAS are reluctant to identify themselves as SUD patients, as their consumption of AAS and other IPEDs is linked to the enhancement of physical appearance, strength and aesthetics, in conjunction with a strict diet and exercise regimen (177, 278). Thus, despite comparable treatment practices, they might be disinclined to pursue SUD treatment if placed in the same environment as individuals undergoing treatment for addiction to psychoactive substances (207). Of importance, previous research on AAS use might have indirectly contributed to stigmatization by portraying people who use AAS as deviant, criminal or “drug abusers” (171).

It may be argued that the intervention model outlined in Substudy 2 may be perceived as a continuation of IPED use through alternative means, and that it merely provides a way for AAS use to persist under a different designation. Nevertheless, the main objective of the intervention was to assist AAS dependent individuals with prolonged usage in achieving permanent cessation. Additionally, a prerequisite for participation was that participants had made prior attempts to quit and currently expressed a desire for permanent cessation. Therefore, the treatment intervention should be seen as an active discouragement of prolonged AAS use rather than promoting it.

Certain aspects of the recruitment experiences in the Substudy 2 gathered from online forums were analyzed and published for methodological purposes (Paper IV). To preserve the anonymity of online forum members, we carefully excluded any sensitive or potentially identifiable information from the quoted and discussed material. We thoroughly reviewed and discussed a research guide on internet research ethics from *The National Committee for Research Ethics in the Social Sciences and the Humanities* (2019)(279) with the Data Protection Officer at Oslo University Hospital prior to publication. Our analysis revealed a common perception that healthcare professionals lack sufficient

knowledge about AAS and may not be genuinely interested in addressing the specific needs of people who use AAS (145, 171).

As also discussed in Paper IV, economical challenges among potential study participants could have influenced negatively on the inclusion process. In retrospect, to enhance study recruitment, we could have compensated participants for the time and effort invested in attending health assessment examinations before and after the 6- and 12-month intervals.

6.3 After intervention

After the end of the intervention, all research participants were followed up accordingly based on individual needs. All participants could continue the SUD therapy at the outpatient clinic at OUH. Moreover, they retained access to an open line via email and phone to the research physicians, before a more comprehensive physical and mental assessment took place at the 6 and 12-month follow-up. In addition, close collaboration between research physicians, their assigned SUD treatment provider and/or participants' GPs was also possible if needed and desired by the participant.

Another ethical consideration included the introduction of low-dose rescue medication in the form of daily 50 mg dermal testosterone application after the intervention. This modification to the original study protocol underwent careful ethical consideration and received approval from the Regional Committee for Medical and Health Research Ethics. The provision for low-dose rescue medication was introduced as an ethical amendment for in total three participants experiencing persistent low LH, TT and FTI levels, and ASIH withdrawal symptoms, despite completing intervention protocol and following SUD therapy. Dermal application of low-dose testosterone treatment was chosen for its ability to achieve physiological testosterone levels while concurrently causing less suppression of endogenous production compared to supraphysiological administration of AAS (280). Since the HPG axis is most commonly normalized 3-18 months after discontinuation of AAS use (24, 75), most public endocrinology units in Norway would require at least 1 year without AAS use before an endocrinological assessment may take place. Furthermore, men with short-term ASIH (< 1 year since AAS cessation) would not be entitled to receive TRT through a reimbursable prescription prescribed by a public endocrinologist, as it does not classify at this stage as an evident chronic form of either primary or secondary hypogonadism (123).

Alternatively, participants had the option to request a (temporary) TRT prescription from their assigned public GP, or from a private physician. Notably, since the commencement of TRT in Norway typically necessitates an initial assessment by an endocrinologist and clinical treatment guidelines for ASIH are lacking, it would therefore be categorized as off-label treatment in these cases. As a result, such a request could be at risk of being rejected by a public GP. It was believed that TRT prescribed as rescue medication following intervention would prevent a restart of non-prescribed testosterone or other illegal AAS for self-initiated substitution therapy. In fact, a potential restart of illicit preparations would pose further health risks, including the exposure to contaminated and counterfeit products,

leading to potential infections and side effects (165). At the 6 and 12-month follow-up, the research physicians reassessed all participants undergoing rescue medication. If there was still no sign of HPG axis recovery by the 12-month follow-up, participants were considered for endocrinologist referral, and subsequent specialist evaluation in a public hospital would be undertaken for the potential initiation of lifelong TRT on a reimbursable prescription.

7 Clinical implications

The use of AAS may lead to extensive medical consequences. As recreational AAS use is a relatively recent form of substance use in the general population, there is an anticipated rise in individuals seeking health services for issues related to long-term AAS use in the coming decades. While not everyone who uses AAS will experience severe side effects, a considerable number may encounter adverse health consequences, exacerbated by a longer duration of use and polysubstance use. There is discrepancy regarding healthcare professionals' familiarity with AAS use, related adverse effects and treatment options. Many who use AAS, partly as a consequence of this, have little trust in healthcare professionals. The hesitancy of individuals using AAS to seek treatment, even when faced with side effects and health concerns, might contribute to persisting health risks.

Our study identified a considerable number of men exhibiting health concerns and symptoms and signs indicative of potential severe CVD, yet refraining from seeking treatment. These findings suggest a lack of awareness among study participants regarding the severity of cardiovascular adverse effects. Although our results imply that CVD might manifest as shortness of breath and prompt treatment seeking, underlying AAS-associated cardiovascular pathology may still be asymptomatic. Moreover, as hypertrophic cardiomyopathy may go unnoticed on a regular electrocardiogram in this particular patient group, echocardiography should be considered a gold standard for diagnosing severe CVD among people with yearlong AAS use.

The findings in this thesis underscore the complexity of factors influencing treatment-seeking behavior among people who use AAS. Addressing gaps in healthcare providers' knowledge of potential AAS health risks and improve patient awareness are crucial for enhancing engagement to health services. This approach could facilitate the early detection and prevention of harms linked to AAS usage such as cardiovascular risks and persistent ASIH.

The effectiveness of endocrine therapies in alleviating ASIH withdrawal symptoms among AAS dependent individuals attempting to discontinue use remains unclear. Although the individual intervention outcomes outlined in Substudy 2 may not carry direct implications for clinical practice at this stage, the research project still offered comprehensive support and surveillance for the participants involved. Furthermore, the findings demonstrated important aspects for recruitment to health research among this patient population.

Findings from this thesis and other recent studies should be made more easily accessible to the general population through social media and other relevant online channels that have extensive reach, in particular among people with AAS use. Moreover, the results indicate that the AAS community tends to place greater trust in men with extensive AAS experience compared to healthcare professionals and researchers, especially in regards to advice about TRT and PCT. A possible solution could involve creating information channels in collaboration with individuals with extensive user

experience. The content could include long-term adverse effects of AAS use, with particular focus on CVD, and what needs to be addressed during visits to the doctor.

The findings of this thesis propose that collaboration between clinicians, researchers and people with AAS use will be essential for gaining a deeper insight into the treatment of ASIH and AAS dependence. As AAS dependence is multifactorial, clinicians ought to evaluate the reasons behind and motivation for AAS use, as well as the potential inclination to discontinue usage. Furthermore, clinicians should investigate treatment possibilities for concurrent underlying health issues, and contemplate lifestyle or pharmaceutical interventions that can cater to the needs of people with AAS use.

8 Conclusion and future perspectives

Persistent stigma surrounds the utilization of services aimed at addressing AAS issues, and there is a lack of scientific evidence supporting the treatment needs of individuals who use AAS. Future research should explore options to lower this stigma and bridge the connection between health care providers and people with AAS use. Additionally, efforts to tailor interventions based on the specific various reasons for seeking treatment may contribute to a more targeted healthcare approach for this population.

This thesis provides valuable insights for healthcare professionals, and may contribute to the advancement of future clinical studies on different treatment aspects for people who use AAS. It is crucial for future studies to actively involve the target population throughout all stages of the study. Future research should aim at increasing awareness of cardiovascular risks associated with AAS use, provide insights into the progression of cardiovascular issues over time and assess the impact of treatment-seeking behavior on long-term outcomes.

For studies investigating off-label use of SERMs in individuals withdrawing from AAS, safety assessments should be conducted before initiating off-label interventions with PCT. Although a limited prior number of observational studies has offered some evidence on the feasibility of PCT among people with AAS use, the sample size included in this thesis was too small to assess any efficacy of intervention. It is therefore advisable for future research to strive for the replication of these findings in bigger samples using a RCT design. Future RCTs comparing CC effect and safety with a control group need to be conducted to validate the concept of PCT, to investigate whether CC might be a potentially safer option to treat ASIH compared to the TRT. This is in particular importance for young men concerned about future fertility. Ultimately, the findings in this thesis may work as a groundwork for upcoming RCTs on endocrine interventions to treat ASIH. However, drawing from our experience, recruiting participants for larger upcoming intervention studies or RCTs within this patient group may present significant challenges, which needs to be addressed early by detailed planning.

In a clinical future perspective, to ensure better care for this patient group, an attempt could be made to establish and explore the effect of a collaboration model including GPs, SUD clinicians, cardiologists, endocrinologists, and other relevant instances, working together as an interdisciplinary team. This treatment approach would capture the entirety of the complex side effects associated with AAS use.

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10 Errata

Navn kandidat: Hans Christian August Bordado Henriksen

Avhandlingstittel: *Exploring treatment aspects of men with long-term anabolic-androgenic steroid use: A dual perspective on health service engagement and the safety and feasibility of endocrine therapy for anabolic-androgenic steroid induced hypogonadism*

Forkortelser for type rettelser:

Cor – korrektur

Celtf – endring av sidelayout eller tekstformat

Side	Linje	Fotnote	Originaltekst	Type rettelse	Korrigert tekst
10	22		… blodprøve, blodtrykksmåling og ekkokardiografi…	Cor	… blodprøve, blodtrykksmåling og ekkokardiografi (ultralyd av hjertet)
10	33		…blodtrykk og ekkokardiografi (ultralyd av hjertet) er avgjørende…	Cor	…blodtrykk og ekkokardiografi er avgjørende…
11	2		Gruppen følger samtidig et…	Cor	Deltakerne følger samtidig et…
18	10-11		…even among older men with established CVD.	Cor	…even among older men with established cardiovascular disease (CVD).

20	1		…prison sentence or receiving treatment…	Cor	…prison sentence or patients receiving treatment…
22	1		Moreover, approximately one third….	Cor	Approximately one third….
22	18		... AAS dependence is usually assessed…	Cor	AAS dependence is usually assessed…
25	8		Also illustrated to the right in the picture: hCG acts as an…	Cor	Also illustrated to the lower left is hCG which acts as an...
27	26		However, SUD treatment does include initiation of…	Cor	However, SUD treatment does not involve initiation of…
31	34		… using the formula by (189)…	Cor	… … using the formula by Devereux et al. (189)…
33	19		… prior to the hypothesized CC response start.	Cor	… prior to the start of the hypothesized CC response.
36	26		… blood tests and urine screenings for AAS and substance use,	Cor	…blood tests, and urine screenings for AAS and psychoactive substance use,

36	34		…based on online forum thread…	Cor	…based on an online forum thread…
38	11		… participants were covered by insurance against…	Cor	… participants were insured against…
41	31		… as a decrease in mean±SD SHBG…	Cor	… as an increase in mean±SD SHBG…
42	23-25		We identified recruitment challenges, based on online recommendations from peers, criminalization of AAS use, and mandatory concurrent SUD treatment negatively affected recruitment, which resulted in…	Cor	We identified recruitment challenges based on online recommendations from peers, criminalization of AAS use, and mandatory concurrent SUD treatment that all negatively affected recruitment, resulting in…
46	25		… as depicted in Paper III…	Cor	…as depicted in Paper V…
47	33		… testicular toxicity (44, 97, 138)- Consequently, this…	Cor	… testicular toxicity (44, 97, 138). Consequently, this…
47	34		…affecting the outcome of ASIH recovery…	Cor	…affecting the outcome of endocrine treatment…

47	36		Regardless of PCT use, the HPG axis recovery following AAS is	Cor	Regardless of PCT, the HPG axis recovery following AAS use is
53	21-22		…ANOVA for numerical data, or with Friedman tests for non-numerical data.	Cor	…ANOVA for numerical data following normal distribution, or with Friedman tests for non-normal numerical data.
58	33		… may go not unnoticed…	Cor	… may go unnoticed…
59	2		… gaps in healthcare provider knowledge…	Cor	…gaps in healthcare providers' knowledge…
60	15		.. investigating the off-label..	Cor	…investigating off-label…
				Celtf	Endre header mellom artikkel I-V med svart fyllfarge samt plassering helt ytterst og øverst i høyre hjørne for å forenkle for leseren å finne riktig artikkel.

Papers I-V

I

Henriksen *et al. Substance Abuse Treatment, Prevention, and Policy* (2023) 18:19
https://doi.org/10.1186/s13011-023-00528-z

Substance Abuse Treatment, Prevention, and Policy

RESEARCH

Open Access

Health service engagement, side effects and concerns among men with anabolic-androgenic steroid use: a cross-sectional Norwegian study

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Abstract

Background Recreational use of anabolic-androgenic steroids (AAS) is a public health concern world-wide associated with a range of physical and psychological side effects. Still, people who use AAS tend to be reluctant to seek treatment. This study aims to explore use characteristics, treatment-seeking behaviour, side effects and associated health concerns among men with AAS use.

Methods The study includes cross-sectional self-report data from 90 men with a current or previous use of AAS exceeding 12 months, where 41 (45.6%) had sought treatment at least once during their lifetime, and 49 (54.4%) had not. Health service engagement was examined with descriptive statistics on reasons for contacting health services, transparency about AAS use, satisfaction with health services and reasons for not seeking treatment. Furthermore, experienced side effects and health concerns were compared between the *treatment seeking* and the *non-treatment seeking* group, using two-sample t-tests and Chi^2 or Fisher exact tests for numerical and categorical variables, respectively.

Results All 90 AAS-using men reported side effects from AAS use. Treatment seekers were significantly younger, experienced more side effects including gynecomastia, excessive sweating, fatigue, depression and anxiety, and expressed more concern for testosterone deficiency. Preventive health check-up was the most common reason for seeking treatment (n = 22, 53.7%), and 38 men (93%) were transparent about AAS use during consultations with health professionals. The main reported reasons for not seeking healthcare services were that the experienced side effects were not considered to be of treatment demanding nature (n = 39, 79.6%) and the belief that healthcare providers had scarce knowledge about AAS use and its health impacts (n = 12, 24.5%).

Conclusions Reluctance to seek treatment among people who use AAS, despite having associated side effects and health concerns, may contribute to continued health risks. It is important to fill the knowledge gap on how to reach and treat this new patient group, and policy makers and treatment providers need to be educated on how to meet their treatment needs.

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Keywords Anabolic-androgenic steroids, Image and performance enhancing drugs, Treatment-seeking behaviour, Health service engagement, Physical health, Mental health, Health concerns, Side effects

Background

Anabolic-androgenic steroids (AAS) constitute the male sex hormone testosterone, as well as manufactured synthetic androgens with similar effect and structure [1]. Non-prescribed AAS have been used among professional elite athletes to enhance performance since the 1950s, but is today increasingly more common among recreational gym-goers who use them to improve body image, build muscles more easily and increase the feeling of well-being [2–4]. A meta-regression analysis have suggested that lifetime prevalence rates among men varies between 4 and 6% [2].

Adverse effects from AAS use

AAS use is associated with several side effects, where the extent and severity of health issues seems to depend on AAS type, dose, accumulated time of use, method of administration and unknown predisposing factors [5, 6]. Adverse health effects include cardiovascular harm, infertility, gynecomastia, neurocognitive impairment and musculoskeletal damage [5, 7–12]. In addition, about 30–50% of people who use AAS develop dependence, characterized by continued AAS use despite adverse physical and mental health effects [13]. The dependence is highly linked to symptoms such as depression, fatigue and sexual dysfunction, which are commonly experienced during AAS cessation due to low endogenous levels of testosterone [14–19].

Health service engagement among people who use AAS

Despite the likely risk of use-related health implications and associated health concerns, people who use AAS often show reluctance to contact health services. A new meta-analysis estimated that only 37% of individuals using AAS seek support from physicians [20]. In addition, Zahnow et al. (2017) showed that 67% do not engage health services despite having AAS-associated health concerns [21]. Among those seeking support from clinicians, many do not disclose their AAS use [21–23]. Frequently reported reasons for not seeking treatment or not disclosing use are beliefs that physicians lack knowledge about AAS [23], or are not able to help [24]. Other reasons include concerns about stigma [25] or that the problem is not significant enough to seek help [21, 26–28]. Many prefer to seek information from peers [29, 30] and online sources [31–33] on how to avoid and handle side effects [34]. However, in Norway, an anonymous national information service on AAS use, its side effects and the treatment options available, have been helpful for some [35]. As use of AAS is still a young form of substance use that first became prevalent among the general population in the late 80s [36], we might expect an increase of patients with health problems related to long-term AAS use in the coming decades [5]. It is possible that reluctance to seeking treatment will constitute a higher continued health risk. To tailor health services to people who use AAS, knowledge on what kind of support they want and what they find useful is essential [29, 37]. In addition, knowledge is needed about AAS-induced side effects and the health service engagement in relation to these. Some studies have explored experiences with customised harm reduction services [30, 38] and endocrine outpatient clinics for people who use AAS [18, 39]. Other studies have included international samples [21, 37, 40] with great variations in how public and private health services are organized and paid for, meaning that study participants in these studies may not have access to similar health services. Hence, there is still a knowledge gap regarding treatment-seeking experiences and tailored treatment options for this heterogeneous patient group [41]. Norway constitutes a particular setting as people with current or previous AAS use have rights to substance use disorder (SUD) treatment, and public health services are widely available. It may therefore be useful to gather more information about health service engagement, AAS-related health concerns and side effects among people in Norway with current or previous use of AAS.

Aims

In a sample of Norwegian men with current or previous AAS use, we explored characteristics of treatment-seeking behaviour. We wanted to investigate health service engagement related to AAS use, whether those who seek health services during their lifetime experience more side effects or health concerns compared to those who do not, rationales for seeking treatment, experiences with the healthcare system, and contributing factors for not engaging health services.

Methods

Setting

In Norway, all inhabitants are appointed a publicly funded General Practitioner (GP), who can refer their patients on indication to specialized health care facilities. However, patients may also choose to bypass their GP and seek treatment directly in private health care facilities at their own expense. In 2012, persons with current or previous AAS use and related health problems were given rights to outpatient specialized SUD-treatment.

The treatment involves psychosocial support of persons with current or previous AAS use, follow-up on withdrawal symptoms commonly experienced during or after AAS cessation, and treatment of health problems related to current or previous use. In 2013, the Norwegian Drug Act was modified, and use and possession of AAS and other image and performance enhancement drugs became illegal.

Study design

The study is part of a longitudinal study investigating the impact of high-dose AAS use on the brain health and behavior at Oslo University Hospital in Norway [42–44]. The present paper utilizes cross-sectional data collected with self-report web questionnaires in 2017–2019 where a national information service for AAS inspired variables linked to health concerns, treatment-seeking behaviour and treatment satisfaction for people with current and previous AAS use [35], together with elements from Zahnow et al. (2017) [21] adapted for a Norwegian context. The self-experienced side effects are meant to cover a broad spectrum of medical and psychological side effects that high-dose AAS use may cause, based upon literature in the field [5, 45], whereas some (e.g. cognitive side effects) are adapted for the purpose of the longitudinal study. Social media and other relevant online forums were used as recruitment tools, and study posters and flyers were shared at various gyms in Oslo. In total, 90 males above 18 years of age with capacity of giving consent and with a cumulative AAS use of at least 1 year were included.

Measures and variables

Demographic factors Demographics included age, education, work status and parenthood, as well as alcohol consumption and use of prescribed psychopharmacological medication (i.e. antidepressants, anxiolytics or antipsychotics). Variables for AAS use characteristics were debut age, current or previous use, accumulated use in years, side effects from use and dependence.

AAS-dependence Dependence was evaluated using a version of the Structured Clinical Interview for DSM-IV (SCID II) [46] based upon the standard substance-dependence criteria of DSM–IV and adapted to apply to AAS-dependence [24, 47]. The adapted SCID comprises seven items: tolerance, withdrawal, substance used more than intended, desire to cut down on use, much time using substance or recovering from effects, important activities given up due to use and continued use despite health problems. AAS dependence was defined as three or more items coded as severe and occurring during the same 12-month period [47].

Substance use and psychopharmacological treatment Alcohol consumption was evaluated by a self-reported version of the 10-item screening test "The Alcohol Use Disorders Identification Test" (AUDIT), where a score of 8 or more depicts harmful alcohol use [48, 49]. Illicit non-prescribed use and drug-related problems were evaluated using the Drug Use Disorders Identification Test (DUDIT), a screening tool for harmful substance use and dependence following the ICD-10 and DSM-IV diagnostic systems [50, 51]. A score of 6 or more on DUDIT depicts harmful use among men. Regular illicit substance use was defined as use of substances other than alcohol on a monthly basis. Psychopharmacological treatment included self-reported prescribed current or lifetime use of either antidepressants, anxiolytics or antipsychotics.

AAS-related side effects Mental health was assessed by questions addressing to what degree they had experienced psychological side effects, with options ranging from not experienced to a mild, moderate or severe degree. The psychological effects included: Fatigue, sleep disorder, depression, mood swings, anxiety, paranoia, irritability, short fuse, aggression, jealousy, increased impulsivity, reduced empathy, and reduced memory and/or concentration. For analysis purposes, the participants' answers were divided into dichotomous variables (yes/no) depending on whether they experienced psychological symptoms or not. For the physical side effects, the participants answered "yes" or "no" to having experienced one or more of the following: stretch marks, acne, excessive sweating, oedema, hair growth, hair loss, ruptured tendons or muscles, sore injection sites, abscess, gynecomastia, reduced libido, sexual dysfunction and testicular atrophy.

Health concerns The participants were asked to rate their level of concern for common AAS-related side effects, with the options "not worried", "a little worried" or "very worried". For analysis purposes, "a little worried" and "very worried" were grouped together to a "worried"-group and concerns were analysed as dichotomous variables (yes/no). The different health concerns for various AAS-related health problems are listed in Table 3.

Health service engagement Contact with health services during lifetime due to AAS-related side effects or health concerns was measured by contact vs. no contact. If contact had been made, a follow-up question was given with information on which health service had been sought: assigned public GP, a public specialist through a referral from their GP (i.e. a SUD department or specialized somatic health care) or private health care (i.e. private general practitioner and/or a specialist in various somatic health disciplines). Hence, the term 'health service' used

in this paper refers to any of the above mentioned healthcare services.

Reasons for seeking treatment The participants were asked to tick off one or more AAS use-related reasons for seeking treatment including preventive health check-ups, mental health issues (depression, anxiety, mood swings, irritability, anger, aggression, suspiciousness, and/or other), impaired cognitive function (reduced memory and/or concentration), cosmetic complaints related to skin and hair (acne, stretch marks, pattern hair loss and/or hair growth), sexual dysfunction, change of sex organs (testicular atrophy), concerns with internal organs (heart, liver and/or kidneys), gynecomastia, musculoskeletal harm and testosterone deficiency (hypogonadism). In addition, other reasons for health service engagement could be specified in an open response.

Disclosure of AAS use The transparency about use in meetings with physicians was measured by answering "yes, the physician brought it to light, but I did not disclose use", "yes, the physician brought it up", "yes, I brought it up myself" or "no, the physician did not bring it up and I did not wish to disclose use."

Health service experience and satisfaction levels The participants were asked whether they experienced healthcare workers to have enough knowledge about AAS (yes/no/other). Participants' experiences with the health services were rated with scales from 1 (worst) to 5 (best). For analysis purposes, 1 (very dissatisfied) and 2 (a little dissatisfied) were combined as 'dissatisfied', and 4 (a little satisfied) and 5 (very satisfied) were combined as 'satisfied'.

Reasons for not seeking treatment Participants who reported not to have engaged health services were given the following response options for not seeking treatment: feeling of shame, fear of stigma, a belief that the physician could not and/or did not wish to provide treatment, a perceived low knowledge on AAS and its health consequences among health professionals, not experiencing side effects to be serious enough, preferring to self-medicate to prevent or treat AAS-related side effects, fear of legal repercussions (i.e. police fines, child protection services, employer and/or driving license services) and economic reasons (i.e. costs for consultations). The participants could choose one or more options and had the possibility to specify other reasons in an open response.

Statistical analyses

Two-sample t-tests were used for between-group comparisons of numerical variables, while Chi^2-tests and Fisher's exact tests were applied to compare categorical and dichotomous variables. A two-sided p-value of ≤ 0.05 was considered statistically significant. All statistical calculations and analyses were performed using STATA (version 17.0, StataCorp LLC, Texas, USA). There were no missing data from the online questionnaires as mandatory answers were used.

Ethics

All research has been carried out in congruence with the Declaration of Helsinki. The Regional Committees for Medical and Health Research Ethics South East Norway (REC) (2013/601) approved the study prior to data collection. Written consent was collected from all participants at the time of inclusion. A total amount of NOK 500 (≈$50) was given as compensation for taking part in the main research project. All participants had the opportunity to discontinue the study at any point.

Results

Demographics and characteristics of AAS use

Demographic data and AAS use characteristics are presented in Table 1. Those seeking treatment were 4.9 years younger (mean age=36.3 years, SD=11.3) than the non-treatment seeking men (41.2 years, 9.5), p=0.029 and had a higher current use of prescribed anxiolytics at the time of inclusion (n=8, 19.5% vs. n=1, 2%), p=0.006. There were no significant differences between treatment and non-treatment seekers regarding AAS debut age, years of accumulated use or proportion of current use.

Physical and psychological side effects

All of the 90 AAS-using men in the study reported one or more side effects from use, where 41 (45.6%) men had ever sought treatment due to AAS-related side effects or associated health concerns, and 49 (54.4%) had not. The mean of total experienced side effects were 15.7 (SD 6.3, range 4–28) for the treatment-seeking group and 13.1 (6.3, 2–28) for the non-treatment seeking group, p=0.049, whereas the numbers for physical side effects were 8.8 (SD 3.5, range 2–15) vs. 7.5 (SD 3.7, range 1–15), p=0.106, and for psychological side effects 6.8 (4.2, 0–14) vs. 5.5 (3.7, 0–13), p=0.123. The individual self-reported psychological and physical side effects are presented in Table 2. Fatigue (63.4% vs. 34.7%, p=0.007), depression (48.8% vs. 26.5%, p=0.029), anxiety (43.9% vs. 22.4%, p=0.030), gynecomastia (48.8% vs. 24.5%, p=0.017) and excessive sweating (80.5% vs. 57.1%, p=0.018) were significantly more reported in the treatment-seeking group.

Concerns about AAS-related health issues

Concerns about AAS-related health effects were generally more common among men who sought treatment, where 73% (n=30) reported having concerns, compared to 53% (n=26) of those who did not seek health services

Table 1 Demographics and characteristics related to AAS use

	Whole sample (*n* = 90)		Treatment seeking group (*n* = 41)		Non-treatment seeking group (*n* = 49)			
	Mean (SD)		Mean (SD)	Range	Mean (SD)	Range	t	p-value
Age (years)	38.9 (10.6)		36.3 (11.3)	22-74	41.2 (9.5)	25-60	2.216	**0.029***
Education (years)	14.8 (2.4)22		14.8 (2.3)	9-19	14.8 (2.6)	10-23	-0.072	0.943
AAS debut age	22.6 (7.8)		21.6 (7.8)	15-55	23.5 (7.9)	16-50	1.161	0.249
Accumulated AAS use (years)	11.9 (8.5)		11.6 (8.7)	1.5-29	12.2 (8.4)	1-29	0.338	0.736
	n	%	*n*	%	*n*	%	χ2	p-value
AAS dependence (SCID, 5 missing)	52 (n = 85)	61.2	24 (n = 40)	60.0	28 (n = 45)	62.2	0.044	0.834
Current AAS use	59	65.6	25	61.0	34	69.4	0.7	0.403
Current employment	70	77.7	31	75.6	39	79.6	0.205	0.651
Student	15	16.7	6	14.6	9	18.4	0.224	0.636
Children	57	63.3	26	63.4	31	63.3	0.002	0.988
AU/week (mean, SD, range, t)	2.2 (2.9)	0-12	2.4 (3.3)	0-12	1.9 (2.6)	0-10	0.797	0.428
AUDIT ≥ 8	17	19.5	6	15.4	11	22.9	0.776	0.378
Regular illicit substance use	26	28.9	10	24.4	16	32.7	0.742	0.389
DUDIT ≥ 6	12	13.3	7	17.1	5	10.2	0.912	0.340
Psychopharmacological treatment, life-time	36	40	19	46.3	17	34.7	1.262	0.261
Psychopharmacological treatment, current	13	14.4	8	19.2	5	10.2	1.565	0.211
Antidepressants, life-time	21	23.3	13	31.7	8	16.3	3.195	0.074
Antidepressants, current	5	5.5	2	4.9	3	6.1	0.066	1.000
Anxiolytics, life-time	23	25.5	12	29.3	11	22.4	0.546	0.460
Anxiolytics, current	9	10	8	19.5	1	2.0	7.571	**0.010***
Antipsychotics, life-time	5	5.5	3	7.3	2	4.1	0.452	0.656
Antipsychotics, current	4	4.4	2	4.9	2	4.1	0.033	1.000

Data are presented as means (standard deviation, SD) and n (%). *Significant difference between the groups (p≤0.05). Fischer's exact test was used when the expected number were based upon less than five cases. AAS = Anabolic-androgenic steroids, SCID = Structured Clinical Interview for DSM-IV, SD = standard deviation, AU = Alcohol units, AUDIT = Alcohol Use Disorders Identification Test, DUDIT = Drug Use Disorders Identification Test.

(p = 0.050). The different health concerns for various AAS-related health problems are listed in Table 3.

Reasons for seeking treatment

The most common reported reasons to seek treatment, as presented in Table 4, were preventive health check-ups, mental health issues, testosterone deficiency, problems related to internal organs and sexual dysfunction. Other reasons not mentioned in Table 4 included musculoskeletal harm (1), high haematocrit levels (1) and skin abscess requiring antibiotics (1).

Experiences with health services for AAS-related health problems

The number of treatment seekers for each health service and the associated satisfaction levels are shown in Fig. 1. 78% (n = 32) of those seeking treatment had contact with a single health service, 15% (6) had contact with two and 7% (3) had contact with three health services (i.e. their general practitioner, a publicly funded specialist *and* private health care). Seven out of eleven participants who sought help for testosterone deficiency, reported to have visited a private health service. During consultations, 88% (36) of treatment seekers disclosed AAS use themselves, whilst 5% (2) shared information about use when physicians brought it up. The use was not brought up at all in 7% (3) of the cases. While 51% (21) believed that the physicians and other healthcare personnel had enough knowledge about AAS, 41% (17) did not.

Reasons for not seeking treatment

Overall, 49 participants had not sought health services for AAS-related issues. The main given reason for not seeking treatment was not experiencing side effects to be of treatment-demanding nature (n = 39, 79.6%). Twelve participants (24.5%) considered their physicians to have little knowledge about AAS, nine (18.4%) preferred to self-medicate and six (12.2%) did not believe that the health services could offer useful treatment. Other reasons for not seeking treatment included fear of legal repercussions (4), fear of judgement or stigma from health professionals (3), doubting physicians' wish to help (3) or feeling too ashamed (2). No other reason for not seeking treatment was reported.

Discussion

AAS use is associated with physical and psychological side effects that often generate health concerns among those who use. In a sample of 90 men with current and former AAS use, we investigated lifetime

Table 2 Side effects from AAS use

	Whole sample (n = 90)		**Treatment group (*n* = 41)**		**Non-treatment group (*n* = 49)**			
Self-reported AAS-related psychological side effects	*n*	*%*	*n*	*%*	n	%	χ2	p-value
Fatigue	43	47.8	26	63.4	17	34.7	7.38	**0.007***
Sleep disorder	59	33.3	30	73.2	29	50.8	1.934	0.164
Depression	33	36.7	20	48.8	13	26.5	4.759	**0.029***
Mood swings	61	67.8	29	70.7	32	65.3	0.301	0.583
Anxiety	29	32.2	18	43.9	11	22.4	4.704	**0.030***
Paranoia	13	14.4	9	22.0	4	8.2	3.434	0.077
Irritability	54	60.0	23	56.1	31	63.3	0.478	0.489
Short fuse	55	61.1	25	61.0	30	61.2	0.001	0.981
Aggression	38	42.2	18	43.9	20	40.8	0.087	0.768
Jealousy	60	66.7	24	58.5	36	73.5	2.234	0.134
Increased impulsivity	38	42.2	15	36.6	23	46.9	0.981	0.322
Reduced empathy	34	37.8	15	36.6	19	38.8	0.046	0.831
Reduced memory	58	64.4	24	58.5	34	69.4	1.147	0.284
Reduced concentration	32	35.6	18	43.9	14	28.6	2.29	0.130
Self-reported AAS-related physical side effects	*n*	*%*	*n*	*%*	*n*	*%*	χ2	p-value
Stretch marks	46	51.1	23	56.1	23	46.9	0.749	0.387
Acne	59	63.3	27	65.9	32	65.3	0.003	0.957
Excessive sweating	61	67.8	33	80.5	28	57.1	5.57	**0.018***
Oedema	63	70.0	29	70.7	34	69.4	0.019	0.890
Hair growth	46	51.1	25	61.0	21	42.9	2.933	0.087
Hair loss	29	32.2	10	24.4	19	38.8	2.115	0.146
Ruptured muscles or tendons	24	26.6	12	29.3	12	24.5	0.261	0.610
Injection site pain	72	80.0	34	82.9	38	77.6	0.403	0.525
Abscess	23	25.6	12	29.3	11	22.4	0.546	0.460
Gynecomastia	32	35.6	20	48.8	12	24.5	5.748	**0.017***
Reduced libido	30	33.3	16	39.0	14	28.6	1.098	0.295
Sexual dysfunction	25	27.8	14	34.1	11	22.4	1.523	0.217
Testicular atrophy	63	70.0	31	75.6	32	65.3	1.129	0.288

Data are presented as numbers (n) and percentages (%). *Significant difference between the groups (p ≤ 0.05). Fischer's exact test was used when the expected number were based upon less than five cases.

Table 3 Health concerns on side effects from AAS use

	Whole sample (n = 90)		**Treatment seeking group (*n* = 41)**		**Non-treatment seeking group (*n* = 49)**		***χ2***	***p-value***
	n	***%***	***n***	***%***	***n***	***%***		
Having AAS-related health concerns	56	62.2	30	73.2	26	53.1	3.840	**0.050***
Internal organs	48	53.3	26	63.4	22	44.8	3.075	0.080
Testosterone deficiency	40	44.4	25	61.0	15	30.6	8.335	**0.004***
Mental health	32	35.6	16	39.0	16	32.7	0.396	0.529
Sexual dysfunction	29	32.2	14	34.1	15	30.6	0.128	0.721
Gynecomastia	26	26	14	34.1	12	24.5	1.013	0.314
Skin and hair	25	28.9	14	34.1	11	22.4	1.523	0.217
Cognitive function	19	21.1	10	24.4	9	18.4	0.486	0.486
Musculoskeletal harm	8	8.9	4	9.8	4	8.2	0.070	1.000

Data are presented as numbers (n) and percentages (%). *Significant difference between the groups (p ≤ 0.05). Fischer's exact test was used when the expected number were based upon less than five cases.

treatment-seeking behaviour, experienced side effects from use and associated health concerns. Less than half of the men (n = 41, 45.6%) had been in contact with health services. These men were younger, experienced somewhat more side effects from use and had more AAS-related health concerns compared to the men who had not sought treatment. Preventive health check-up was reported as the main reason for engaging health services, while not regarding the experienced side effects to be serious enough was the most common reason not to.

Table 4 Reasons for seeking treatment (n = 41)

	n	%
Preventive health check-up	22	53.7
Mental health	12	29.3
Testosterone deficiency	11	26.8
Internal organs	11	26.8
Sexual dysfunction	8	19.5
Skin and hair	5	12.2
Gynecomastia	5	12.2
Other	3	7.3
Testicular atrophy	3	7.3
Cognitive function	2	4.9

Given reasons for engaging health services (several responses possible) are presented as numbers (n) and percentages (%).

Despite the fact that the proportion who contacted health services in our sample might be considered low, it is found even lower in other studies [20, 21]. A recent systematic review and meta-analysis estimated the prevalence of seeking support from physicians to be 37% among those who use AAS, but with large variations depending on age, access to needle and syringe exchange programs, and geographical locations [20]. Interestingly, the highest health service engagement was seen in Australia (67%). Australia and Norway have similar public information services that have educated physicians on how to monitor and follow up on AAS use [35, 52], which might have positively influenced the treatment-seeking behaviour.

Similarly to previous studies, the most common reasons for not seeking professional help was not considering the side effects to be of treatment demanding nature [23, 26, 27], or the belief that physicians lacked knowledge on the topic of AAS [21–23, 40]. As some physicians might not have adequate knowledge on AAS or routines of mapping use among their patients [23, 53, 54], people who use AAS tend to seek information from each other or elsewhere, in settings which is often referred to as "bro-science" in different online drug communities [55]. The bro-science culture has been perceived as a safe online environment for sharing AAS expertise, exercise and diet advice, as well as recommendations on physical and mental health self-monitoring [31, 56, 57]. Many consider this self-research and trial-and-error practice more trustworthy than taking advice from healthcare workers [29]. AAS-related unspecific health examinations used as preventive measures have previously shown to affect health service engagement positively [16, 21]. In fact, preventive health check-ups was reported as the most common reason for seeking health services in our sample. However, the health gain of preventive measures in asymptomatic persons who use AAS remains little studied. In contrast to previous studies [21, 35], treatment seekers in our study were younger of age. It is possible that younger people who use AAS are more concerned about their health. As AAS use is linked to potential severe health risks such as cardiovascular disease

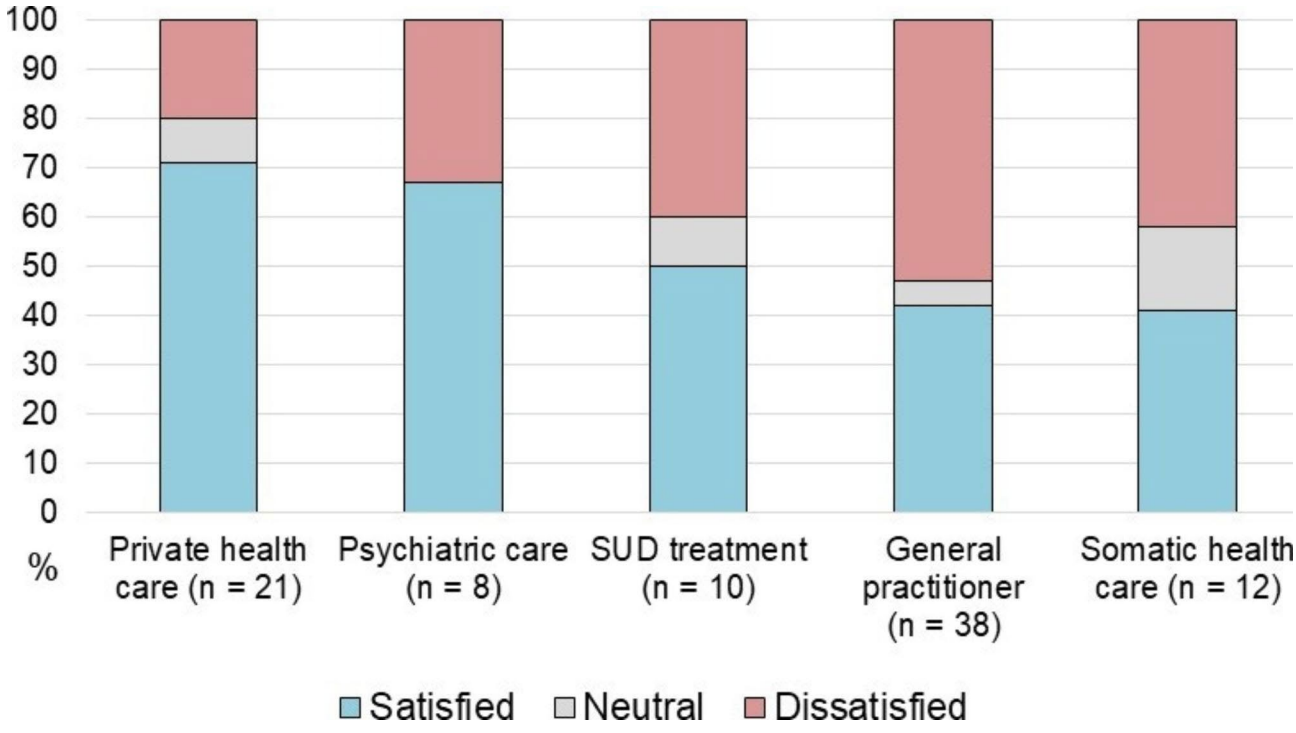

Fig. 1 Number of participants who visited the different health services and associated satisfaction level for each service. Data are presented as percentages of satisfied, neutral or dissatisfied of the total number

including sudden cardiac death [58], this possible new trend of younger and seemingly more concerned treatment seekers might work in favour in preventing future serious adverse effects.

Testosterone deficiency due to AAS-induced hypogonadism (ASIH) is a common side effect from AAS use, characterized by fatigue and depressive symptoms, and known to impair both libido and sexual function [14]. Symptoms of ASIH usually become apparent during or after AAS cessation [14], contributing to AAS restart among many [24, 29, 47]. In most cases, the hypothalamic-pituitary-testicular (HPG) axis recovers within 3–18 months, although some experience reduced endogenous testosterone levels with associated symptoms years after withdrawal [59]. In the current study, concerns for testosterone deficiency were dominant among treatment seekers. Still, only 27% reported this as a reason for seeking treatment, which could be explained by the lack of clinical guidelines on how to treat ASIH. Testosterone substitution or post cycle therapy (PCT), a treatment to enhance endogenous testosterone levels after AAS cessation [60], is generally not recommended during AAS withdrawal [17, 61], as HPG impairment tends to be only temporary. In addition, physicians are also often unwilling to prescribe such treatment, not only due to the lack of research on the area but also to AAS' illegal status in the country [62]. However, non-prescribed PCT is common among people who use AAS [39, 63], and they seek information online and among peers [29, 32–34]. This might be part of the reason why so few seek health services due to ASIH following AAS cessation. Although PCT may reduce symptoms of ASIH, mental health problems seem to be harder to alleviate. In fact, depression, anxiety and fatigue were all side effects more commonly reported among those who sought treatment, and mental health issues was the second most common reason for seeking health services, a finding that is in concordance with previous studies [21, 35]. AAS use has recently shown to be associated with increased use of prescribed psychopharmacological treatment including anxiolytics [64], which was also reflected in the present study as treatment seekers reported significantly more current use of prescribed anxiolytics compared to the non-treatment seeking group. Moreover, it is likely that predefined perceptions of which treatment each health service can provide will influence health service engagement [27]. This could explain why a high proportion of men who sought help for testosterone deficiency due to ASIH chose to engage private health care clinics. The high satisfaction levels with private health care might reflect easier access to clinical examinations, testosterone substitution or PCT, including less reporting practises in private clinics. At the same time, mental health was the main motivating factor for seeking SUD treatment, as this therapeutic approach focuses mainly on psychosocial interventions and symptom-relieving treatment, targeting conditions such as depression, anxiety and sleep disorder [28].

Previous studies have addressed how a high proportion of people who use AAS do not seek treatment despite experiencing AAS-related side effects and health concerns [21, 22, 27, 65, 66]. More than half of the sample in the present study had never sought treatment, despite having an average duration of AAS use that exceeded ten years, 53% having current health concerns and 62% fulfilling the criteria for AAS dependence. In addition, all of the *non*-treatment seekers reported having experienced adverse effects from use with an average of 13 different side effects. For instance, more than 60% of men from this group reported side effects such as reduced memory, mood swings, acne, oedema and testicular atrophy. As long-term use is associated with multiple and even more severe health risks [5, 7, 8, 11, 14–16], it is likely that underlying pathology in these individuals remains undiagnosed and untreated.

Previous studies have suggested that more AAS knowledge among healthcare workers is needed to make treatment-seeking more appealing and less stigmatizing [67]. Since 2014, the National Steroid Project through Oslo University Hospital in Norway has systematically spread information to the Norwegian public on AAS use through social media [68] as well as educated health professionals on how to treat AAS-related health issues [35]. In addition, as one of few countries, people who use AAS in Norway have rights to specialized SUD treatment in the public health care system. These factors could have contributed to a higher percentage of health service engagement in our sample compared to other studies, but also to the notable transparency about AAS use, as disclosure was reported by 93% of the treatment seekers during health care visits. These encouraging findings differ considerably from previous studies [21–23], even though 24% of those who disclosed use were involved in SUD treatment, meaning that transparency about AAS use was likely a precondition for starting treatment.

Limitations

Our study involved self-report questionnaires that could be susceptible for exaggerations, social desirability-bias and missing data through incomplete surveys, although the latter was reduced by using online questionnaires with mandatory answers. The answers might also be subject to recall and reporting bias if use ended years ago, or if health care visits were far back in time. Reported health concerns in our study gives a picture of current worries about adverse events, even though use may have ended several years ago. The study shows that measurement of lifetime treatment-seeking related to adverse effects of AAS use might be an important measure for people

who use AAS, especially among those who never engage health services.

Conclusion

In our study, treatment-seeking behaviour among men who use AAS was associated with age, health concerns, experienced side effects from use and how serious these effects were perceived. Even though long-term AAS use is likely to have a negative impact on health, most of those who use tend to avoid health services. It is likely that such reluctance to treatment-seeking will constitute a higher continued health risk. Any health service may be a potential starting point to assess and treat side effects from long-term AAS use. It is therefore important to fill in the knowledge gap on why so many abstain from seeking treatment, in order to encourage more to engage health services in the future. One important contributing factor to treatment-seeking behaviour, which is supported by this and other studies, is increased AAS knowledge among health professionals. Persons suffering serious adverse effects from long-term AAS use constitute a relatively new patient group. In the current study, we mapped differences in AAS-related health problems among those who engage health services vs. those who do not through self-reported data. However, adverse effects from AAS use might progress slowly and go unnoticed for a longer period, posing in particular a major health risk if involving cardiovascular damage. Hence, there is a need for further research investigating whether treatment seekers also differ from non-treatment seekers on objective health measures. In addition, there is need of more clinical research on harm reduction approaches for individuals with current AAS use and a desire to continue use, as well as treatment options for those with a wish to cease use. Clinicians would also benefit from increased knowledge on AAS-related health risks and how to correctly monitor this patient group with relevant examinations. In that way, harms associated with AAS use might be detected and minimized at an early phase.

List of Abbreviations

AAS	Anabolic-androgenic steroids
ASIH	AAS-induced hypogonadism
AU	Alcohol unit
AUDIT	Alcohol Use Disorders Identification Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DUDIT	Drug Use Disorders Identification Test
GP	General practitioner
HPG	Hypothalamic–pituitary–gonadal axis
ICD-10	International Classification of Diseases 10th Revision
NOK	Norwegian krone
PCT	Post cycle therapy
REC	Regional Committees for Medical and Health Research Ethics
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SUD	Substance use disorder

Acknowledgements
Not applicable.

Author Contribution
Astrid Bjørnebekk is Principal Investigator and was responsible for the study design and data collection. Ingrid Amalia Havnes and Marie Lindvik Jørstad developed questions regarding treatment-seeking behaviour. All authors planned the analyses. Hans Christian Bordado Henriksen conducted the data analysis and wrote the first draft of the manuscript. Ingrid Amalia Havnes, Astrid Bjørnebekk and Marie Lindvik Jørstad provided critical feedback on the manuscript. All authors contributed substantially to the manuscript, and all have approved the final version.

Funding
This research was funded by the South-Eastern Norway Regional Health Authority (Grant No. 2016049, 2017025, 2018075 and 2020088 to Astrid Bjørnebekk), internal research grants from the Division on Mental Health and Addiction (to Astrid Bjørnebekk) and South-Eastern Norway Regional Health Authority (Grant No. 2020090 to Ingrid Amalia Havnes).
Open access funding provided by University of Oslo (incl Oslo University Hospital)

Data Availability
Not applicable.

Declarations

Ethical approval and Consent to participate
All research has been carried out in congruence with the Declaration of Helsinki. The Regional Committees for Medical and Health Research Ethics South East Norway (REC) (2013/601) approved the study prior to data collection. Written consent was collected from all participants at time of inclusion.

Consent for publication
Not applicable.

Competing interests
The authors have no conflicts of interest to declare.

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Received: 22 December 2022 / Accepted: 14 March 2023
Published online: 03 April 2023

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Publisher's Note

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Received: 16 October 2023 | Revised: 14 December 2023 | Accepted: 15 December 2023

DOI: 10.1111/sms.14554

ORIGINAL ARTICLE

WILEY

Treatment-seeking behavior and cardiovascular morbidity among men with anabolic-androgenic steroid use: A cross-sectional study

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Norges Forskningsråd; Helse Sør-Øst RHF

Abstract

Aims: To determine associations between anabolic-androgenic steroid (AAS) use-related morbidity including cardiovascular disease (CVD) and engagement to health services.

Methods: In this cross-sectional study, 90 males with at least 12 months cumulative current or former use of AAS were included. The participants were divided into a treatment-seeking group (TSG) and a non-treatment seeking group (non-TSG) based on their responses to a self-report web questionnaire. All participants were screened for symptoms that could be indicative of CVD through a clinical interview, and examined with blood samples, blood pressure measurements and transthoracic echocardiography.

Results: In the total sample ($n = 90$), mean age was 39 ± 11 years with cumulative AAS use of 12 ± 9 years. Among men in the TSG with current use there were higher prevalence of dyspnoea (50% vs 7%) and reduced left ventricular ejection fraction (LVEF) in conjunction with left ventricular hypertrophy (LVH) (36 vs. 9%) and/or high blood pressure (55% vs. 19%) compared to men in the non-TSG. Among men with current AAS use and established LVEF <50% ($n = 25$) or LVH

($n = 21$), 44% (11) and 43% (9) respectively, had never engaged health services due to AAS-related adverse effects. Deviant liver- and kidney parameters were frequently observed in the total sample but without between-group differences.

Conclusions: Treatment-seeking behavior among current AAS users may be associated with increased levels of dyspnoea and established CVD. Despite objective signs of severe CVD among a substantial amount of study participants, it is of great concern that the majority had never sought treatment for AAS-related concerns.

KEYWORDS

anabolic androgenic steroids, acute kidney injury, androgens, cardiovascular disease, chemical and drug induced liver injury, health care seeking behavior

1 | INTRODUCTION

1.1 | Background

Anabolic-androgenic steroids (AAS) are testosterone and its synthetic derivatives, which have been used for decades, to increase physical strength and to build muscles more easily.[1] It is estimated that about 2%–3% of the general male population in Europe and the US have used AAS at least once during their lifetime, with recreational gym goers and non-athletes constituting the largest subpopulation of AAS users.[2] Cardiovascular disease (CVD) such as reduced left ventricular (LV) ejection fraction (LVEF), valve regurgitation, increased left ventricular mass (LVM), reduced arterial elasticity and hypertension, are strongly linked to both current and past usage of AAS.[3–9] These conditions pose serious health risks, increasing the likelihood of both myocardial infarction and sudden cardiac death.[10–12] Our research group has recently described biventricular cardiomyopathy with severely affected left myocardial function among current and former long-term AAS users.[13] A longitudinal study also revealed that individuals who tested positive for AAS in urine had twice the risk of developing CV morbidity and mortality, compared with those that tested negative.[14] Another study showed a threefold risk of developing cardiomyopathy and atrial fibrillation among AAS users compared with healthy controls as well a fivefold higher risk of thromboembolic events.[15] Illicit AAS use is also linked to other multiple acute and long-term health risks, including endocrine and metabolic harms, mental health problems, and neurocognitive deficits,[4,15–18] where the specific physical side effects include infertility, deviant liver- and kidney parameters, dyslipidaemia, polycythaemia, and reduced brain volume.[1,19–21] In addition, long-term use of AAS in supraphysiological doses disrupts endogenous testosterone production through negative feedback of the hypothalamic-pituitary-gonadal (HPG) axis, and may result in anabolic steroid-induced hypogonadism (ASIH).[17] ASIH symptoms include fatigue, reduced libido, sexual dysfunction, and depression that typically manifest after discontinued AAS use.[21] The AAS prevalence together with its negative health consequences, make AAS use a public health problem.[2]

1.2 | Treatment-seeking behavior for AAS related side effects.

The adverse effects associated with long-term supraphysiological AAS levels, would suggest frequent visits to health services among AAS users. However, recent studies have revealed that many are hesitant to seek healthcare assistance for AAS-related issues, despite the evident risk of health implications associated with use.[22–24] This is concerning as underlying and potentially serious AAS risks may go undetected without targeted medical examinations. It remains unclear whether it is the individuals who actively seek health services who also experience the most complications from AAS use. In a recent study from our research group, we found that treatment-seeking behavior among AAS users was associated with younger age, greater health concerns and more self-reported side effects from AAS use.[24] However, there is a significant knowledge gap on whether individuals who seek health services for AAS-related issues differ in terms of objective measures of physical health including CVD.

In this study, we investigated the associations between treatment-seeking behavior and objective measures on physical health including CVD, in a sample of men with current or former AAS use. Specifically, we aimed to determine differences between AAS users who actively seek treatment facilities for AAS-related health issues and those who do not, in regards to demographics, objective

measures including CV pathology, endogenous hormone levels, and potential harms to the liver or kidneys. Notably, we particularly aimed to bring attention to the potential underlying and undetected pathology exhibited by the group that had never sought health services for AAS-related effects.

2 | MATERIALS AND METHODS

2.1 | Setting

In Norway, inhabitants are entitled to a publicly funded general practitioner (GP) where they can receive treatment or be referred to specialized somatic health services, typically involving a cardiologist or an endocrinologist. Additionally, patients may contact a fully private GP or a private specialist directly without a referral, but at their own expense. In 2013, use and possession of AAS became illegal when the Norwegian Drug Act was amended, and people with AAS-related health problems received patient rights to outpatient substance use disorder (SUD) treatment.[25]

2.2 | Study design and population

This study is based on cross-sectional data from a longitudinal research project that investigates long-term effects of AAS use on cognition, brain, and cardiovascular health at Oslo University Hospital, Norway.[7,13,18,26] Data collection was conducted in 2017–2019. Study participants were recruited through social media and other relevant online forums that targeted people engaged in heavy weight and resistance strength training and bodybuilding. In addition, posters and flyers were distributed at selected gyms in Oslo. The participants were males >18 years of age, capable of giving consent, with either a current or former cumulative AAS use of at least 1 year. A self-report web questionnaire was used to collect data on socioeconomic demographics, consumption of tobacco or alcohol, history and nature of AAS use, and treatment-seeking behavior for AAS-related issues. The estimated lifetime AAS dose was determined by calculating the average weekly dose reported over lifetime and multiplying it by the number of weeks they had been exposed to AAS, consistent with previous research.[18,19] In this specific study, the primary focus was on the lifetime patterns of seeking treatment, with categorization into current or former AAS use considered secondary. The participants were categorized into a treatment-seeking group (TSG) and a non-treatment-seeking group (non-TSG) based on their responses to the self-report web questionnaire. Participants were classified as treatment seekers if they reported to have been in contact with any healthcare provider at least once during or after AAS use due to one or several AAS-related side effects or health concerns (organ health, hypogonadism, sexual health, mental health, changes to hair or skin, cognitive function, gynecomastia, musculoskeletal harm, or other effects). Healthcare providers included their public assigned GP, a public specialist in SUD treatment or somatic health care through a referral from their GP, and/or private health care. Private health care could encompass either a private GP or a private specialist in various somatic health disciplines. Current AAS use was classified based on participants' response to the question "Do you still use AAS?" with the subsequent inquiry about the duration since AAS discontinuation. Former use was defined as at least 1 year since AAS cessation. A follow-up question prompting participants to specify their use phase, allowed for responses such as "I am on-cycle," "I'm off (between cycles)," "I am continuously on," "I have quit using AAS," or "I use TRT prescribed by a doctor." It is important to highlight that the majority of participants that reported to receive prescribed TRT, also exhibited non-medical AAS use alongside their prescribed TRT. Note that the sample is largely overlapping with the sample described in recent studies.[13,24]

2.3 | Clinical measurements

Health professionals at the outpatient clinic of Department of Cardiology, Oslo University Hospital (OUH), conducted both the clinical interview and the physical examination. The participants were systematically asked about symptoms that could indicate CVD such as dyspnoea, chest pain, palpitations, dizziness, and syncope. Blood pressure measurements were obtained using an automatic sphygmomanometer equipped with a standard bladder cuff for most patients, and larger cuffs were utilized for those participants with larger arm circumference. Sign of hypertension was defined as a systolic blood pressure of ≥140 and/or or a diastolic pressure ≥90 mm Hg, while sign of prehypertension, also known as high normal blood pressure or borderline hypertensive, was defined as a systolic blood pressure of ≥130 and ≤139 and/or or a diastolic pressure ≥80 and ≤89 mm Hg.[27]

2.4 | Echocardiographic measurements

Transthoracic echocardiographic examinations were performed at Department of Cardiology at OUH.[13]

Echocardiographic measurements were obtained by one investigator using Vivid E95 (GE Vingmed Ultrasound, Horten, Norway). The data were then analyzed offline by another investigator, blinded to AAS use status, using the software, EchoPAC v203 (GE, Horten, Norway). Left ventricular mass was estimated from parasternal views using the formula provided by Devereux et al.[28] and adjusted for body surface area using the Du Bois' formula.[29] Left ventricular hypertrophy (LVH) was defined as LV mass/BSA >115 g/m^2 in accordance with recent EAPC and EACVI recommendations on evaluation of the athlete's heart.[30] LV mass index (LVMI) was not calculated in cases with poor image quality or inadequate image alignment. LVEF was calculated by modified Simpson's biplane method and categorized into three groups: ≥50% (normal), 41%–49% (reduced), and ≤40% (severely reduced).[31]

2.5 | Laboratory analyses

All reference ranges are according to laboratory standards of OUH (Table S1) where all blood samples were obtained. Laboratory measures of hematocrit, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were analyzed at the routine laboratory (all with Roche Diagnostics) at the Department of Medical Biochemistry, OUH. The eGFR was calculated using the CKD-EPI formula and reported in units of mL/min/1.73 m^2. An eGFR of less than 30 mL/min/1.73 m^2 was defined as severely reduced kidney function.[32] All hormones were analyzed at the Hormone Laboratory, Oslo University Hospital: follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG) (all with Simens, Immulite), total testosterone (TT) (Hormone Laboratory, LC-MSMS), free androgen index (FAI was calculated automatically by the following formula: testosterone (nmol/L)×10/SHBG (nmol/L)), oestradiol (Diasorin, Liason), and thyroid-stimulating hormone (TSH) and free thyroxine (fT4) with Perkin-Elmer, DELFIA. The analyses at the Department of Medical Biochemistry and the Hormone Laboratory were all accredited according to ISO 15189 and ISO 17025, respectively.

As the majority of the objective measures included in the study is affected by current AAS use,[33] we distinguished between current and former users, and assessed the groups separately for all objective measures. Blood analyses among men with former AAS use (i.e., at least 1 year since AAS cessation) was included as Supplementary material.

2.6 | Statistical analyses

Normality was visually assessed with histograms. Numerical variables following a normal distribution were presented as mean ± standard deviation (SD) and two sample *t*-tests were used to compare differences between the TSG and the non-TSG. Numerical data that were not normally distributed were presented as medians (25th–75th percentiles) and nonparametric tests such as the Wilcoxon rank sum tests (Mann–Whitney) were used for between-group comparisons. The chi-square tests were employed for comparison of categorical and/or dichotomous variables, and Fischer's exact test was used when the expected number were based upon less than five cases. A two-sided *p*-value of <0.05 was considered statistically significant. To correct for multiple testing, the Benjamini–Hochberg procedure was implemented to adjust *p*-values where appropriate (i.e., in tables that included *p*-values <0.05) to control for the false discovery rate (FDR). All statistical calculations and analyses were performed using STATA (version 17.0, StataCorp LLC, Texas, USA).

2.7 | Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics South East Norway (REC) (2013/601). All research was carried out in accordance with the Declaration of Helsinki. Prior to participation, all participants received oral and written information about the study and written informed consent was collected from all subjects. Participants were compensated with NOK 500 (≈$50) for participating in the study. All participants could refrain from the study at any point. All pathological findings were evaluated by a physician and investigated further when indicated.

3 | RESULTS

Of note, as objective measures may vary considerably among those who currently use AAS compared to those who have quit, the total sample is assessed separately for current and former AAS users on cardiovascular examinations including echocardiography, and on blood measures (Tables 2–6; Figures 1 and 2; Table S2).

3.1 | Demographics and characteristics of AAS use

Demographic data and AAS use characteristics are presented in Table 1. In the total sample of 90 participants, mean AAS

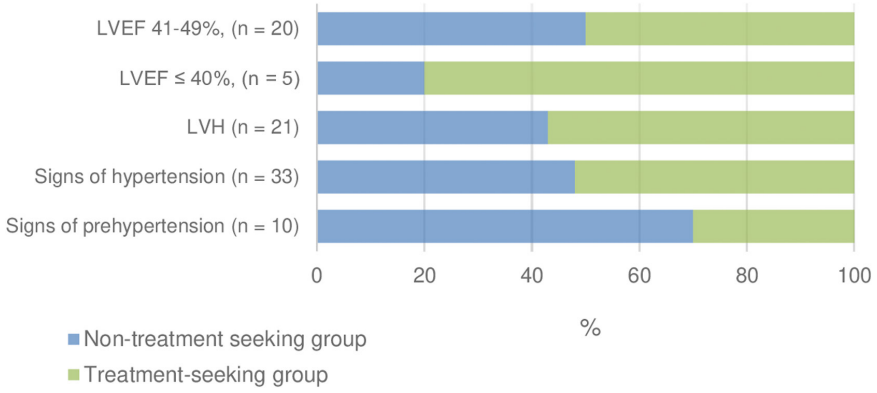

FIGURE 1 Distribution of observed cardiovascular conditions in the two subgroups among men with *current* AAS use. The chart displays the percentage of treatment seekers versus non-treatment seekers within the total population (100%) who exhibited established cardiovascular condition following echocardiographic and blood pressure measurements. LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

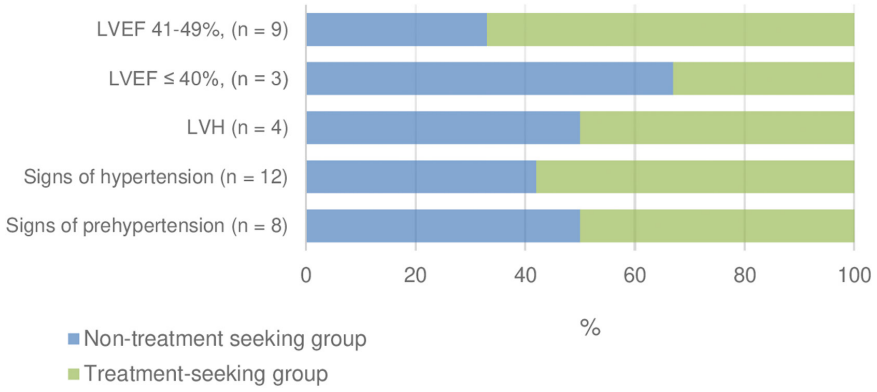

FIGURE 2 Distribution of observed cardiovascular conditions in the two subgroups among men with *former* AAS use. The chart displays the percentage of treatment seekers versus non-treatment seekers within the total population (100%) who exhibited established cardiovascular condition following echocardiographic and blood pressure measurements. LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

debut age was 23 years with a mean accumulated AAS use of 12 years. The TSG consisted of 41 (46%) participants whereas the non-TSG comprised 49 (54%). The two groups were similar on demographics and background characteristics with the exception of age, where AAS users in the TSG were found to be approximately 5 years younger than those in the non-TSG ($p=0.03$). However, this age difference was not significant after correction for FDR (pFDR=0.36). At time of study inclusion, 59 (66%) men in the total sample reported current use of AAS, with no differences between the two subgroups. Participants with former AAS use had a median time of 2 years (25th–75th percentiles 1–4.5 years) since last AAS use.

3.2 | Clinical measurements

Potential cardiac-related symptoms and blood pressure measurements among current and former users are listed in Tables 2 and 3, respectively. Fifty-eight percent of the sample with current AAS use reported one or more cardiac-related symptom, with no differences between the TSG and non-TSG. The proportion of current AAS users that reported dyspnoea was significantly higher in the TSG compared to the non-TSG ($p=0.000$, p-FDR=0). No differences were seen between the TSG and non-TSG among those with former use. As shown in Figure 1, 48% ($n=16$) of current AAS users with sign of hypertension and 70% (7) with sign of prehypertension had not engaged health services. Among those with former AAS use, 42% (5) with sign of hypertension and 50% (4) with sign of prehypertension had not sought prior treatment (Figure 2). There were 14 missing from the total sample on cardiac-related symptoms and four missing on blood pressure measurements.

3.3 | Echocardiography and other vascular measures

CVD, including LV systolic dysfunction and LVH, was observed in both the TSG and non-TSG, with seven

TABLE 1 Comparisons of demographics and characteristics between the TSG and the non-TSG.

	All ($N=90$)	TSG ($n=41$)	Non-TSG ($n=49$)	t or χ^2	p-value	p-FDR
Age (years)	38.9 ± 10.6	36.3 ± 11.3	41.2 ± 9.5	2.216	0.03*	0.36
BMI (kg/m^2)	30.5 ± 4.3	30.5 ± 4.7	30.4 ± 4.0	−0.116	0.91	0.99
Education (years)	14.8 ± 2.4	14.8 ± 2.3	14.8 ± 2.6	−0.072	0.94	0.99
Current student (yes/no)	15 (17%)	6 (15%)	9 (18%)	0.224	0.64	0.98
Current employment (yes/no)	70 (78%)	31 (76%)	39 (80%)	0.205	0.65	0.98
Children (yes/no)	57 (63%)	26 (63%)	31 (63%)	0.0002	0.99	0.99
Smoking (yes/no)	8 (9%)	3 (7%)	5 (10%)	0.23	0.62	0.98
Alcohol consumption (yes/no)	58 (64%)	28 (68%)	30 (61%)	0.487	0.49	0.98
Weekly alcohol units	2.2 ± 2.9	2.4 ± 3.3	1.9 ± 2.6	−0.797	0.43	0.98
AAS debut age	22.6 ± 7.8	21.6 ± 7.8	23.5 ± 7.9	1.161	0.25	0.98
Current AAS use (yes/no)	59 (66%)	25 (61%)	34 (69%)	0.7	0.40	0.98
Accumulated AAS use (years)	11.9 ± 8.5	11.6 ± 8.7	12.2 ± 8.4	0.338	0.74	0.99

Abbreviations: AAS, anabolic-androgenic steroids; BMI, body mass index; FDR, false discovery rate (Benjamini-Hochberg) corrected p-values; non-TSG, non-treatment-seeking group; TSG, treatment-seeking group.

*Significant difference between the groups ($p<0.05$).

TABLE 2 Comparisons of potential cardiac-related symptoms and blood pressure measurements between the TSG and non-TSG with current use.

	All ($N=52$)	TSG ($n=22$)	Non-TSG ($n=30$)	t or χ^2	p-value	p-FDR
Potential cardiac-related symptom (yes/no)	30 (58%)	16 (73%)	14 (47%)	1.162	0.28	0.56
Dyspnoea (yes/no)	13 (25%)	11 (50%)	2 (7%)	12.711	0.000*	0*
Chest pain (yes/no)	9 (17%)	5 (23%)	4 (13%)	0.783	0.38	0.61
Heart palpitations (yes/no)	14 (27%)	5 (23%)	9 (30%)	0.341	0.56	0.70
Dizziness (yes/no)	8 (15%)	4 (18%)	4 (13%)	0.229	0.63	0.70
Syncope (yes/no)	10 (19%)	4 (18%)	6 (20%)	0.027	0.87	0.87
	$N=56$	$n=23$	$n=33$			
Systolic BP (mmHg)	144 ± 17	148 ± 17	141 ± 17	−1.590	0.12	0.3
Diastolic BP (mmHg)	77 ± 10	80 ± 8	75 ± 10	−1.728	0.09	0.3
Sign of hypertension	33 (59%)	17 (74%)	16 (48%)	3.621	0.06	0.3
Sign of prehypertension	10 (18%)	3 (13%)	7 (21%)	0.617	0.43	0.6

Note: Fisher's exact test was used when the expected number were based upon less than five cases.

Abbreviations: AAS, anabolic-androgenic steroids; BMI, body mass index; FDR, false discovery rate (Benjamini-Hochberg) corrected p-values, non-TSG, non-treatment-seeking group; TSG, treatment-seeking group.

*Significant difference between the groups ($p<0.05$).

participants missing from the total sample on LVEF-categories and four missing on LVMI. A higher proportion of treatment seekers were found among current AAS users with combined LVEF <50, LVH and hypertension, as well as those with combined LVEF <50 and hypertension or combined LVEF <50 and LVH (see Table 4). The same differences were not found among those with former AAS use, see Table 5. Notably, among current AAS-using participants with reduced LVEF ($n=25$) and LVH ($n=21$), 44% (11) and 43% (9), respectively, had never sought treatment for AAS-related adverse effects (Figure 1). At the same time, among men with former AAS use and reduced LVEF (12) or present LVH (4), 42% (5), and 50% (2) had never engaged health services, respectively (Figure 2).

3.4 | Hormone parameters

Table 6 presents hormone levels in participants with current AAS use (missing 8–10 in the TSG and 5–7 in non-TSG group). No significant differences were observed between the TSG and non-TSG in hormone measurements reflecting endogenous testosterone production. Overall, the

TABLE 3 Comparisons of potential cardiac-related symptoms and blood pressure measurements between the TSG and non-TSG with former use.

	All ($N=24$)	TSG ($n=11$)	Non-TSG ($n=13$)	t or χ^2	p-value
Potential cardiac-related symptom (yes/no)	16 (67%)	6 (55%)	10 (77%)	1.343	0.25
Dyspnoea (yes/no)	6 (25%)	2 (18%)	4 (31%)	0.504	0.48
Chest pain (yes/no)	4 (17%)	2 (18%)	2 (15%)	0.034	1.00
Heart palpitations (yes/no)	7 (29%)	3 (27%)	4 (31%)	0.035	0.85
Dizziness (yes/no)	3 (13%)	0	3 (23%)	0.261	0.22
Syncope (yes/no)	6 (25%)	1 (9%)	5 (38%)	2.741	0.10
	$N=30$	$n=16$	$n=14$		
Systolic BP (mmHg)	138 ± 15	138 ± 17	137 ± 13	−0.035	0.97
Diastolic BP (mmHg)	75 ± 12	76 ± 11	73 ± 13	−0.712	0.48
Sign of hypertension	12 (40%)	7 (44%)	5 (36%)	0.201	0.83
Sign of prehypertension	8 (27%)	4 (25%)	4 (29%)	0.049	0.32

Note: Fisher's exact test was used when the expected number were based upon less than five cases. Significant difference between the groups ($p<0.05$).

Abbreviations: AAS, anabolic-androgenic steroids; BMI, body mass index; non-TSG, non-treatment-seeking group; TSG, treatment-seeking group.

TABLE 4 Comparisons of echocardiographic findings and sign of hypertension between the TSG and non-TSG with current AAS use.

	All ($N=54$)	TSG ($n=22$)	Non-TSG ($n=32$)	χ^2	p-value	p-FDR
LVEF ≥50%	29 (54%)	8 (36%)	21 (65%)	4.489	0.03*	0.06
LVEF 41%–49%	20 (37%)	10 (45%)	10 (31%)	1.128	0.29	0.29
LVEF ≤40%	5 (9%)	4 (18%)	1 (3%)	3.158	0.06	0.07
LVH	21 (39%)	12 (55%)	9 (28%)	3.586	0.06	0.07
LVEF <50, LVH and ↑BP	9 (16%)	7 (32%)	2 (6%)	5.970	0.015*	0.045*
LVEF <50 and ↑BP	18 (33%)	12 (55%)	6 (19%)	6.790	0.009*	0.045*
LVEF <50 and LVH	11 (20%)	8 (36%)	3 (9%)	5.668	0.017*	0.045*
LVH and ↑BP	14 (26%)	9 (41%)	5 (16%)	4.156	0.041*	0.07

Note: ↑BP defined as a systolic blood pressure of ≥140 and/or a diastolic pressure ≥90 mmHg. Fisher's exact test was used when the expected number were based upon less than five cases.

Abbreviation: BP, blood pressure; FDR, false discovery rate (Benjamini-Hochberg) corrected p-values; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; non-TSG, non-treatment-seeking group; TSG, treatment-seeking group.

*Significant difference between the groups ($p<0.05$).

TABLE 5 Comparisons of echocardiographic findings and sign of hypertension between the TSG and non-TSG with former AAS use.

	All ($N=29$)	TSG ($n=16$)	Non-TSG ($n=13$)	χ^2	p-value
LVEF ≥50%	17 (59%)	9 (56%)	8 (62%)	0.083	0.77
LVEF 41%–49%	9 (31%)	6 (38%)	3 (23%)	0.697	0.40
LVEF ≤40%	3 (10%)	1 (6%)	2 (15%)	0.645	0.57
LVH	4 (14%)	2 (13%)	2 (15%)	0.021	1.00
LVEF <50, LVH and ↑BP	0	0	0	–	–
LVEF <50 and ↑BP	4 (14%)	3 (19%)	1 (8%)	0.871	0.60
LVEF <50 and LVH	1 (3%)	1 (6%)	0	0.905	1.00
LVH and ↑BP	2 (7%)	1 (6%)	1 (8%)	0.010	1.00

Note: Fischer's exact test was used when the expected number were based upon less than five cases. ↑BP defined as a systolic blood pressure of ≥140 and/or a diastolic pressure ≥90 mmHg. Significant difference between the groups ($p<0.05$).

Abbreviations: BP, blood pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; non-TSG, non-treatment-seeking group; TSG, treatment-seeking group.

TABLE 6 Comparisons of blood parameters between the TSG and the non-TSG with current long-term AAS use.

Blood panel	All ($N=59$) Mean ± SD /median (25–75th percentiles)	TSG ($n=25$) Mean ± SD /median (25–75th percentiles)	Non-TSG ($n=34$) Mean ± SD/median (25–75th percentiles)	*p* value	*p*-FDR
P-FSH, U/L	0.1 (0.1–1)	0.1 (0.1–1.2)	0.1 (0.1–1)	0.89	0.95
P-LH, U/L	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.75	0.95
P-SHBG, nmol/L	20.7 ± 16.4	22.3 ± 15.8	19.8 ± 17.0	0.45	0.88
P-TT, nmol/L	31 (12–57)	13 (5–78)	34 (16.5–50)	0.20	0.85
P-FAI	15.0 (4.2–59.3)	6.1 (2.7–52.7)	21.3 (5.3–62)	0.30	0.85
P-oestradiol, nmol/L	0.12 (0.07–0.26)	0.09 (0.06–0.24)	0.13 (0.07–0.29)	0.52	0.88
P-TSH, mIU/L	1.7 ± 0.8	2.1 ± 1.1	1.5 ± 0.5	**0.017***	0.29
P-fT4, pmol/L	15.1 ± 3.3	16 ± 3.4	14.6 ± 3.2	0.18	0.85
P-hematocrit	0.49 ± 0.04	0.50 ± 0.04	0.49 ± 0.04	0.49	0.88
P-hemoglobin, g/dL	16.7 ± 1.2	16.8 ± 1.3	16.7 ± 1.1	0.79	0.94
P-ALT, U/L	41 (33–70)	59 (39–78)	46 (39–58)	0.10	0.84
P-AST, U/L	45 (29–62)	58 (32–67)	45 (43–47)	0.26	0.85
P-creatinine, μmol/L	88 (100–109)	105 (91–109)	98.5 (83–121)	0.75	0.94
eGFR, mL/min/1,73 m^2	79.5 ± 20.3	78.7 ± 23.2	80 ± 19.1	0.86	0.94
P-total cholesterol, mmol/L	4.3 ± 1.0	4.1 ± 1.2	4.4 ± 0.8	0.47	0.88
P-LDL, mmol/L	3.0 ± 0.9	2.9 ± 1.0	3.1 ± 0.8	0.59	0.91
P-HDL, mmol/L	0.8 ± 0.3	0.8 ± 0.4	0.8 ± 0.2	0.95	0.95

Note: Hormone, liver, kidney, and metabolic parameters in men with *current* AAS use. Presented as mean (SD) or median (25th–75th percentiles).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FAI, free androgen index; FDR, false discovery rate (Benjamini Hochberg) corrected *p*-values; FSH, follicle-stimulating hormone; fT4, free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; non-TSG, non-treatment-seeking group; P, plasma; SHBG, sex hormone binding globulin; TSG, treatment-seeking group; TSH, thyroid-stimulating hormone; TT, total testosterone.

*Significant difference between the groups ($p<0.05$).

participants with current use had low gonadotropin levels (FSH and LH) and high testosterone levels, indicative of active AAS use. Table S2 presents the hormone levels, as well as liver, kidney, and metabolic parameters, for participants with former AAS use, with no between-group differences (1–5 missing in the TSG and 4–8 in the non-TSG).

3.5 | Liver, kidney, and metabolic parameters

There were no significant differences on liver, kidney or metabolic parameters between the TSG and non-TSG with current or former AAS use (8–13 missing in the TSG and 5–11 in the non-TSG), see Table 6 and Table S2, respectively. However, deviant results were observed in both groups with current use ($n=42$): Common observations included elevated levels of hematocrit (16, 38%), hemoglobin (18, 43%), AST (18, 43%), and creatinine (17, 40%). It is worth noticing that these blood parameters were largely within the physiologic range among men with former AAS use (see Table S2). Notably, among those with current AAS use, two men with long-term use exceeding 20 years showed signs of severely reduced kidney function, indicated by an eGFR of <30 mL/min/1.73 m^2. Both men had concurrent signs of myocardial disease, but only one had sought healthcare for AAS-related adverse effects.

4 | DISCUSSION

This is the largest study to date exploring treatment-seeking behavior in relation to objective health measures such as CVD in long-term AAS users. Our findings demonstrated how the majority of treatment seekers with current AAS use, exhibited potential cardiac-related symptoms and simultaneous heightened prevalence of impaired LVEF. In addition, experienced shortness of breath, and reduced LVEF in combination with LVH and/or hypertension, were more common in the TSG compared to the non-TSG. Although the average cumulative AAS use was 12 years among our participants, 54% of the men had never engaged health services for any AAS-related side effects. Our findings showed that a substantial proportion of both current and former users in the non-TSG had potential symptoms and signs of CVD. In fact, among the

men in the non-TSG with current AAS use, 47% had one or more symptom that could be cardiac-related, 34% had reduced LV systolic function, 28% LVH, and 48% possibly undiagnosed hypertension. Among the men with former use, as much as 77% had one or more symptom that could be cardiac-related, 38% had reduced LVEF, 15% had signs of LVH, and 36% possibly undiagnosed hypertension.

Not seeking treatment despite experiencing use-related symptoms is not a new phenomenon among AAS users.[22,23,34] Many AAS users do not consider related side effects significant enough to seek professional help,[24,34] while others fear stigmatization from healthcare professionals or perceive physicians to be too uninformed on AAS.[22,35,36] In fact, adequate AAS knowledge among health personnel has previously shown to be a contributing factor to treatment-seeking among AAS users.[25] However, while some do seek health services as a preventive measure,[15,24] use is not necessarily disclosed in meetings with physicians.[22] Consequently, serious side effects from AAS use may be overlooked on regular check-ups, leading to false beliefs of good health and ultimately continued AAS use with further morbidity risk. Indeed, in a sample of 100 men who used AAS in a cyclic pattern including 21 men who initiated their first cycle during the study, the observed physical effects from AAS use were reversed after (temporary) AAS cessation.[33] However, AAS may still lead to substantial risk of CVD in long-term users and also be detectable among those with former use.[13] Notably, despite being a common finding on echocardiography, LVH is often not detected in AAS users with screening tools like ECG.[4,6,8,13] As a result, the effectiveness of preventive health examinations such as ECG by visits to the GP or private health services remains a subject of question and should be addressed in future research. Furthermore, to predict the magnitude of adverse effects associated with AAS use proves challenging when relying solely on self-reported weekly or cumulative doses.[33] This difficulty arises from substantial variation in cycles, including the length and dosages, differences with respect to type of AAS used, and the fact that illegally obtained AAS often do not correspond to the specifications on the label.[37]

In our study, we included CV measures and blood panels to investigate whether any underlying pathology was associated with treatment-seeking behavior. Remarkably, CV findings were highly frequent in the non-TSG among both former and current users. This shows that many AAS users do not engage health services, despite experiencing potential severe adverse effects from use. For instance, hypertension is a known important risk factor for heart failure, heart valve diseases and coronary heart disease,[11,27] and both reduced LV systolic function and hypertension are associated with higher risk of sudden cardiac death.[12,27] Fifty-nine percent of the men with current use and 40% of the men with former use were identified as having sign of hypertension, and nearly half of these had never sought health services for AAS-related morbidity. Additionally, 18% of current users and 27% of former users exhibited sign of prehypertension. According to the 2023 ESH Guidelines for the management of arterial hypertension,[27] lifestyle advice and opportunistic screening for hypertension, are recommended for patients with prehypertension, given their heightened long-term risk of CV events and mortality. The AAS users that had sought life-time treatment due to AAS-related side effects and reported current use, there were also more reports of dyspnoea and a higher prevalence of reduced LV systolic function in combination with LVH and/or high blood pressure, when compared to the non-TSG. This suggests that the presence of some cardiac-related symptoms and established CVD may increase the likelihood of pursuing medical intervention. However, drawing associations between symptoms categorized as "cardiac-related" in our study and confirmed cardiac pathology proves challenging, as these symptoms are nonspecific for CVD and may not be directly connected. Despite this, 50% of the TSG with current AAS use reported dyspnoea, 63% exhibited LVEF <50 and 18% had LVEF <40, suggesting that the experienced dyspnoea could potentially be cardiac-related in some of these individuals.

While the CV adverse effects from AAS use are well documented,[3–5,9,14] potential renal toxicity lacks comparable research attention.[1] In our study, several men exhibited abnormal creatinine and eGFR levels, and two participants with current long-term AAS use displayed signs of severely reduced kidney function. However, whether AAS holds true nephrotoxic effects with potential clinical significance has been disputed.[33,38] The underlying cause of renal impairment associated with AAS use might be multifactorial, involving damage to the glomeruli by increased lean body mass and muscle breakdown, as well as overconsumptions of proteins in diet.[20] Furthermore, renal biopsies of AAS users have revealed structural changes in kidney tissue,[39] indicating a potential direct toxic effect of AAS on cells involved in GFR.[20] According to laboratory standards at OUH at time of blood collection, we used serum creatinine levels to measure the eGFR with the CKD-EPI equation.[32] While eGFR is typically deemed a reliable predictor of decreased kidney function in the general population,[32] it may be not be as attributable among AAS users. This could be explained by the increased daily production of creatinine in muscle-building AAS users due to elevated skeletal muscle mass, the enhancing impact of AAS on endogenous creatine production, and the frequent simultaneous use of dietary supplements aimed to boost muscle creatine stores.[38] Regardless of whether AAS are detrimental to kidney function, it is crucial to note

that long-term AAS usage could lead to increased aortic stiffness and hypertension which ultimately might result in renal damage if left untreated.[5] Thus, the clinical significance of AAS-related kidney damage should not be underestimated, as even a slight decrease of GFR is associated with increased risk of chronic kidney disease, which in turn is associated with overall mortality and higher risk of CVD events.[40] On the other hand, liver toxicity from AAS use is primarily linked to oral androgens, causing elevated bilirubin levels and jaundice.[41] While most participants in our study had ALT levels within normal range, median AST was pathologically high in the TSG and in the upper normal range in the non-TSG with current use. However, AST was considerably lower among those with former use, indicating a gradual normalization after AAS cessation. In fact, higher levels of liver aminotransferases among current AAS users have previously been attributed to intense workout-sessions and muscle building, and could therefore be of less clinical relevance.[33] Notably, a higher AST than ALT, in co-occurrence with high creatinine kinase (CK) levels may be of more clinical use when assessing liver function in recreational strength athletes who use AAS, as it may be indicative of muscle damage rather than liver pathology.[42]

While no differences were observed between the TSG and non-TSG in relation to endogenous testosterone production, the sex hormone panel confirmed ongoing AAS use among current users. In both the TSG and non-TSG groups, low levels of gonadotropins (FSH and LH) due to the suppression of the HPG axis[43] were found, as well as high levels of TT and FAI due to excessive consumption of exogenous androgens. In contrast, individuals that had ceased AAS use ≥1 year prior to study inclusion, had to a greater extent normal levels of gonadotropins and testosterone, supporting previous findings that ASIH usually lasts 3–12 months following cessation.[43] Although ASIH is a commonly observed and feared side effect among AAS users due to its distressing withdrawal symptoms,[17] it does not necessarily lead to an increase in the rate of treatment seeking.[24] This could partly be explained by the absence of clinical guidelines on how to treat ASIH,[44] and the fact that users often self-medicate with non-prescribed post-cycle therapy and testosterone replacement therapy to prevent ASIH symptoms following AAS cessation.[17,44]

Despite minimal differences between the TSG and the non-TSG, we consider the potential high morbidity level in the non-TSG to be one of the key findings of our study. From previous observations of the same sample of AAS-using men engaging health services,[24] we know that treatment-seeking behavior among AAS users is associated with more health concerns and a higher symptom-burden. Hence, our primary focus for this paper was on individuals who have not sought contact with the healthcare system and who have underlying health conditions, as opposed to exploring what attracted the other group to health services. It has previously been questioned whether harms related to AAS use have been overestimated, with many individuals reporting only mild side effects from use.[33] However, our findings suggest otherwise and stress the importance of further education of both people who use AAS and health professionals on the use and risks of AAS. Our study provides insights into the reluctance among AAS users to contact health services, despite experiencing symptoms and signs of underlying AAS-related disease. Although further research is needed to understand the reasons behind the lack of health service engagement, our study should be considered an addition to the existing body of research on treatment-seeking behavior among AAS users.

4.1 | Limitations

Our study has important limitations worth noting. It is possible that AAS-related physical side effects might be exaggerated in our sample, since those who experience symptoms could be more prone to become part of a research project investigating health, and study population might therefore not be fully representative of the target population. Life-time treatment seeking for AAS-related symptoms was measured, but further details on the exact time of health service engagement and AAS use status were not explored. Some of the answers given in the questionnaires, especially those involving a precise length of accumulated AAS use, might be subject to recall and reporting bias if use ended years ago. It is worth noting that AAS users often engage healthcare for preventive purposes, and the motivation for seeking treatment may therefore not necessarily stem from concerns from having dyspnoea or other "cardiac-related" symptoms. Furthermore, the cause of these symptoms and its potential association with CVD remains difficult to determine without a full clinical history, an adequate physical examination and additional investigations. Moreover, objective data collection was incomplete on some measures, especially on blood panels, due to a neglect of participant attendance or the incorrect completion of requisition forms. As previously discussed, eGFRs based on creatinine levels might not be as attributable in this particular population due to several confounding factors among AAS users. Lastly, CK was not measured and could therefore not be used to distinguish between liver and muscle damage among participants with higher AST than ALT.

4.2 | Perspective

AAS use is common among recreational athletes and visitors of fitness centers. This study examined the link between long-term AAS use, physical health problems and treatment seeking. Although deviant liver- and kidney function tests were highly present among participants in our study, the associations with AAS and its clinical significance remain unclear. Signs and symptoms indicative of CVD were prevalent in the majority of current AAS users, and some of these were more present among AAS users who had sought health services compared to those who did not. Our findings suggests that the presence of CVD in this particular group of AAS users may result in symptoms such as dyspnoea, thereby prompting these individuals to seek medical attention. However, despite notable health issues, most of the study participants had never sought medical help for AAS-related issues. Symptoms and signs indicative of potential severe cardiovascular disease were present in a significant number of AAS users in our study that refrained from health service engagement. Our findings may indicate a lack of knowledge among AAS users regarding the potential severity of cardiovascular adverse effects. It emphasizes the importance of increased awareness of AAS-related health risks and of seeking timely medical care to minimize further cardiovascular harm. Both users and clinicians need to acknowledge that underlying CV pathology associated with AAS use may be asymptomatic and even undetectable on certain screening tools. Therefore, blood pressure monitoring and echocardiography are important tools to diagnose AAS-related CVD at an early stage, particularly among AAS users with long-term use.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the manuscript, and have approved the final version.

FUNDING INFORMATION

This research was funded by the South-Eastern Norway Regional Health Authority (Grant nos. 2016049, 2017025, 2018075, and 2020088 [to AB] and Grant No. 2020090 [to IAH]), and by Norwegian Research council, #309762 Precision Health Center for optimized cardiac care (ProCardio).

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to privacy for the individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Henriksen HCB, Havnes IA, Jørstad ML, et al. Treatment-seeking behavior and cardiovascular morbidity among men with anabolic-androgenic steroid use: A cross-sectional study. *Scand J Med Sci Sports*. 2024;34:e14554. doi:10.1111/sms.14554

III

Off-label use of Clomiphene citrate to Treat Anabolic-androgenic Steroid induced Hypogonadism upon cessation among men (CloTASH) - a pilot study protocol

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Word Count

Abstract: 293

Main body of text excluding Abbreviations and Declarations: 3654

Abstract

Introduction:
Non-prescribed anabolic-androgenic steroid (AAS) use is widespread and may induce hypogonadism, and metabolic, cardiovascular and mental health risks. The study aims to explore feasibility and safety of off-label clomiphene citrate therapy, whether the treatment will reduce the symptoms of androgen deficiency, and to study changes in health risks after cessation.

Methods and analysis:
This is a non-randomized proof of concept pilot study to test the feasibility of an off-label hormone intervention. In this open-labeled intervention study, we shall include males with AAS dependence intending to quit AAS use. Clomiphene citrate will be given for a period of 16 weeks to stimulate the endogenous testosterone production. Measures of physical and mental health will be examined from ongoing AAS use, during the intervention period, and at follow-up 6- and 12-months post-cessation.
Change in self-reported symptoms of hypogonadism (fatigue, depression, anxiety, sexual dysfunction) and other withdrawal symptoms will be compared with data from a group of men who ended AAS use temporarily without any medical intervention.

Discussion:
This pilot study is the first study to test feasibility of off-label use of CC with the intention to restart endogenous testosterone production upon cessation of AAS among men with AAS-induced hypogonadism. The study may provide valuable clinical insights, enabling the exploration of whether adjustments are needed for the intervention. The results may be used to determine the sample size and informing the design of future RCTs or case comparison studies.

Ethics and dissemination:
The study is initiated by investigators, funded by public grants and is approved by the Regional Committee for Medical and Health Research Ethics (REC) in Norway, Norwegian Medicines Agency and the Data Protection Officer for Research at Oslo University Hospital.
Trial registration: EudraCT, EudraCT 2020-005938-15, Registered by Norwegian Medicines Agency 3rd November 2021.
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-005938-15/NO

Keywords: anabolic-androgenic steroids, image and performance enhancing drugs, hypogonadism, post cycle therapy, clomiphene citrate, intervention study, pilot study, feasibility study

1 Introduction

Anabolic-androgenic steroids (AAS) include testosterone and synthetic derivatives, often used with an intent to build muscle mass, decrease body fat and improve overall athletic performance [1]. Non-prescribed AAS are predominantly utilized by male recreational athletes in cyclic patterns, with intermittent breaks or continuous administration where the 'off-cycle' includes AAS at a lower level [2]. Global lifetime prevalence of AAS use among men is estimated to be 6.4 %, but is found higher in subpopulations such as recreational athletes [3], prisoners [4] and patients in substance use disorder (SUD) treatment [5]. Associated health risks and behavioral outcomes make AAS use a public health concern [6-8]. As a substantial proportion of men who use AAS long term move into middle age, health professionals are likely to encounter an increasing number of patients who experience adverse effects from long term AAS use [8].

AAS use is associated with a wide range of adverse effects on mental [9, 10] and physical health [1, 11] including negative effects on the cardiovascular system such as left ventricle systolic dysfunction, myocardial hypertrophy, hypertension [12-14], severe biventricular cardiomyopathy [15], acute myocardial infarction [16] and sudden cardiac death [17]. Increased carotid intima-media thickness, reduced arterial elasticity and lower carotid artery compliance are early predictors of atherosclerosis and cardiovascular risk that are found among men with long term AAS use [18]. In addition, AAS use may lead to altered renal, hepatic and metabolic functions alongside increased total body fat percentage and visceral and subcutaneous adipose tissue, hypercholesterolemia and reduced insulin sensitivity [19]. High androgen levels might lead to gynecomastia and several dermatological conditions [20], and infertility during on-going use is common due to the disruption of hypothalamic-pituitary-gonadal (HPG) axis [21, 22].

One in three people using AAS seem to develop a dependence syndrome, characterized by a pattern of escalating doses and reduced breaks between cycles, or continuous use with a stable dose or cyclic pattern with higher doses, despite experiencing adverse effects and a desire to cease use [23-25]. The neuroendocrine mechanism of AAS-dependence is linked to suppression of the hypothalamic-pituitary-gonadal (HPG) axis leading to AAS-induced hypogonadism [21]. The features of androgen deficiency (fatigue, depression, anxiety and sexual dysfunction) will first occur weeks after AAS cessation. For most men, the endogenous testosterone production

recovers after 3-12 months [25], but this phase is typically hard to endure [26], often resulting in restart of AAS use and development of a pattern of continuous use. When AAS use is ceased temporarily or permanently, some may self-initiate Post Cycle Therapy (PCT) with non-prescribed hormonal substances in various combinations and doses with the intention to restore the HPG-axis faster [27, 28].

Despite experiencing health problems associated with AAS use, many individuals fail to receive treatment [29]. According to a recent meta-analysis, only a third of people who use AAS seek medical support [30]. In a recent study from our research group, more than half of the sample of men with AAS-related health issues did not seek health service [31]. This reluctance to engage with health services may be attributed to limited treatment options and insufficient awareness of AAS among clinicians. Many individuals who use AAS feel stigmatized, and fear being identified with or labelled as either drug users or sport cheats, with this acting as a further barrier to service engagement [32]. As one of few countries, Norway has integrated AAS and other performance and image enhancing drugs (PIEDs) in the national Drug Policy. The possession and use of AAS and other PIEDs became criminalized in 2013, and people with current or previous AAS use got access to SUD treatment in the specialist health service. Presently, there is no consensus, nationally or internationally, on whether endocrine treatment should be used in the treatment of AAS-induced hypogonadism [33]. Nonetheless, endocrinologists with extensive clinical experience with this patient group have proposed potential interventions [34-36].

Rahnema and colleagues presented a treatment model to prevent severe symptoms of hypogonadism during cessation of AAS including use of clomiphene citrate (CC), a Selective Estrogen Receptor Modulator (SERM), to restart the HPG-axis [21]. CC selectively binds to estrogen receptors and acts as a receptor antagonist with week estrogen activity in the hypothalamus which leads to blocked negative feedback inhibition. This leads to increased gonadotropin-releasing hormone (GnRH) pulsation in the hypothalamus, increased release of luteinizing hormone (LH) from the pituitary gland and finally increased levels of endogenous testicular testosterone. CC is approved for short-term treatment of female infertility. CC as off-label treatment has been found safe, tolerable and effective to improve serum levels of testosterone, symptoms of hypogonadism and infertility in men with hypogonadism of other causes than AAS use [37-40]. In the reviewed studies, dosages of 25 mg daily for up to 12

months, 50 mg daily for up to 6 months, and 25-50 mg every second day for 1, 2 and 3 years or more were administered. The majority of these investigations reported no occurrence of major side effects. Side effects reported were: headache, dizziness, mood changes, blurred vision/visual change, breast tenderness/gynecomastia, secondary polycythemia without need for phlebotomy and a few cases of elevated liver enzymes [38, 40]. Two case reports of psychotic episodes and one case of suicide attempts have been published [41]. Deep vein thrombosis risk is found lower among men treated with CC when compared with testosterone replacement therapy (TRT) [42]. Despite these findings, more knowledge is needed on feasibility of a model with CC among men with a desire to cease long term continuous AAS. The primary aim of the present study is to explore whether the 16 weeks therapy model with CC leads to stimulation of endogenous LH and testosterone production, if the treatment model is safe, and if the model is more effective in reducing AAS-withdrawal symptoms compared to no intervention. The secondary aims are to detect health risks during ongoing AAS use in the intervention group only and assess whether and to what extent the health risks are reduced 12 months after cessation of AAS.

2 Methods and analysis

We aim to include 25-30 AAS-dependent men who struggle to cease their use in this proof-of-concept study. The subjects will receive 25mg CC every second day following AAS cessation for 16 weeks. Participants in another study of men who ended AAS use temporarily without the intervention will be used for comparison on self-reported withdrawal symptoms.

2.1 Study Design

The study includes two sub-studies with
A) *Within-subjects repeated measures design* to monitor the intervention group with physical and mental health parameters and blood sampling prior to intervention start and while still using AAS, during 16 weeks of intervention, and at follow-up at 6 and 12 months, see Table 1.

B) *Single center – single group – case-comparison design*:
Male participants with AAS dependence and continuous AAS use with the intention to cease use permanently comprise the intervention group. The data from the intervention group will be compared with data from an ongoing study of men who intend to cease a cycle of AAS use

temporarily without receiving intervention. Participants from both studies will self-report withdrawal symptoms and other subjective health measures during ongoing use and after cessation. The intervention group will self-report withdrawal symptoms every 2 weeks for 16 weeks of intervention, see Figure 1.

Table 1

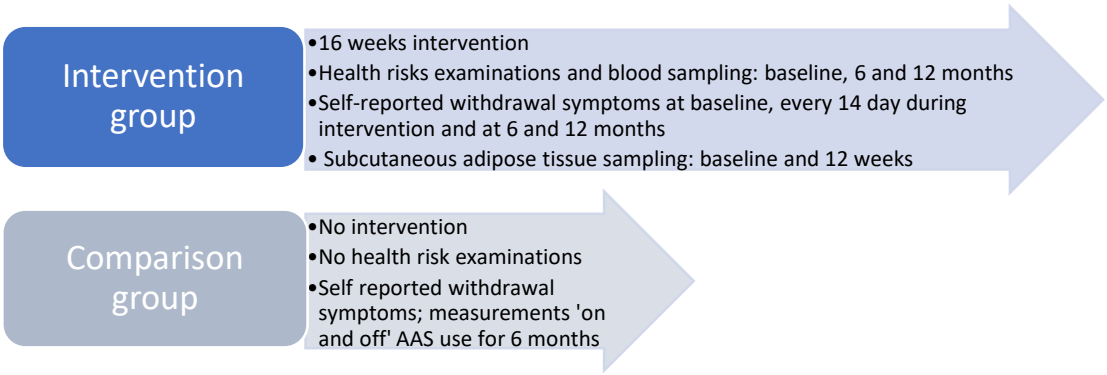
Flow chart of study events during the study period for the intervention group, modified version of SPIRIT.

	STUDY PERIOD											
TIMEPOINT	**Enrolment**	***Wk*$_0$**	***Wk*$_2$**	***Wk*$_4$**	***Wk*$_6$**	***Wk*$_8$**	***Wk*$_{10}$**	***Wk*$_{12}$**	***Wk*$_{14}$**	***Wk*$_{16}$**	***Wk*$_{26}$**	***Wk*$_{52}$**
ENROLMENT:												
Eligibility screen	X											
Informed consent	X											
Referral SUD treatment	X											
Psychiatric evaluation	X											X
Research visit physician	X	X		X		X		X		X	X	X
INTERVENTIONS:												
CC 25mg eod (target T≥20 nmol/L)			♦	—	—	—	—	—	—	—	♦	
RESCUE MEDICATION:												
Testogel 50mgx1		♦	—	♦								
HCG, 1500 2x/week (if T<10 nmol/L)				♦	—	♦						
HCG, 1500 3x/week						♦	—	♦				
ASSESSMENTS CLINICAL EXAMINATIONS:												
BP (MmHg), HR, Weight (kg), BMI (kg/m^2)		X		X		X		X		X	X	X
ECG		X										X
Cor/pulm, acne, striae, gynecomastia		X									X	X
Ultrasound common carotid artery (intima thickness, Carotid Artery Reactivity (CAR)		X										X
Testicular volume ultrasound, scrotal examination, abdominal circumference		X									X	X
DXA (body composition, fat distribution)		X										X
ASSESSMENTS LABORATORY TESTS:												
Biobank full blood and serum		X									X	X
Biobank fat tissue		X										X
Urine AAS and Drug test		X				X				X	X	X
T, SHBG, FTI, LH, FSH, Estradiol, Prolactin		X		X		X		X		X	X	X
Hb, EVF, Ca, Kreatinin, eGFR, ASAT, ALAT, ALP		X		X		X		X		X	X	X
Cholesterol, LDL, HDL, triglyc		X									X	X
Glucose, C-peptid, immune markers		X										
TSH, fT4		X									X	X

Semen analysis and sperm function test		X									X	X
ASSESSMENTS - ONLINE QUESTIONNAIRE:												
Demographics, background information		X										
HSCL 10		X	X	X	X	X	X	X	X	X	X	X
Suicidal ideation (MADRS)		X	X	X	X	X	X	X	X	X	X	X
Sexual function (HRQOL)		X	X	X	X	X	X	X	X	X	X	X
Shortened fatigue Questionnaire		X	X	X	X	X	X	X	X	X	X	X
WHO-5 Wellbeing Index		X	X	X	X	X	X	X	X	X	X	X
Jenkins Sleep Scale (JSS)		X	X	X	X	X	X	X	X	X	X	X
Pain, body image, aggression - VAS		X	X	X	X	X	X	X	X	X	X	X
Body Perception Questionnaire (BPQ)		X	X	X	X	X	X	X	X	X	X	X
Intervention - treatment satisfaction			X	X	X	X	X	X	X	X		
SUD - treatment satisfaction			X	X	X	X	X	X	X	X	(X)	(X)
SAFETY MEASURES:												
Safety Monitoring CTCAE v 5			X	X	X	X	X	X	X	X		
Eye examination	X									X		

Figure 1

Timeline for data collection for the intervention group and the comparison group



2.2 Participants

For inclusion and exclusion criteria for the intervention group and comparison group, see Table 2.

Table 2

Inclusion and exclusion criteria for the intervention group and the comparison group

	Intervention group	**Comparison group**
Inclusion criteria		
Age	≥18 years	≥18 years
AAS use	Continuous AAS use ≥6months	Cycle, ≥6weeks between cycles
Dose	Supraphysiological	≥400mg/week
AAS dependence	3 or more items last 12 months: tolerance, withdrawal, increased amount, unsuccessful efforts to reduce or cease use, ↑time to obtain/use substances, ↓social/recreational/ occupational activities due to use, continued AAS use despite mental and/or physical side effects	No
Plan to cease AAS use	Wish to cease use, previous unsuccessful attempts	No
SUD treatment	Being enrolled in or referred to SUD treatment	No
Hormonal and liver status at intervention start	Serum testosterone < 25nmol/l, liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST) < 3 x upper limit of normal range (ULN) (normal range ALT 10-70 U/L, AST 15-45 U/L)	No
Exclusion criteria		
Mental health	Previous or current: Severe depression, bipolar disorder, psychosis	Reduced cognitive function (IQ<80) and/or previous or current: Severe depression, bipolar disorder, psychosis. Use of medications that may impact CNS functioning (e.g., antipsychotics, methyl phenidate, TRT)
Physical health	Hypersensitivity to clomiphene citrate, hyperprolactinemia, untreated thyroid or adrenal disease, hemoglobin >18.0 g/dl, current/previous thromboembolic disease, cardiovascular disease (arrhythmia, ischemic heart conditions, heart failure)	Traumatic brain injury with consciousness >1 min, or neurological disorders (e.g., MS, ischemia) or severe somatic disorders (e.g. cancer)
Substance use	No illicit substance use during intervention, <8 alcohol units/week	Problematic use of alcohol or illegal substances (Alcohol Use Disorders Identification Test and Drug Use Disorders Identification Test C)

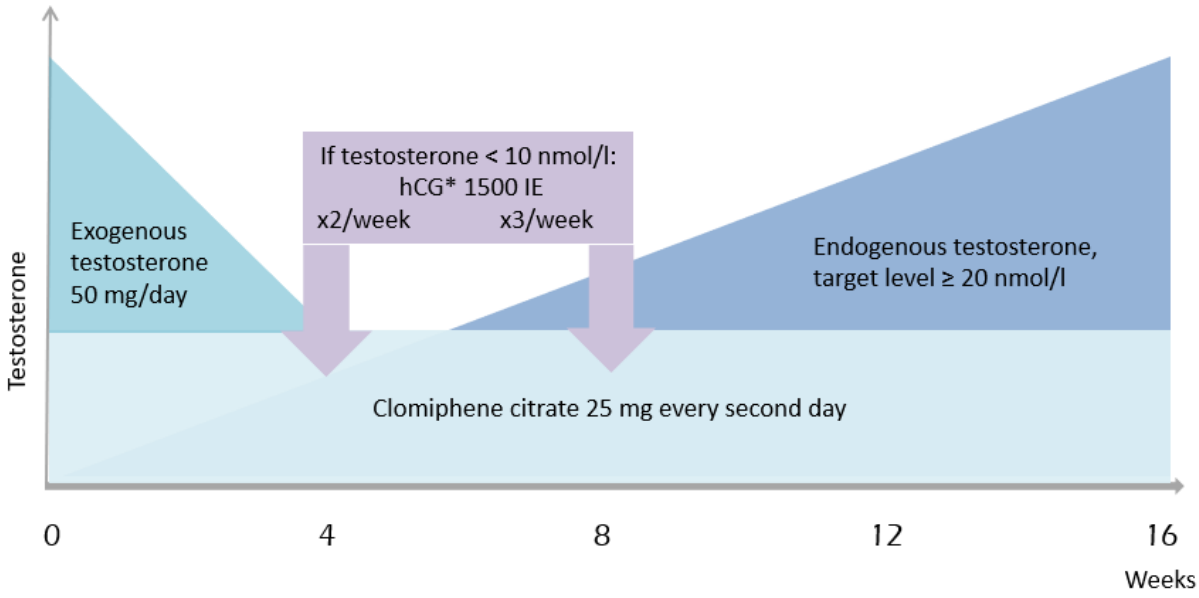
Recruitment for the intervention group**:** The National Steroid Project at Oslo University Hospital (OUH) will recruit participants for the intervention study through a national information service [43], the outpatient SUD clinic at OUH, flyers in various gyms and through advertisements on social media; Facebook, Instagram, TikTok, Snapchat and AAS user forum.

Recruitment for the comparison group**:** Advertisements on social media.

2.3 The intervention

The slightly modified version of the 16 week therapy model outlined by Rahnema and colleagues involves administration of 25mg CC per orally every second day for 16 weeks [21]. Testosterone 50mg is given transdermal daily for the first 4 weeks as rescue medication before the expected endogenous Testosterone (T) response, see Figure 2. The target T level during the intervention is set at 20 nmol/l. If the endogenous LH and T (T < 10 nmol/l) response is poor after 4 weeks, human chorionic gonadotropin (hCG) will be added as 1500 IE subcutaneous injection twice a week, as rescue medication. If the endogenous T response is still poor after 8 weeks, the same dose will be given three times a week for four more weeks or throughout the intervention. If poor response on endogenous LH and T levels below lower limit of normal range after 16 weeks intervention *and* the participant experiences severe symptoms of hypogonadism; TRT and referral to endocrinologist will be considered.

Figure 2
The 16 week off-label intervention with clomiphene citrate



2.4 Outcomes and instruments

Primary outcomes:

1) *Changes in self-reported symptoms of hypogonadism*, mental health state, and symptoms associated with AAS use. The following will be assessed for both the intervention and comparison group: fatigue, depression, suicidal ideation, anxiety, wellbeing, sexual dysfunction, sleep quality, aggression, and body dysmorphia.
2) *Side effects related to CC* will be specifically evaluated for the intervention group.

Secondary outcomes:

Change in measures of physical health from baseline to follow-up for the intervention group:

- Weight, body mass index (BMI), degree of striae, acne, androgen alopecia and gynecomastia
- Endocrine status, metabolic status, liver and kidney function (blood tests)
- Cardiovascular status: Blood pressure, electrocardiogram (ECG), vascular morphology (carotid intima-media thickness and pulse wave velocity) and -function (flow-mediated dilation and carotid artery reactivity)
- Body composition; total fat mass, visceral and subcutaneous fat tissue, total lean mass and bone mineral density
- Testicular volume and sperm quality
- Immunological biomarkers, analyzed from biobanked blood and adipose tissue samples

Change in measures of mental health risks from baseline to follow-up after 12 months:

- Depression and anxiety levels, AAS dependence, body image concerns, aggression, AAS use, and adherence to SUD treatment

Study participants included for the intervention will be screened for eligibility at baseline and examined to assess mental health status, comorbidity, AAS history, AAS dependence and SUDs with validated instruments, see flow chart for study events (Table 1).

2.4.1 Self-reported mental health, well-being and AAS withdrawal symptoms

To investigate mental health state, wellbeing and AAS-withdrawal symptoms after AAS cessation, the following self-reporting questionnaires will be administered via a web-app every second week for 16 weeks for both groups and at follow-up at 6 and 12 months for the intervention group: Hopkins Symptom Checklist-10 (HSCL-10) to evaluate psychological distress [44], suicidal ideation item Montgomery and Åsberg Rating Scale (MADRS) [45], items from Health-related quality of life (HRQOL) to evaluate sexual function [46], Shortened Fatigue Questionnaire [47], WHO-5 Wellbeing Index [48] and Jenkins Sleep Scale (JSS) [49], Body Perception Questionnaire [50]; and Visual Analog Scale (VAS) to measure aggression, cognitive function, body image and pain. Treatment satisfaction will be assessed for the intervention group only using VAS.

2.4.2 Biological assessments for the intervention group

Biological assessments will include urinalysis, semen analysis, routine biochemistry, non-routine hormone tests, markers of glucose, lipid and bone metabolism and immunological gene expression profile.

Urine will be screened for AAS and psychoactive substances at inclusion, during intervention and at follow-up. Additionally, routine blood analyses will be conducted at the time of inclusion and every 4 weeks. These regular assessments serve both safety purposes and to monitor physiological markers associated with AAS-induced side effects. Throughout the intervention period and at the 6-month and 12-month follow-ups after discontinuation of AAS usage, a comprehensive set of analyses will be carried out. These include evaluation of sex hormone levels, metabolic and hematological status, glucose, insulin production and resistance, liver and kidney function, electrolytes, and immune markers.

Blood and adipose tissue are sampled in fasting condition between 8:00 and 10:00. Blood samples, including serum, EDTA and citrated plasma and RNA (Paxgene tubes) for gene

expression profiling at baseline and after 6 and 12 months are prepared and stored in a biobank at -80°C. Adipose tissue samples are taken from the gluteal region at baseline and after 12 months, immediately snapfrozen and stored in a biobank at -80°C until gene expression profiling.

2.4.2.1 Physical examination

The physical examination will encompass various assessments to evaluate change in the participants' health status from current use, during and after the intervention and includes: blood pressure (BP), heart rate (HR), Electrocardiogram (ECG), weight, height, body mass index (BMI), auscultation of heart and lungs, evaluation of striae, acne, and gynecomastia. As cardiac hypertrophy is often not detected on ECG screenings among people who use AAS [51], the participants will be referred to routine echocardiography at their local hospital.

Semen samples will be analyzed prior to intervention and 6 and 12 months after the intervention start to evaluate change in measures of testicular function and fertility (sperm count, morphology, motility; and vitality) during and after AAS use [22].

Testicular volume will be measured by orchidometer and ultrasound at baseline and follow up at 12 months as increased volume flowing upon cessation of long term AAS use is seen as sign of improved testicular function [25].

The vascular morphology and -function will be evaluated by the thickness of intima media of the common carotid artery and by the carotid artery reactivity (CAR). In addition, endothelial function and pulse wave velocity will be measured at inclusion and at follow-up with established methodology at the Section of Vascular Investigation, OUH [18].

Body composition and fat distribution, including visceral and subcutaneous adipose tissue, will be assessed by dual energy X-ray absorptiometry (DXA-scan) to evaluate whether there is a difference in body composition (Total lean mass (kg) (TLM), Total fat mass (kg) (TFM), Body fat %, Visceral and subcutaneous adipose tissue (VAT) (g), Android fat (g), fat distribution and bone mineral (BMD)g/cm2 with T-score and Z-score in the following sites: Lumbar spine (LS) (L1-L4), Total hip, Proximal radius, Ultradistal radius, Total body during AAS use and 12 months after AAS-cessation.

2.4.2.2 Biomarker analyses

From the established biobank circulating inflammatory biomarkers including selected cytokines, chemokines and adhesion molecules will be analyzed. Molecular factors in focus are interleukins, tumor necrosis factor, interferon-γ, fibroblast and endothelial growth factors, vascular cell adhesion molecule 1, monocyte chemotactic factor 1 and Brain Derived Neurotrophic Factor.

Analyses of adipose tissue will encompass a comprehensive assessment, of biochemical factors relevant to cardiovascular and other health risks, including immune markers and individual markers' genetic expression. RNA will be isolated from both the fat tissue and blood samples for further investigation of the regulation (mRNA) of proteins of interest during AAS use and 12 months after cessation of AAS. Notably, alteration in the extracellular matrix within adipose tissue has been linked to glucometabolic disturbances, such as insulin resistance/sensitivity, diabetes, and obesity, which are all relevant health concerns related to AAS use.

2.4.3 Registration of adverse events

As a safety measure, an eye examination will be conducted at an optometrist at inclusion and after the intervention. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 is used to classify adverse events at follow-up examinations every 4th week during the intervention The participants can contact the research physicians (HCBH and IAH) by phone or mail during the intervention period for any experienced side effect(s). Any event requiring medical intervention is registered (CTCAE level 2 or above). Medication-related Severe Adverse Events (SAEs) and Suspected Unexpected Severe Adverse Reactions (SUSARS) are reported to the Norwegian Medicines Agency within 7 days for fatal/life threatening events/cases and for other SUSARs, within 15 days.

2.5 Data analysis plan

Data analyses will follow a full analysis set, with a per protocol plan. Descriptive statistics will be used when appropriate and for reported adverse events.

For between-group comparisons and to control for the effect of baseline characteristics, we plan to use General Linear Mixed Models (GLMM) with a within subject repeated measures design at

baseline, 6 months and 12 months. In cases where the outcomes do not meet the normality assumption, we will apply a General Alinear Mixed Models (GAMM) approach. The results of statistical analyses will be performed using 95% CIs, and a two-sided P value of < 0.05 will be used to indicate statistical significance. General linear models may be utilized in cases where GLMM/GAMM is considered inappropriate. Two sample t-tests will be used for between-group comparisons of numerical variables, when we see no need to adjust for confounding variables. Numerical data not following normal distribution will be presented as medians (25^{th}-75^{th} percentiles), using non-parametric tests such as the Wilcoxon rank sum tests (Mann-Whitney) to compare differences between groups. Chi^2-tests and Fischer's exact will be applied for categorical variables. Per protocol analysis will be applied in cases of missing data to detect any discrepancy that might affect the robustness of the results. All statistical calculations and analyses will be conducted using up-to-date versions of the statistical software STATA and SPSS.

2.6 Sample size determination

In line with the proof of concept study design, a small sample of up to ten cases is sufficient to evaluate if the intervention works as described in theory [21]. This approach allows for the exploration of potential side effects and the subjective experiences of the participants. Every single case within the intervention group holds significant clinical relevance and is of interest.

The first AAS case control study from our research group [52-54] found significant effects between the groups for measures of psychopathology with effect sizes ex =.27. With a power of 80% and a wish to detect effects of moderate level (Cohen's d=0.4), a total sample of 52 participants is needed.

A Danish study comparing measures of cardiovascular health and symptoms of hypogonadism (depression, fatigue, sexual dysfunction), among three groups (men with former and current AAS use and healthy controls), utilized a reduced significance level of 0.0167 (due to three groups). The study found that each group required a sample size of 25 to detect clinically relevant differences of 5% [55, 56]. However, for two comparison groups and a significance level 0.05 a lower group size is needed. In the current study, the recruitment target for both the intervention group and comparison group is 25-30.

2.7 Scientific Rationale for Study Design

The chosen design served three primary purposes a) to assess the feasibility and acceptability of the intervention, b) to evaluate its safety, and c) to examine its effect on symptoms and objective measures of hypogonadism. The cohort design for the intervention group allowed for investigating potential health risks reduction following cessation of AAS use. Although a randomized controlled trial (RCT) is considered the gold standard methodology, conducting a preliminary test of the intervention before proceeding to an RCT is essential. Additionally, this approach facilitates the determination of effect sizes for use in sample size calculations for future RCTs [57]. However, it is acknowledged that the comparison group may differ from the intervention group on certain variables, as they may not share the same intention to permanently cease AAS use.

The study exclusively recruits male participants as we investigate the effect of treatment of androgen deficiency due to AAS-induced male hypogonadism. The primary endpoints (symptoms of hypogonadism such as depression, anxiety, fatigue, reduced libido, and erectile dysfunction, and other symptoms related to AAS use) were developed in collaboration with a user panel comprising people with prior AAS experience and clinicians from the outpatient SUD clinic with experience of providing treatment to the patient group. These endpoints are considered reliable clinical indicators of the intended intervention effect.

2.8 User Participants' Input into Design

The research questions and design for the proposed study have been discussed and developed in collaboration with a user panel of five men with former AAS use. The research questions, design, inclusion criteria and variables (background information, health risk examinations and self-report questionnaire) for the proposed study was discussed and developed in workshops with the user panel, clinicians and researchers. The panel strongly approved testing the proposed off-label intervention as well as health risk examinations before, during and after the intervention. The user panel were also clear that if randomized control design was chosen, it would lead to drop-out in the control group. Members of the panel took part in testing of the self-report questionnaire and development of ads for social media. They also suggested recruitment

strategies in certain gyms, social media and through information to general practitioners and SUD treatment facilities.

2.9 Status of the study

Due to the COVID-19 pandemic, the study was delayed, and recruitment started in January 2022. Further funding for the study was not secured and inclusion ended January 2023. Data collection will continue until January 2024, with the results scheduled for presentation in 2024.

3 Discussion

This non-randomized proof of concept pilot study with a small number of participants, is the first study to test off-label use of CC with the intention to restart endogenous testosterone production upon cessation of AAS use among men with AAS-induced hypogonadism. It is also the first longitudinal study to compare changes in health risks in a sample of men with AAS dependence that withdraw from long term continuous AAS use.

The study will compare symptoms of AAS-induced hypogonadism and other AAS-related side effects between the group receiving CC and a group of male AAS users not receiving the intervention. The comparison group differs from the intervention group as the participants may have less serious AAS use and may have less symptom burden during use as they mostly use AAS as cycles with an intention to cease use only temporarily.

Detailed and frequent monitoring using objective biological measures is a strength and the study may provide valuable clinical insights, enabling the exploration of whether adjustments are needed for the intervention. Furthermore, the results may be used to determine the sample size and informing the design of future RCT or case comparison studies.

List of Abbreviations

AAS	Anabolic-androgenic steroids
SUD	Substance Use Disorder
HPG	Hypothalamic-Pituitary-Gonadal
PCT	Post Cycle Therapy
PIEDs	Performance and Image Enhancing Drugs
CC	clomiphene citrate
SERM	Selective Estrogen Receptor Modulator
GnRH	Gonadotropin-releasing Hormone

LH	Luteinizing Hormone
TRT	Testosterone Replacement Therapy
ALT	Alanine transaminase
AST	Aspartate transaminase
OUH	Oslo University Hospital
hCG	human Chorionic Gonadotropin
T	Testosterone
BMI	Body Mass Index
ECG	Electrocardiogram
BP	Blood Pressure
HR	Heart Rate
CAR	Carotid Artery Reactivity
DXA	Dual energy X-ray absorptiometry
TLM	Total Lean Mass
TFM	Total Fat Mass
VAT	Visceral Adipose Tissue
GLMM	General Linear Mixed Models
GAMM	General Alinear Mixed Models
RCT	Randomized Control Trial
CTCAE	Common Terminology Criteria for Adverse Events
SAE	Severe Adverse Events
SUSAR	Suspected Unexpected Severe Adverse Reaction

Declarations

Ethics approval and consent to participate

The CloTASH off label pilot intervention study is approved by the Norwegian Regional Committee for Medical Research Ethics (33872), the Norwegian Medicines Agency (21/18081-9) with EudraCT-number 2020-005938-15 and the Data Protection Officer at Oslo University Hospital (20/27593). All participants will receive oral and written information about the study and written formal consent will be collected.

The ongoing study for the comparison group: “Cycling with anabolic steroids: studying how large fluctuations in sex hormones affect brain chemistry, functional network, cognition and emotions” is approved by Norwegian Regional Committee for Medical Research Ethics (2013/601) and the Data Protection Officer at Oslo University Hospital (18/10139-3). Written consent are collected from all participants prior to inclusion. Participants are compensated with NOK 500 (≈$50) for taking part in the study and have the opportunity to discontinue the study at any point.

The research will be carried out according to the Helsinki declaration [58]. Emphasis is placed on voluntary participation and that refraining from participation is possible at any stage in the study period prior to data publication without affecting the access to SUD outpatient treatment. All participants in the intervention are insured against adverse events attributable to study drug occurring during or after participation, through Project leader´s membership in the Norwegian Drug Liability Association. The participants in the intervention group are not compensated for

taking part in the study, but study medication and physical health examinations in the study will not involve any costs. The participants will pay deductibles as patients in outpatient substance use disorder treatment and at potential follow-ups through somatic health services where indicated. All pathological findings of clinical relevance will be evaluated by physicians connected to the study and investigated further on indication.

Consent for publication
Not applicable

Availability of data and materials
Not applicable as this is a protocol paper.

Competing interests
The authors declare that they have no competing interests.

Funding statement
The study was supported by the South-Eastern Norway Regional Health Authority [grant #2020090 to IAH and grants # 2017025 and 2020088 to AB] and internal research grants from Division of Mental Health and Addiction, Oslo University Hospital to IAH, HCBH and AB. The funding sources had no further role in the study.

Authors' contributions
IAH, APJ, PWJ conceived the study. IAH drafted the first manuscript and HCBH contributed substantially. APJ and HCBH critically revised earlier versions of the manuscript. All authors contributed to planning of the study, writing of the protocol and the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Acknowledgements
Not applicable.

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IV

DRUGS: EDUCATION, PREVENTION AND POLICY
https://doi.org/10.1080/09687637.2023.2244655

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RESEARCH ARTICLE

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Challenges recruiting men with a desire to cease anabolic-androgenic steroid use to a pilot involving hormone therapy intervention

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ABSTRACT

Introduction: Long-term use of anabolic-androgenic steroids (AAS) might lead to distressing withdrawal symptoms following cessation. This paper aims to share challenges in recruiting patients to a pilot intervention study with parallel substance use disorder (SUD) treatment and to explore barriers to participation among AAS forum members.

Methods: Eligible AAS-dependent men were recruited to receive hormone therapy for 16 weeks, and exclusion reasons were registered. Audience engagement from social media advertisements was measured. Information about the study was posted in an AAS online forum, and discussion among forum members was thematically analyzed.

Results: Twelve of 81 potential participants were included, whereas ten completed the intervention. Participants were excluded due to residency outside the study area, illicit substance use or severe medical conditions. Challenges in recruitment were linked to the COVID-19 pandemic, funding and advertisements on social media. AAS forum members suggested modifications to the intervention, were skeptical to the SUD-patient requirement, feared prosecution or other negative outcomes and/or preferred to seek online advice on self-initiated testosterone replacement therapy or post cycle therapy.

Conclusion: AAS-related online recommendations among peers, criminalized AAS use setting and obligatory SUD treatment might have affected recruitment. Based on lessons learned, recommendations for future similar studies are presented.

ARTICLE HISTORY
Received 30 March 2023
Revised 15 July 2023
Accepted 1 August 2023

KEYWORDS
Anabolic-androgenic steroids; image and performance enhancing drugs; post cycle therapy; clomiphene citrate; recruitment challenges; substance use disorder treatment; netnography; social media

Introduction

Anabolic-androgenic steroids (AAS) constitute a sub-group of image and performance enhancing drugs (IPEDs), designed to mimic the effects of endogenous testosterone (Kicman, 2008). In recent decades, the use of AAS has become increasingly more common in the general population, especially among young men, to boost muscle strength and to improve aesthetics and performance (Brennan et al., 2017). However, AAS use is associated with multiple bodily harms, including endocrine, cardiovascular and metabolic disturbances (Horwitz et al., 2019; Melsom et al., 2022; Pope et al., 2014; Rasmussen, Schou, Madsen, Selmer, Johansen, Hovind, et al., 2018; Rasmussen, Schou, Madsen, Selmer, Johansen, Ulriksen, et al., 2018; Rasmussen et al., 2017), as well as reduced cognition, risk behavior and other substance use (Bjornebekk et al., 2019; Havnes et al., 2020; Zahnow et al., 2018). AAS-induced hypogonadism (ASIH), which is caused by AAS' long term feedback inhibition on the hypothalamic-pituitary-gonadal (HPG) axis, commonly leads to distressing withdrawal symptoms among those who try to cease use (Botman et al., 2023; de Ronde & Smit, 2020; Rahnema et al., 2014). Symptoms of ASIH include fatigue, reduced libido, erectile dysfunction and depression, which might persist for months to years following AAS cessation or, for some, even be irreversible (Coward et al., 2013; Kanayama et al., 2015; Rasmussen et al., 2016). Resumed and sustained AAS use may alleviate these distressing withdrawal symptoms. This is a central mechanism in the development of AAS dependence, which about one in three of people who use AAS are reported to develop (Skauen et al., 2023).

Despite AAS-related health problems, which include dependence and withdrawal symptoms, treatment-seeking among people who use AAS is found to be low (Amaral et al., 2022; Havnes et al., 2019; Pope et al., 2004; Zahnow et al., 2017). Reported reasons for not seeking treatment is not considering experienced AAS-related side effects to be of treatment demanding nature (Henriksen et al., 2023; Zahnow et al., 2017), having the perception that health professionals lack knowledge about AAS (Bonnecaze et al., 2020; Zahnow et al., 2017),

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fear of stigmatization (Yu et al., 2015) or negative sanctions from health professionals (Havnes et al., 2019) and not having access to desired hormonal treatment to alleviate withdrawal symptoms after cessation (Harvey et al., 2019; Havnes & Skogheim, 2020; Underwood et al., 2021). People who use AAS tend to seek information from peers and online on how to use AAS and self-monitor own health (Andreasson & Henning, 2022; Bojsen-Moller & Christiansen, 2010). This often involves seeking and giving advice on how to self-medicate at the end of an AAS cycle to restore endogenous testosterone production (Tighe et al., 2017), a practice termed post cycle therapy (PCT) (Griffiths et al., 2017; Rahnema et al., 2014; Smit & de Ronde, 2018). The non-prescribed prescription drugs most commonly used for this purpose are approved for the treatment of infertility and breast cancer in women and include selective estrogen receptor modulators (SERMs, also called anti-estrogens), human chorionic gonadotropin (hCG) and aromatase inhibitors (Bonnecaze et al., 2021). PCT is not scientifically proven to be an effective treatment for ASIH, despite being easily accessible and frequently used after an AAS cycle (Westerman et al., 2016).

Previous literature on treatments for AAS-related physical and mental harms is limited and consists mainly of case reports (Bates et al., 2019). Even though the lack of evidence-based guidance might be challenging in clinical settings, there have been attempts at designing general guidelines for treating ASIH (Botman et al., 2023). However, there is still a knowledge gap regarding the efficacy and safety of medical interventions targeting AAS withdrawal symptoms, dependence and support during and after cessation. The Oslo University Hospital (OUH) has 15 years of experience providing substance use disorder (SUD) treatment to people with a desire to cease AAS use. SUD treatment for this patient group involves alleviating withdrawal symptoms by providing psychosocial support, prescribing psychopharmacological medication and addressing co-occurring mental and physical health problems (Havnes et al., 2019; Kanayama et al., 2010; Pope et al., 2010). However, SUD treatment does not directly target ASIH and the withdrawal symptoms associated with low endogenous testosterone production. Consequently, the Department of Endocrinology and the Department of Addiction Treatments at OUH initiated a collaborative pilot study to investigate the effect of hormone therapy for men in SUD treatment discontinuing AAS use, as a potential supplement to the already existing SUD treatment.

People who use AAS may be seen as a socially disadvantaged hard-to-reach group as use is associated with social and economic challenges including reports of troubled childhood (Ganson et al., 2021), high unemployment rates (Ljungdahl et al., 2019), concurrent substance use (Havnes et al., 2020) and higher crime records (Lundholm et al., 2015). In addition to the barriers to seek treatment described above, people who use AAS may also have barriers to recruitment and participation in health research (Bonevski et al., 2014). As participants in this hormone therapy intervention were required to have patient status in SUD treatment, it is important to explore and understand potential barriers to engagement in clinical research participation *and* to healthcare treatment-seeking among people who use AAS. The aims of this paper are to describe the recruitment process and the related challenges that were experienced in this intervention study and to generate insight into potential reasons that those invited to join the study did not participate. We will use a dual approach: First, by sharing recruitment experiences, and secondly, to analyze online engagement among members from an AAS community forum on the intended hormone therapy intervention with obligatory SUD treatment. Finally, we will present lessons learned and future recommendations, which could be of relevance for future intervention studies seeking to address the treatment needs of people who use AAS.

Methods

Setting

The Norwegian healthcare system is publicly funded, as all residents are covered by the National Insurance Scheme (World Health Organization. Regional Office for et al., 2013). Every citizen is entitled to a general practitioner that may refer their patients to specialized treatment at publicly funded hospitals. Even though most costs related to public health services is covered, patients would still normally pay a small user fee for each healthcare visit. Patients are then given a healthcare exemption card if they reach a maximum amount in user fees for treatment services per year (present maximum user fee is NOK 3040 ≈ 300 USD) (The Norwegian Health Economics Administration, 2023).

Use and possession of AAS and other IPEDs became illegal in Norway through a legislation change in 2013. At the same time, as one of few countries, people who use AAS in Norway were given rights to specialized psychosocial treatment for SUDs in the public healthcare system. The SUD treatment program involves biopsychosocial treatment of people with current or previous AAS use, and professional follow-up on related socioeconomically issues. The National Steroid Project was created by OUH in 2014 to provide a free and anonymous helpline for people who use AAS and their next of kin, as well as inform health professionals and the Norwegian public on associated health risks, treatment options, and economic, social or legal consequences related to AAS use (Havnes et al., 2019).

The pilot study

This paper describes the challenges in recruitment for the single-site, open longitudinal proof of concept pilot study *Health risks and off-label use of clomiphene citrate to Treat Anabolic-androgenic Steroid (AAS) induced Hypogonadism upon cessation among men – a pilot study (CloTASH)* at OUH. The pilot study tested a modified version of a 16 weeks treatment model with the SERM clomiphene citrate (CC, clomiphene or Clomid), as proposed by Rahnema et al. (2014), with 25 mg CC given every second day for 16 consecutive weeks, transdermal testosterone applied daily for the first four weeks and hCG injections added in cases of poor endogenous hormone response. The study aimed to include 25–30 men referred to SUD treatment with AAS dependence and a desire to end AAS use permanently. All participants who received the

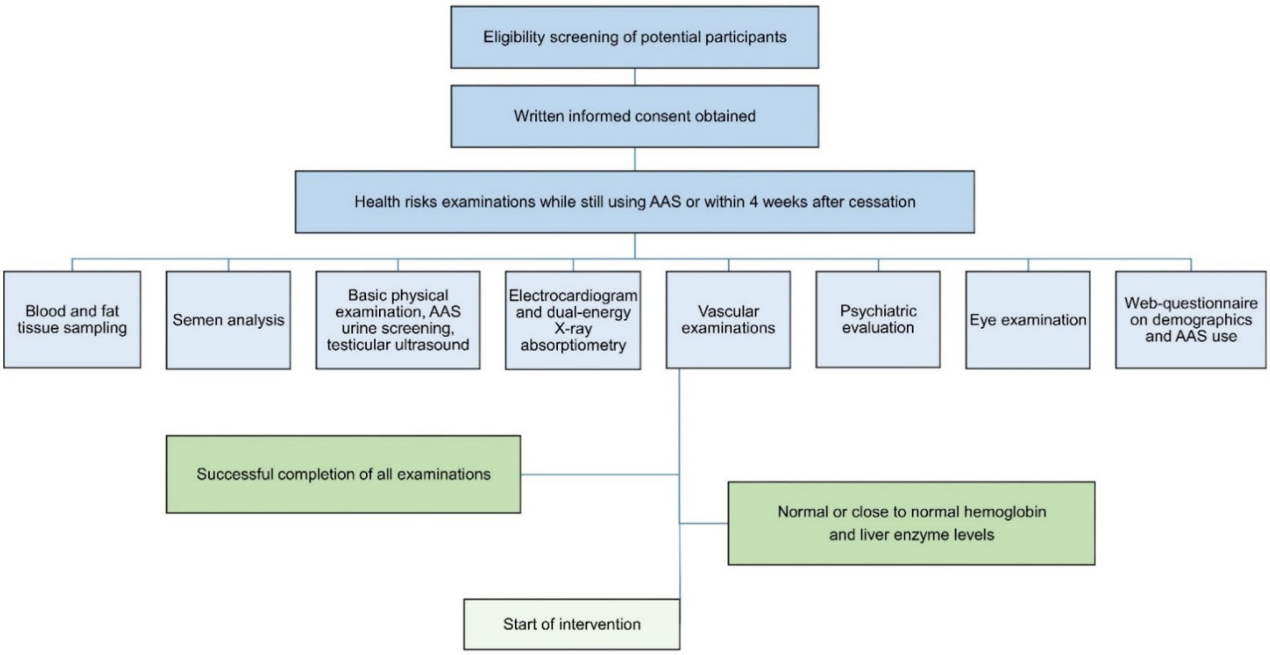

Figure 1. Inclusion examinations of health risks associated with AAS use.

intervention participated in thorough physical and mental health examinations prior to starting treatment, while still using AAS or within four weeks of cessation. For a full list of examinations at the time of inclusion, see Figure 1. Participants were monitored with self-report questionnaires every two weeks and physical examinations every four weeks throughout the 16 week intervention. They had follow-ups at six and 12 months to investigate whether the potential health risks that were identified at the time of inclusion were reversed. When planning the pilot study, the research group established a user panel consisting of five persons with previous AAS use and experience from either SUD or psychiatric treatment. A systematic review investigating recruitment of hard-to-reach groups found that community involvement in the planning process for clinical intervention studies is important to make both study protocols and recruitment more feasible (Bonevski et al., 2014). The research questions, intervention, clinical examinations and web questionnaires for the pilot study were discussed in workshops with the user panel, who strongly approved of and supported the study. Persons with user experience were also involved in the development of social media advertisements.

Inclusion and exclusion criteria

We included men who used AAS and wished to permanently quit, above 18 years of age, with consent capacity, fulfilling criteria for AAS dependence according to the DSM-IV (Pope et al., 2010), and with continuous use for the six months prior to the intervention. In addition, requirements for initiating the intervention included serum-testosterone levels <25 nmol/L (reference range 9–30), hemoglobin levels <18 g/dl (13.4–17), alanine transaminase <210 U/L (10–70) and aspartate transaminase <135 U/L (15–45), i.e. <3x upper limit for normal reference range for liver transaminases (liver enzymes). All participants were required to participate in follow-ups at the SUD outpatient clinic during the intervention. Residency in or nearby Oslo was also required for study participation. Exclusion criteria were severe mental illness (i.e. current or previous severe depression with suicidal ideation or attempts, bipolar disorder or psychosis), severe cardiovascular disease (i.e. previous thromboembolic events, myocardial infarction or cardiac arrest), prescribed testosterone replacement therapy (TRT) for hypogonadism from causes other than AAS use, ongoing non-prescribed use of other hormones, illicit substance use or previous adverse effects from clomiphene.

Recruitment procedure

The National Steroid Project at OUH was the primary contributor to participant recruitment. To reach out to men who use AAS, the following recruitment strategies, listed chronologically, were continuously assessed and improved in order to be as effective as possible: Advertisements containing study information were initially posted on the OUH website, on social media platforms (Facebook, Instagram, Snapchat, TikTok), in an online AAS forum and in several online fitness forums. Audience engagement with the social media advertisements was measured in *reach*, representing the number of unique users who saw the advertisement, and *clicks*, representing the number of people who clicked on the advertisement and were redirected to the official study website at OUH. The study was also advertised through flyers and posters in over 35 gyms and fitness centers in and around Oslo, and a degree of snowball sampling effect was expected. The Norwegian School of Sport Sciences and one of the Norwegian gym chains with the most members, Fresh Fitness Norway, broadcasted the study several times on their social media

pages. The National Steroid Project sent out letters with study information to every general practitioner located in Oslo and in selected areas of Eastern Norway. Several lectures about the ongoing clinical study and AAS-related health risks were held for relevant healthcare professionals in Norway throughout 2021 and 2022, including SUD clinicians at OUH, who were invited to refer male AAS patients already undergoing SUD treatment directly to the study researchers responsible for inclusion. Lastly, study researchers were interviewed in Norwegian newspapers to spread information about the study.

Qualitative analysis of a discussion about the study in an online AAS forum

When information about the study was shared in an online forum for people who use AAS, with the intention of making the study known and to recruit participants, it generated a discussion among 20 forum members, with a range of 1–12 posts each. The subjects of discussion included the choice of hormone therapy intervention, criminalization of AAS use and how the study was organized within the SUD treatment facilities. To gain insight into potential barriers to participate in the pilot study, we were inspired by early observational netnography as to thematically analyze the content of a single online forum thread, as 'netnography is not defined in relation to the size of a dataset, but to its depth' (Kozinets, 2020). Kozinets describe four basic steps which include '(1) research inquiry (explore potential barriers to participate in the study), (2) data collection (one single forum thread where information about the study was posted and discussed by forum members), (3) data analysis and 4) research communication'. Step 3, the data analysis, was conducted as a thematic analysis by first and last author who read and reread the posts several times. The posts were then individually coded with a focus on potential barriers to participate in the pilot study. First and last author jointly discussed coding and themes until consensus, resulting in three main themes: (I) Suggesting modifications to the intervention, (II) Fear of negative outcomes, and (III) Proposed alternatives. Step 4 (research communication) involved ethical considerations as described in the Ethics section below, and relevant quotes were selected to exemplify the themes and sub-themes.

Ethics

Ethical approval for the pilot study was obtained from the Norwegian Regional Committees for Medical Research Ethics (33872), the Norwegian Medicines Agency (21/18081-9) and the Data Protection Officer at Oslo University Hospital (20/27593). The research was performed in accordance with the principles stated in the Declaration of Helsinki. Prior to participation in the intervention, all eligible participants received oral and written information about the study. Written informed consent was provided by all participants.

All study examinations, medication and follow-ups were provided free of charge, but travel expenses were not reimbursed. As patients of the public SUD treatment program at OUH, participants were required to pay for each visit at the outpatient clinic. The initial plan for the pilot project was to offer *optional* SUD treatment to those participants who were in need of it either during or after the 16 week long intervention. However, the clinical administration at the outpatient department at OUH had ethical objections to this approach and regarded mandatory SUD treatment as a necessary support for all study participants. This was based on many years of experience with the patient group and an understanding that some patients with a desire to permanently cease AAS use develop severe depression and suicidal ideation shortly following cessation (Lindqvist et al., 2014; Thiblin et al., 1999). In addition, as this intervention had not previously been scientifically tested, we did not know whether it would have an effect on men with long-term AAS use.

All participants could withdraw from the study at any stage prior to data publication, without any consequence for their access to psychosocial treatment at the outpatient SUD clinic. Any pathological finding at the time of inclusion or during intervention was evaluated by the research physicians and investigated further clinically when indicated. All participants were insured against potential adverse medical events related to the use of study drugs, through the principal investigator's membership in the Norwegian Drug Liability Association.

To ensure ethical standards of online research and to secure the anonymity of online forum members, we excluded sensitive or potentially identifiable information from the material quoted and discussed. A research guide for internet research ethics (The National Committee for Research Ethics in the Social Sciences and the Humanities, 2019) was reviewed and discussed with the Data Protection Officer at Oslo University Hospital prior to publication:

1. *Distinction between public and private*: The AAS online forum consists of many thousand members. The overview of different threads in the forum is openly available to all, but it is necessary to create a user account with a password in order to read the posts. The forum members from the thread whose posts we analyzed did not reveal information about personal identity.
2. *Concerns for vulnerable groups*: We did not consider the online forum users to be a vulnerable group.
3. *Responsibility to inform and obtain consent*: It was not possible to obtain consent as forum users cannot interact with each other through direct messages, and members use pseudonyms as usernames, thus the real identity of each online member was not known. The researcher who posted the study advertisement in the forum did not participate in an exchange of opinions nor in the active discussion with the intent to 'provoke' a reaction from the forum users. The researcher responded to direct questions about healthcare personnel's obligation to report AAS use. One forum member sent an e-mail to the principal investigator regarding the study protocol and subsequently reposted the response from the researcher in the thread online for continued discussion among forum members.

4. *Confidentiality and anonymity* were ensured by not stating the name of the forum, replacing user names with pseudonyms, avoiding sensitive information and translating quotes from Norwegian to English.
5. *Sharing of data*: Data will not be shared.

Results – challenges in recruitment

The recruitment period lasted for one year, 1 January 2022–31 December 2022. Overall, 17 of 81 men were considered eligible for study participation, but five reconsidered and chose not to participate without further explanation. The remaining 12 men provided written informed consent to participate. One of these participants withdrew from the study before starting the intervention. Another participant dropped out of the study in the middle of intervention and restarted AAS use due to distressing withdrawal symptoms. The 10 remaining participants completed the intervention according to the study protocol. The recruitment process in this pilot proved challenging for several reasons that will be discussed in the next sections, and which ultimately resulted in a lower number of eligible participants than intended (25–30). However, the study had already been postponed due to COVID-19 and, due to funding limitations, the recruitment period could not be extended.

Advertisements through social media

Information about the study initially reached men who use AAS through the National Steroid Project's direct helpline (Havnes et al., 2019) and through snowball sampling. However, people who use AAS have previously shown to be a hard-to-reach group (Bonnecaze et al., 2020; Harvey et al., 2019; Richardson & Antonopoulos, 2019; Zahnow et al., 2017), and recruitment during the first months was unprogressive, despite following careful advice from user representatives connected to the study. All recruitment channels were made linguistically appropriate for the intended receivers, as this previously has shown to be of importance to reach socioeconomically disadvantaged groups (Bonevski et al., 2014). However, spreading information about this study through posters and flyers distributed at local gyms and the hospital's website, did not result in more participants. In addition, the Norwegian gym culture was heavily affected by the COVID-19 pandemic and many gyms in Oslo were entirely or partly closed through the years of 2020–2022. It was therefore anticipated that people who use AAS might turn to social media and online platforms for connecting with peers during the pandemic. Hence, we approached various social media platforms with paid advertisements and posted information about the study on an AAS online forum. Paid advertisements on social media appeared to be an efficient way of reaching out to many in a short time span, as depicted by the amount of reach and clicks gained by the paid study advertisements, see Table 1. TikTok was the social media platform that generated the most reach and clicks, followed by Snapchat and Meta (Facebook and Instagram). However, some of our advertisements on social media (Meta) were blocked due to violation of community guidelines: (1) the term 'anabolic steroid' could provoke suspicion of illegal sale of drugs via its services, and (2) a photo of a bare, muscular male torso was not accepted. This was solved through time consuming negotiations, as well as the use of wider terms, such as 'performance enhancing substances' and neutral illustrations.

Difficulty reaching the target population and recruiting within the study area

Although most advertisements were intended to recruit participants from a specific geographical area (the capital Oslo), the reach was widespread and many men with AAS use but with residency in other parts of the country showed interest in participation. However, those living non-commutable distances from Oslo could not be included, as visits to the study centers and SUD outpatient clinic throughout the intervention period would be impractical. A total of 81 men who used AAS expressed interest in participation, mostly through direct contact with the National Steroid Project on email or telephone, although some also contacted the other researchers directly. During the initial round of eligibility screening, 33 potential participants were excluded due to residing a non-commutable distance from Oslo. Moreover, seven men were excluded due to being enrolled in SUD treatment at facilities other than OUH. See Figure 2 for more details.

Exclusion due to safety concerns

The remaining 41 men went through a second round of inclusion and exclusion screening, where a final decision on eligibility was jointly made between the study physicians, and 24 men were mainly excluded due to safety concerns. Six potential participants who reported substance use problems were excluded to avoid potential confounding of study data containing physical and mental health measures, and given the risk of unforeseen interactions with clomiphene, transdermal testosterone and hCG. Four men with serious cardiovascular disease were excluded since thromboembolic events

Table 1. Audience engagement with paid advertisements on social media (Meta, Snapchat and TikTok) measured in Numbers of reach and clicks.

	Time period	Meta[a]		Snapchat		TikTok	
Ad content (Illustrations, terminology)	2022	Reach[b]	Clicks[c]	Reach	Clicks	Reach	Clicks
Bare, muscular male torso Anabolic steroids	May–Sept	25670	469	59420	1290	n/a	n/a
Neutral background Performance enhancing substances	Sept–Dec	39391	1129	17203	395	865979	5273
	Total	65061	1598	76623	1685	865979	5273

[a]Meta comprise Facebook and Instagram.
[b]Number of unique users who viewed the advertisement.
[c]Number of people who clicked on the advertisement and were redirected to the official study website at OUH.

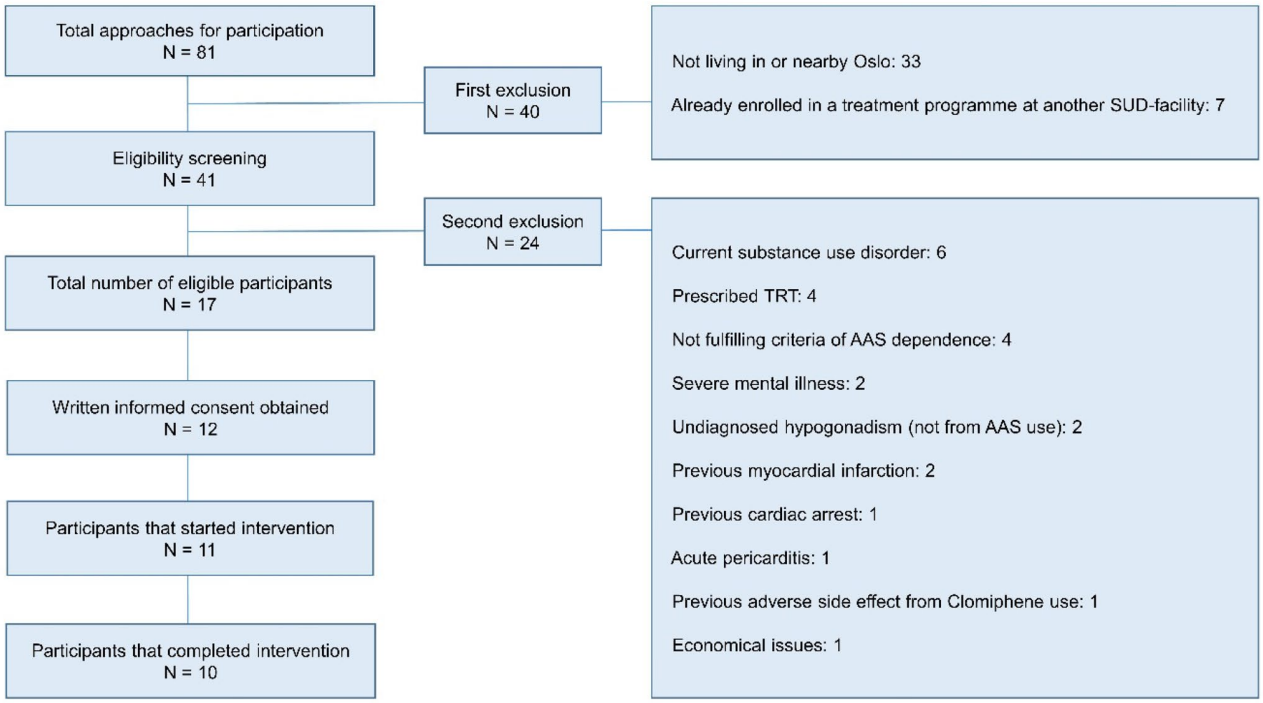

Figure 2. Flowchart of participant inclusion and exclusion. SUD: substance use disorder; AAS: anabolic-androgenic steroids; TRT: testosterone replacement therapy.

have been reported in isolated cases of infertile but otherwise young and healthy men treated with off-label clomiphene (Choi et al., 2021; Zahid et al., 2016). Two men were excluded based on medical history that indicated undiagnosed primary hypogonadism due to testicular failure and not due to previous AAS use. Finally, two men were excluded due to severe mental illness and one was excluded from participation due to previous visual disturbance related to clomiphene use.

Economic barriers

The medication and all of the examinations and follow-ups in the study were provided free of charge. However, participants had to cover the cost of transport to and from OUH every fourth week during the intervention. Additionally, most participants were not entitled to a healthcare exemption card, and thus had to pay a user fee for each visit at the outpatient clinic as patients of the SUD treatment program. This might have discouraged persons with economic challenges, which was the case for one participant. Of notice, economic incentives has previously proven to be effective to increase retention rates and satisfaction levels among participants with substance use in longitudinal designed studies (Festinger et al., 2005, 2008).

Recruitment-relevant insights from members of an AAS forum

Several forum members expressed positive attitudes towards the pilot study and saw it as a sign of changed attitude towards people who use AAS. Several had a desire to cease AAS use,[1] but expressed no intention to participate in the study. Some suggested modifications to the intervention, some feared negative outcomes of participation and some who wished to cease AAS use proposed self-treatment as alternative to study participation, see Table 2.

Table 2. The themes and sub-themes that were generated during the thematic analysis of the online discussion among AAS forum members in response to the pilot study advertisement.

Themes	Sub themes
Suggested modifications	Different substance, dose or treatment period
	Establish the scientific rationale for the intervention
	Evaluate and share published research with the forum members
Fear of negative outcomes	Questioning confidentiality: researchers versus treatment providers
	Fear of sanctions from SUD treatment providers
	Low levels of testosterone during the intervention
Proposed alternatives	Psychopharmacological treatment if unsuccessful intervention
	Side effects from intervention medicine
	Monetary incentives to compensate for risk
	Private health examinations
	Follow advice from other forum members on PCT
	Self-initiated TRT
	Research projects that are perceived as more useful from the perspective of forum members

Suggested modifications to the intervention

The choice of medical intervention was discussed among forum members. ScienceGuy questioned why the anti-estrogen Nolvadex was not used instead of CC. Another forum member, Diplomate, answered that Nolvadex could influence other hormone levels negatively and lower the bioavailability of

testosterone, and that more research has been done on CC, potentially facilitating ethical approval. He also stated that CC has a '*nicer profile when the goal is to increase the testosterone level without disturbing much else*'.

ScienceGuy sent emails to the principal investigator with questions about the choice of medication, dose and scientific rationale for the chosen dose. He received a response that referred to the publication by Rahnema et al.(Rahnema et al., 2014) describing the treatment model, as well as justification for the dose based on recent scientific reviews, which he copied and posted online. There were several posts where scientific knowledge and excerpts from published papers were shared among the forum users. The following discussion took place between ScienceGuy and Diplomate, who had slightly different opinions:

> ScienceGuy*: I don't find any scientific justification for choosing Clomid 25mg eod [every other day] in the Rahnema paper.*
>
> Diplomate*: Earlier cohort studies have used 25mg every day, so 25 mg eod seems reasonable, I think. It is better to try out lower doses prior to experimenting with higher doses. Dose-response of anti-estrogens has a steep effect curve, so there is a lot to gain by using low doses.*
>
> ScienceGuy: *Yes, perhaps. Microdosing of 25–50mg eod would be more reasonable for studies lasting longer – 1, 2 or 3 years. For short-term studies lasting 1, 3 or 6 months 50–100mg ed [every day] would be more reasonable.*

Fear of negative outcomes

Some forum members feared that participation in the study would result in negative outcomes, such as being reported by health professionals to the police for using AAS, not achieving the desired effect from the intervention, being offered psychopharmacological agents instead of TRT or individual health risks.

The online community questioned confidentiality and data protection in the research project. It was suspected that the research project could be a setup by the police to catch people who use AAS:

> Skeptical: *There are examples where users have been in similar projects, where they have been exposed to a set-up to be caught by the police. I am skeptical until I see proof of the opposite. Everyone else should be as well.*

This fear was rejected by others:

> Diplomate: *Police provocation is not allowed in Norway – such as a set-up or provoking criminal acts to arrest somebody, so there is no danger here.[.] It is common practice that you sign a consent declaration before the project starts, where your rights are described. This is legally binding, meaning that, if the hospital goes behind your back and gives information about you to the police, it will have legal consequences for them [the researchers]. But this will not happen, the hospital is interested in doing serious research, that's it.*
>
> Supporter: *[.] To set up a 'fake' research project to catch 3 gym rats like me who use AAS for cosmetic reasons and commit a completely harmless crime with no victim, seems to be a very strange way of using resources. Then it would be cheaper and give more results to simply have a police raid at the nearest gym at 8 at night.*

Forum members were critical towards both the illegalization of AAS use since 2013 and the current SUD treatment provided for people who use AAS. Negative experiences with SUD treatment were expressed. An online source ('handbook') published by OUH for treatment of people who use AAS (National Advisory Unit on Substance Use Treatment, 2015) was quoted and criticized for a lack of knowledge, absence of desired treatment options and perceived reporting practices among treatment providers. Hence, several warned against SUD treatment:

> LegalTRT: *After reading the «handbook» I get the impression that users of AAS are placed in the same category as drug addicts and gaming addicts, that they have a disease that needs treatment, and that the only solution is to quit all performance enhancing substances forever. It says that the patient should not be offered any form of PCT (nolvadex, clomid, HCG). Furthermore, one should not be offered addictive substances for anxiety or sleep problems, but rather C-drugs, such as antidepressants, antihistamines and antipsychotics. All in all, I have the impression that it is really dangerous to ask for help in the health service for AAS use. In reality you are not offered any real help as long as TRT is not the first choice. When you are threatened with losing your driver's license or being reported to the child welfare services, it's just way too stupid.*

Several forum members had gone from 'using steroids' to 'self-initiated TRT' and described a fear of not achieving the desired effect from the intervention, which would result in unstable or too low levels of testosterone. The latter is described by one forum member who found it illogical and wrong that SUD treatment use psychopharmacologic medications with unwanted side effects to treat symptoms of hypogonadism, a scenario that the study participants feared would happen in cases of low effect from the intervention:

> LegalTRT: *Is it possible that the rest of the world sees that messing with PCT is nonsense when good treatment already exists? Whether it is [testosterone] gel, nebido [injectable testosterone depot formulation] or test cyp [testosterone cypionate]? That HAS been researched and is being used all over the world? No, to hell with it, let's try PCT and give them medication so they will not feel too bad when the testosterone has left the body.*
>
> *Do you have sleep problems? Here, take some Quetiapin. Oh dear, do you get depressed? Here, take some Cipralex, then you'll feel better.*

Other health risks were also mentioned. One forum member had previously experienced reduced vision from clomiphene use and would therefore not risk further visual disturbances by participating in the study. Another member who had struggled to cease use wished to participate, but was disappointed to learn that his medical illness disqualified him from doing so. He considered taking clomiphene non-prescribed instead. One forum member suggested that monetary incentives should be provided to compensate for risk, resulting in a slightly reprimanding response from another forum member:

> LegalTRT*: 'Do you struggle to find participants? Perhaps you should offer some cash to encourage people to participate. It doesn't come without risk to take a non-approved substance like Clomid/clomiphene in a way it isn't approved. If you are going to risk life and health, you must get something in return'.*

Diplomate*: 'Offer some cash? They offer close medical follow-up for persons who desire to quit AAS use with a substance that most in this forum are already familiar with. Completely free of charge. That's quite a good payment, if you ask me. I think several in here should cool down.'*

Proposed alternatives

Forum members who intended to cease use with either supra-physiologic AAS or self-initiated TRT saw better alternatives to participation in the research project. One member stated that the medical examinations provided by the research project could easily be accessed through other health services instead:

LegalTRT: *Those who care can get it checked out by themselves.*

Several options for prescribed PCT and TRT or self-initiated TRT were also suggested:

Try2Quit: *I will try to get off again. I'm on TRT and am not doing cycles anymore. I have used HCG during TRT for several years, and I have gotten prescribed Enklomifen instead of Clomid.*

LegalTRT: *If you find the right physician, you get the right treatment. I know about one who prescribes testosterone almost automatically if the levels are under 12 nmol/l. But if you don't find one, you can set up your own TRT like most in here do.*

Several discussed what they perceived as lack of knowledge within the healthcare system and referred to self-medication as the best solution for maintaining a stable testosterone level:

StableTesto: *Not the least, it is demanding [to seek treatment] due to a shockingly low level of knowledge in the public health system regarding both steroids and hormone therapy. Even among endocrinologists who are supposed to be the experts, outdated ideas and standards are used. AND very little, if any, consideration is given to the mental effects of quitting testosterone. [.] It is clear that we can't trust [the knowledge of] public physicians. So it has to be ourselves, or private physicians so expensive that the first hour [of consultation] costs more than several years of underground testosterone consumption. So, we are left to self-medicate if we want a healthy, stable level of testosterone instead of yo-yoing with the hormonal system.*

The knowledge among health professionals and the methodology used by the researchers were questioned, and it was suggested that making use of the knowledge in the online community would be the best option:

Broscience: *To be honest, I think we who are users on the forum have a better chance to help people to quit AAS than the health services and the [research] project. We have the most knowledge and experience. We know what kind of protocols can work, and we can do «everything» that may help without superintendence. Unfortunately.*

ForumTrust: *I trust Diplomate and the other guys here on the forum more than those tired physicians…[.] I have gotten so much help from this forum that a physician could never have provided.*

Another forum member suggested that future research should focus more on men 30–50 years of age, who have used AAS for several years and who self-medicate with TRT following AAS cessation:

LegalTRT*: Like me, I have used steroids for more than 10 years. To follow a protocol for a year to regain testosterone production is most probably just nonsense and something I would never expose myself to when I know that there are legal, good medications that offer what I need in a good, effective and safe way.[.] Is it strange that people do not want to participate in projects like this? No. Is it strange that we self-medicate? No. Do we want it like this? No.*

What we users would need is a study where you [the researchers] investigate the effect of getting active and former steroid users (with too low level of testosterone) off self-medication and on legal TRT with access to gel, nebido and test cyp. For us who have used, or abused as you [the researchers] see it, steroids for many years have, as I see it, little use for your project. You should focus on our group [people who self-medicate], because the majority who need help the most belong to our group. Most people who start [with steroids] use for many years, the rest stop after first or second cycle.

This last post from LegalTRT was applauded by the Diplomate who suggested it forwarded to the researchers in the pilot study as a proposal for further research projects.

Discussion

In this proof of concept pilot study providing off-label hormone therapy to men with a desire to cease continuous AAS use, we aimed to include 25–30 men with a desire to cease continuous, long-term AAS use. However, we experienced a variety of challenges in recruitment of research participants, many of which could have been solved if addressed earlier during the planning of the study. Even though 81 men expressed interest in participation, 40 were excluded early in the process due to residency in other parts of Norway and 24 were excluded mainly due to safety reasons such as concurrent SUD, or history of severe cardiovascular disease or mental disorder. In the end, only ten men who were found eligible for participation successfully completed the study intervention.

Exclusion challenges

The decision to exclude participants due to safety concerns can be ethically challenging, given the physical and mental health risks posed by continued AAS use (Horwitz et al., 2019; Piacentino et al., 2015). However, there is a knowledge gap regarding the effectiveness and safety of various PCT models for treating ASIH (Bates et al., 2019). Even though clomiphene has previously shown to be safe and effective for treating hypogonadism from causes other than AAS use (Krzastek et al., 2019; Moskovic et al., 2012; Taylor & Levine, 2010; Wheeler et al., 2019), it has not yet been used off-label in clinical research to treat ASIH. The more common side effects of clomiphene comprise headache, dizziness, mood changes, breast tenderness and gastrointestinal symptoms (Choi et al., 2005; Wheeler et al., 2019), while rarer and more serious adverse effects have been reported, which involve vision changes (e.g. blurred vision; Purvin, 1995), liver damage (Zhang et al., 2018) and thromboembolic events (Solipuram et al., 2021). Serious adverse effects from previous use of clomiphene should therefore be an exclusion criterion for study participation.

Obligatory SUD treatment

Norway is one of few countries where AAS use has been included in the drug policy, from which follows that AAS use and possession is criminalized and that people who use AAS are entitled to SUD treatment. However, fear of being reported to the police might serve as a barrier to participating in SUD treatment. Five men who were deemed eligible to participate in the intervention chose not to in the end. Fear of reporting practices among health professionals might have played a role in this, as described by forum members that discussed the intervention and the obligatory SUD treatment, as well as in previous studies (Havnes et al., 2019; Havnes & Skogheim, 2020). These legal repercussions could include issues with child protection services or driver's license authorities, or that having a medical file that involves AAS use may potentially influence access to future life insurance. Moreover, men who in a previous study contacted The National Steroid Project's information service feared that the health professionals would report their AAS use to employers or to the police if they were enrolled in SUD treatment (Havnes et al., 2019). It is therefore likely that fear of sanctions would not only influence negatively on the engagement towards public treatment services but also towards entering a clinical study administered by a public university hospital. This is further strengthened by the fact that we continuously tested urine samples for the use of AAS or other illegal substances, that SUD treatment was made compulsory for every study participant, and that patient records were logged electronically. Thus, some may have been reluctant to enter SUD treatment, as they did not wish to have their AAS use documented in their medical file or did not necessarily identify as having a SUD use. There is reason to believe that all these factors might have dissuaded those who received information about the study from participating. However, we found support in the argument for obligatory SUD treatment among user involvements in the planning of the protocol. Yet, despite previous positive experiences with SUD treatment for AAS cessation, some individuals from our user panel initially warned that the mandatory enrollment to SUD treatment might be met with skepticism. Still, as there was a risk of prolonged symptom burden in cases of delayed or low treatment response, a joint decision was made to refer all eligible participants to SUD treatment at the time of study inclusion. Additionally, in the occasions of co-occurring mental health problems, other comorbidities or socioeconomic and interpersonal challenges, SUD treatment would be considered beneficial. Finally, it may be considered both ethical and financial feasible to include participants as patients in the public healthcare system as it not only requires less study funding due to clinical examinations being part of the treatment but also ensures documentation and follow-up of pathological findings according to the Norwegian health legislation.

Barriers to participate in the study

We directly targeted the community of people who use AAS by posting study details in an online AAS forum. Forum members were skeptical to having the study organized within the public SUD treatment system. Furthermore, they criticized and suggested modifications to the proposed intervention: the choice of study drug (clomiphene citrate); the dosage, which were perceived as too low, or the treatment period, which some thought was too short. This shows that there are diverse perspectives on PCT among those who self-medicate, as the intervention design was largely based on recommendations from men who use AAS, both from a user panel of persons with previous AAS use and from user involvement in the original protocol (Rahnema et al., 2014).

The criminalization of AAS use might also have worked as a barrier to study participation as some forum members advised against it due to fear of sanctions or police reporting, either by the researchers or the SUD treatment providers, as previously described (Havnes et al., 2019; Havnes & Skogheim, 2020).

Research suggests that people who use AAS seek information from peers online (Andreasson & Henning, 2022; Frude et al., 2020; Henning & Andreasson, 2021; Smith & Stewart, 2012; Tighe et al., 2017). This was found to be the case in this study where forum members gave advice about various PCT protocols and self-treatment regimens, as well as how to self-initiate TRT at the end of an AAS cycle instead of using PCT, to both stabilize endogenous testosterone levels and improve mental health. It seems that customized, online recommendations from peers might be more attractive to some persons who use AAS than participating in studies that investigate health risks and the effects of PCT. Forum members expressed a bigger trust in the general knowledge of people who use AAS than physicians. A netnography by Underwood et al. (2021) found that some are motivated to self-initiate TRT due to low willingness to prescribe TRT among physicians, a perceived lack of AAS knowledge among healthcare professionals, and that non-prescribed testosterone is easily accessible at a low price. Moreover, self-initiated TRT was found to be used in a similar way as prescribed medical TRT, and often seen as a better alternative than cessation. The authors suggest that the 'repair/enhancement dichotomy' is more useful when discussing AAS use, rather than label non-prescribed testosterone use as abuse (Underwood et al., 2021). This thematic was also discussed among forum members in the current study where cycling as enhancement was perceived as 'AAS use', as opposed to 'self-initiated TRT' which was perceived as self-treatment and a way of discontinuing 'AAS use'. Although non-prescribed products used for TRT and PCT are easily available (Cox et al., 2023; McBride et al., 2018), these products may be counterfeit (i.e. they are over- or under dosed, do not contain active substances or are made up of other substance(s) than the ones labeled) (Magnolini et al., 2022) and may together with contaminated AAS lead to health problems (Frude et al., 2020). Hence, some choose to manufacture AAS at home for personal use instead, as this is perceived to lower the risk for counterfeit and contaminated substances (Brennan et al., 2018). Although various self-treatment regimens could lead to bodily harms, it may still be seen as a form of harm reduction strategy. Forum users desired access to legal and prescribed TRT for men with low endogenous testosterone levels, instead of using illicit substances or quitting use. Thus, previous experiences with unsuccessful AAS cessation may therefore have worked as a barrier to participation in the study.

Strengths and limitations

It may be considered a strength that AAS user involvement played a role in the planning and recruitment phase of this pilot study. However, the user panel consisted of people with previous AAS use *and* positive SUD or other treatment experiences, with a desire to obtain more knowledge about their health status following cessation of AAS. By conducting a short survey among men with *current* use or by including them earlier in the planning phase, we could have potentially garnered insights into factors that would make participation more appealing. It may be seen as a strength that we included a thematic analysis of the discussion among members of an online AAS forum in response to the study advertisement, as this gave us valuable information about possible barriers to participation. However, it should be considered a limitation that this analysis was not planned beforehand and that the data was solely collected from a single thread with 20 active forum members.

Lessons learned and recommendations for future studies

- Individuals with current or previous AAS use should be involved in an early planning phase, which could include both online surveys and meetings with researchers
- Future studies exploring off-label use of anti-estrogens on people who withdraw from AAS should consider safety assessments prior to starting off-label interventions with PCT
- Similar future studies that use social media for recruitment, should be cautious of using sensitive titles (e.g. 'anabolic steroids') or graphics showing bare skin, as these advertisements risk being banned on various social media platforms.
- Enrollment of participants into a parallel, public SUD treatment program, ensures a safer, more ethical and more cost-effective study execution, but may contribute to challenges in recruitment.
- Future studies should consider free SUD (or other) treatment, cover travel expenses or compensate participants with economic incentives for time spent on health examinations.
- In cases of study postponements due to unforeseen circumstances, which in our case was the COVID-19 pandemic, further funding is needed to be able to prolong the recruitment period.
- The inclusion examinations turned out to be demanding for some participants, as the examinations were performed at different clinics and by multiple examiners, and thus could rarely be conducted on the same day. For future studies, this could be solved by reducing the location sites with single-center trials, and thus minimize the number of examinations and forgo assessments of AAS-related health risks. This could be particularly relevant for smaller studies or pilot studies.
- The expressed interest for the study across the country suggests that a multicenter trial may lead to higher inclusion rates.
- The contribution of the National Steroid Project and its direct helpline proved to be an important recruitment strategy and seemed to be the most effective way of recruiting participants with an intention to cease AAS use. Having access to an initial noncommittal and anonymous information session with a healthcare professional seem to be a motivating factor to enter a research project with a parallel SUD treatment program. Similar services should therefore be considered utilized for future treatment studies in this particular patient population.
- While hormone therapy following AAS cessation aims to treat the endocrine part of the AAS dependence, SUD-treatment focuses more on other central parts of dependence such as body image disorder and reward effects. For future similar studies, SUD treatment could be considered an option, rather than a requirement, limited only to participants who experience suicidal ideation during AAS withdrawal, body image disorder, lack of reward effects or comorbid mental health problems in need of treatment. This could be based on an initial evaluation prior to inclusion, as well as close monitoring by study researchers with clinical expertise throughout the intervention period.
- Some men have no desire to cease AAS use despite access to legal PCT, mainly due to previous experience with burdensome withdrawal symptoms after cessation. Instead they choose to self-initiate TRT at the end of an AAS cycle or after cessation of continuous AAS use.
- For some, customized, online recommendations from peers is more appealing than participation in studies that investigate the effects of PCT, especially if participation involves SUD patient status with records of AAS use in the medical file.
- Naturalistic observational studies may be considered an option to intervention studies, either to explore the effect of non-prescribed PCT or to compare the effects of non-prescribed PCT with self-initiated TRT. However, this approach might be subject by various sources of error.

Conclusion

Challenges in recruitment included difficulty reaching the target group with information about the study, as well as other barriers, such as financial limitations, obligatory enrollment to SUD treatment, self-initiated TRT as an option to cease use, criticism from potential participants of the medical protocol used for the intervention and fear of being prosecuted as AAS use is criminalized in Norway. Our experienced challenges and lessons learned may be considered a valuable contribution to research on its potential guidance of future clinical trials on treatment for people who use AAS.

Note

1. The term "use" among forum members mainly referred to the use of AAS in supra-physiologic doses and cycles, and not necessarily to the use of self-initiated TRT.

Acknowledgements

This study has benefited from the contributions of a user panel, who provided helpful feedback in the recruitment process. Special thanks go to Christina Brux for useful comments and for language editing on an earlier draft of the manuscript.

Author's contributions

IAH is Principal Investigator and was responsible for the study design together with APJ. CW and HCBH were the main contributors to active participant recruitment. HCBH, IAH and APJ were responsible for eligibility screening, inclusion examinations and data collection. HCBH and IAH planned the analyses for this paper and jointly conducted the thematic analysis. HCBH wrote the first draft of the manuscript and IAH drafted the qualitative part. APJ and CW provided critical feedback on the manuscript. All authors contributed substantially to the manuscript, and have approved the final version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the South-Eastern Norway Regional Health Authority under Grant No. 2020090 to Ingrid Amalia Havnes and internal research grants from Oslo University Hospital to Ingrid Amalia Havnes and Hans Christian Bordado Henriksen.

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V

Endocrinology, Diabetes & Metabolism

Clomiphene citrate for treating male hypogonadism arising from long-term anabolic-androgenic steroid use – a pilot study

Journal:	*Endocrinology, Diabetes & Metabolism*
Manuscript ID	Draft
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Henriksen, Hans Christian; Oslo University Hospital; University of Oslo Institute for Clinical Medicine Jørgensen, Anders ; Oslo University Hospital; University of Oslo Institute for Clinical Medicine Bjørnebekk, Astrid; Oslo University Hospital Neupane, Sudan; University of Oslo Institute for Clinical Medicine Havnes, Ingrid Amalia; Oslo University Hospital; University of Oslo Institute for Clinical Medicine
Keywords:	anabolic androgenic steroids, hypogonadism, clomiphene
Abstract:	Introduction Long-term anabolic-androgenic steroid (AAS) use poses several health risks, including secondary hypogonadism. There is a knowledge gap on treatment targeting the hypothalamic-pituitary-gonadal (HPG) axis among men with anabolic steroid-induced hypogonadism (ASIH). This study aims to investigate the safety and feasibility of endocrine therapy in restoring endogenous testosterone levels and alleviating ASIH symptoms in men withdrawing from long-term continuous AAS use. Methods In this proof-of-concept, single-site, open longitudinal pilot study, 25 mg clomiphene citrate (CC), was given every second day for 16 weeks to AAS dependent men with continuous AAS use and a desire to permanently discontinue use. Physical exams including blood collection and online questionnaires were completed every four and two weeks, respectively. Results Ten participants, median age (interquartile range) 32 years (30-45), with mean ± standard deviation AAS use of 11 ± 4 years, completed the intervention. Mild and reversible adverse events included headaches, dizziness, and mood swings, and no serious adverse events occurred. During the intervention, there was a significant decrease in levels of haematocrit, haemoglobin and ALT (alanine aminotransferase), as well as an increase in serum FSH (follicle stimulating hormone), LH (luteinizing hormone) and SHBG (sex hormone binding globulin). Five of ten participants reached a total testosterone level within normal range (9-30 nmol/l). The HPG axis response varied greatly among participants,

	and was not aligned with the severity of ASIH related withdrawal symptoms. Conclusions The findings indicate that endocrine therapy with CC is generally safe but only partly feasible in addressing ASIH and aiding people struggling to terminate long-term AAS use. Subsequent randomized clinical trials should be executed to establish the concept.

Clomiphene citrate for treating male hypogonadism arising from long-term anabolic-androgenic steroid use – a pilot study

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Disclosure statement: No potential conflict of interest was reported by the authors.

Funding: This work was supported by the South-Eastern Norway Regional Health Authority under Grant No. 2020090 to Ingrid Amalia Havnes and internal research grants from Oslo University Hospital to Ingrid Amalia Havnes and Hans Christian Bordado Henriksen.

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Keywords: anabolic androgenic steroids, hypogonadism, clomiphene

Abstract

Introduction

Long-term anabolic-androgenic steroid (AAS) use poses several health risks, including secondary hypogonadism. There is a knowledge gap on treatment targeting the hypothalamic-pituitary-gonadal (HPG) axis among men with anabolic steroid-induced hypogonadism (ASIH). This study aims to investigate the safety and feasibility of endocrine therapy in restoring endogenous testosterone levels and alleviating ASIH symptoms in men withdrawing from long-term continuous AAS use.

Methods

In this proof-of-concept, single-site, open longitudinal pilot study, 25 mg clomiphene citrate (CC), was given every second day for 16 weeks to AAS dependent men with continuous AAS use and a desire to permanently discontinue use. Physical exams including blood collection and online questionnaires were completed every four and two weeks, respectively.

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Conclusions

The findings indicate that endocrine therapy with CC is generally safe but only partly feasible in addressing ASIH and aiding people struggling to terminate long-term AAS use. Subsequent randomized clinical trials should be executed to establish the concept.

Introduction

Anabolic-androgenic steroids (AAS) constitute a subgroup of image and performance-enhancing drugs (IPEDs) including testosterone and synthetic androgens yielding similar chemical and biological effects (1). Since the 1980s, non-prescribed AAS have predominantly been used by male recreational athletes in supraphysiological dosages (2), to enhance muscle mass, reduce body fat, and elevate athletic performance (3). AAS usage among men has been driven, in part, by the heightened focus on the muscular male physique and aesthetic appearances in Western societies (4). AAS are usually consumed in patterns of weeks-long cycles with breaks in between, or continuously with low doses with or without periodically alternating higher doses (5). AAS have become a public health concern, as use is widespread worldwide and can have adverse consequences on physical and mental health (6). It is estimated that the global lifetime AAS use rate is 3.3%, with a higher prevalence among males (6.4%)(7).

The use of AAS is linked with several health risks that among other affect the endocrine, metabolic and cardiovascular system (8-11). Physical outcomes include hypertension, cardiomyopathy, dyslipidaemia, gynecomastia, hepatotoxicity, sexual dysfunction, and hypogonadism (12, 13). Long-term AAS use inhibits the endogenous testosterone production by its negative feedback mechanisms on the hypothalamic-pituitary-gonadal (HPG) axis (14), also known as anabolic steroid-induced hypogonadism (ASIH). ASIH is a form of central hypogonadism, wherein the pulsatile secretion of gonadotropic releasing hormone (GnRH) from the hypothalamus is reduced, and the pituitary gland's output of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responsible for regulating testicular testosterone production and spermatogenesis, becomes temporary diminished or absent (15). The ‘withdrawal’ symptoms of ASIH are manifested when AAS usage is discontinued. They include fatigue, reduced libido, erectile dysfunction, and depression (16) that may involve elevated risk of suicide (17-19). As ASIH-symptoms during or after AAS cessation are difficult to endure, many restart AAS use, making ASIH a central contributor to the pathology of AAS dependence (20). It is estimated that one third of people who initiate AAS use develop dependence, marked by persistent AAS use despite enduring adverse physical and mental effects (21). The HPG axis tends to normalize within 3-18 months after AAS cessation among men with cycling AAS use (22) or fewer years of accumulated use (23). However, this period might be extended and even lead to permanent hypogonadism in some, especially in people with longer duration of use (24, 25). There is a knowledge gap on treatment targeting HPG axis among AAS dependent men with continuous long-term AAS use.

Many people who use AAS tend to self-monitor symptoms of androgen deficiency and ASIH that follows AAS cessation through a practice called ‘post-cycle therapy’ (PCT) (26, 27). PCT comprises hormonal agents such as selective oestrogen receptor modulators (SERMs), human chorionic

gonadotropin (hCG) and aromatase inhibitors (16). These drugs are normally prescribed for treatment of infertility or breast cancer in women (28). As a LH-analogue with longer half-life, hCG acts on Leydig cells in the testicles, stimulating the synthesis and release of endogenous testosterone (29). hCG may also contribute to increased spermatogenesis in infertile hypogonadism stemming from supraphysiological androgen levels and gonadotropin suppression (30). Clomiphene citrate (CC) is another popular PCT component belonging to the drug class SERM (16), and which has previously been used in treating male hypogonadism unrelated to AAS use (31, 32). CC targets the reduced serum LH and total testosterone levels that are associated with secondary hypogonadism (31). The drug mechanism of action is to increase the release of pituitary LH and FSH, thus restoring and preserving testicular testosterone production and spermatogenesis, without suppressing the HPG axis (33). In addition, the clomiphene stimulation test has also been observed to provide a transient response in gonadotropin and testosterone levels in men with former long-term AAS use (34), supporting previous findings of ASIH as a reversible condition (22, 23). Commonly reported side effects of CC include gastrointestinal symptoms, headache, dizziness, mood swings, and gynecomastia (31, 35, 36). Case reports of more severe adverse events are also registered such as liver injury (37), suicidal behaviour and psychotic episodes (38), thromboembolic events (39), and visual disturbances (40).

Indeed, CC and hCG combined has demonstrated to be an effective therapeutic approach in promoting a sufficient HPG axis response to recover spermatogenesis (41), and has also been proposed as a treatment option among infertile men with former AAS use (42). Additionally, the use of off-label PCT protocols has widespread accessibility among people who use AAS (43). Despite this, no previous experimental study has evaluated their safety and effectiveness in treating ASIH. There is an urgent need to understand its usefulness and to develop clinical protocols for administering appropriate endocrine therapy during or after AAS discontinuation. In this proof-of-concept pilot study, we aim to investigate 1) the safety of endocrine therapy with CC, transdermal testosterone and hCG among AAS-dependent men withdrawing from long-term use, 2) to what extent endocrine therapy helps to restore endogenous levels of testosterone after AAS cessation, and 3) the treatment model's feasibility in alleviating symptoms of hypogonadism.

Materials and Methods

Setting

The healthcare system in Norway operates on a publicly funded basis, where all residents are entitled to public healthcare through the National Insurance Scheme (44). Use and possession of AAS and other IPEDs were made illegal in Norway following a legislative change in 2013, and individuals using AAS were given the right to substance use disorder (SUD) treatment within the public

healthcare framework (45). SUD treatment for this group of patients typically follows a biopsychosocial approach (45). The National Steroid Project accompanied by a cost-free and anonymous helpline was established by Oslo University Hospital (OUH) in 2014. Its purpose is to aid those who use AAS and their next of kin, as well as to educate healthcare professionals and the general public about AAS-associated side effects, socioeconomic and legal hazards, and the available treatment options in Norway (46).

Study design

This is a single-site, open longitudinal pilot intervention study at OUH in Norway, titled '*Health risks and off-label use of clomiphene citrate to Treat Anabolic-androgenic Steroid (AAS) induced Hypogonadism upon cessation among men – a pilot study (CloTASH)*'. The present paper utilizes longitudinal data including blood tests and self-report web questionnaires, collected in the period of 2022-2023. Participants underwent physical examinations and blood collection every fourth week and completed online questionnaires every second week throughout the 16-week-long intervention. Longitudinal data on AAS health risks from follow-up at 6 and 12 months will be subject for future publications when data sampling is completed and full analyses are available.

Eligibility criteria

We enrolled men who were currently using AAS or had quit use < four weeks prior to intervention and had a simultaneous desire to permanently discontinue use. All participants were above 18 years of age, possessed the ability to provide informed consent, met the AAS dependence criteria as outlined in DSM-IV (47), had engaged in consistent AAS use for the six last months and had serum testosterone levels ≤ 25 nmol/L (reference range 9–30) before the intervention. Residence in or near Oslo and patient enrolment at the SUD outpatient department at OUH throughout the intervention were mandatory for all participants. Exclusion criteria included prior or present severe mental illness, cardiovascular disease, substance use disorder, high haemoglobin and elevated liver enzymes. The paragraph "Safety measures" (below) gives a further detailed description of exclusion criteria.

Recruitment

The recruitment phase spanned from January 1, 2022, to December 31, 2022 as previously described (48). Participants were recruited through The National Steroid Project at OUH and various recruitment channels such as social media, online AAS forums and flyers and posters at local gyms in Oslo. In addition, letters containing study information were sent to all general practitioners in Oslo and selected areas of Eastern Norway, encouraging them to hand out the study brochure to potential participants. Out of the initial pool of 81 men, 17 AAS-dependent males seeking to permanently cease AAS use were deemed eligible for participation, but five subsequently withdrew from the study without providing specific reasons. Among the 12 remaining participants, one participant withdrew just prior to intervention start, while another participant restarted AAS use and dropped out of the study after seven weeks of treatment. Ten participants successfully completed the full intervention as outlined in

the study protocol (48). All participants also underwent comprehensive physical and mental evaluations before commencing treatment, either while still using AAS or within four weeks of quitting. This was both a safety measure prior to starting intervention and a current assessment of health risks associated with AAS use.

The intervention

In this pilot study, we tested an adapted version of a 16-week hormone therapy model with CC as main component, as initially proposed by Rahnema et al. (2014) (16). In this modified version, 25 mg CC were administered every second day for a continuous period of 16 weeks with 50 mg transdermal testosterone applied daily during the first four weeks. In addition, hCG injections (Ovitrelle 250 µg/0.5 ml prefilled pen = choriogonadotropin alfa/recombinant hCG equivalent to approximately 6500 IU) were added in the treatment scheme among those participants with inadequate endogenous total testosterone (TT) response below 10 nmol/l. An initial dose of 1500 IE hCG was given twice per week during week 4-8, and if insufficient testicular response persisted at week eight, the dosages were increased to 1500 IE 3x per week during week 8-12 (i.e. maximum eight weeks of hCG injections). Of note, participants presenting with low levels of both TT and sex hormone binding globulin (SHBG) and a concurrent high free testosterone index (FTI, also called free androgen index) were not given hCG. See Figure 1 for a detailed illustration of the treatment model. A TT level of ≥ 20 nmol/l during or at the end of intervention was set as a target. Consequently, participants demonstrating a successful response to treatment could conclude the intervention before week 16. In the end, the treatment response was regarded as effective if TT exceeded 20 nmol/l during the intervention *or* was within the normal reference range for TT at the end of the intervention (i.e. ≥ 9-30 nmol/l). The intervention would be considered non-responsive in cases of TT below 9 nmol/l by week 16.

Laboratory analyses

Blood samples were obtained and analysed at the laboratory of the Department of Medical Biochemistry, OUH. Blood was collected at inclusion, while participants were still using AAS or had recently quit use (< four weeks prior), and every fourth week during the 16 weeklong intervention. Laboratory panels indicative for safety measures included haematocrit, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), calcium, creatinine, estimated glomerular filtration rate (eGFR) and prolactin. Sex hormone panel included follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, SHBG, TT and FTI. FTI was calculated by the formula: testosterone (nmol/l) x 10/SHBG (nmol/l). Urine samples were collected and analyzed at inclusion and continuously during the intervention at Centre for Laboratory Medicine, Østfold Hospital Kalnes, by a liquid chromatography (Agilent 1260 Infinity II)–tandem mass spectrometry (Agilent 6470 Triple Quad) method. Sample extraction was performed using Solid Liquid Extraction (SLE) plates (Biotage), with added instant buffer I and β-glucuronidase. Urine samples were screened for illicit psychoactive substances and psychoactive medications, as well as the

20 most prevalent AAS. The criterion used to determine exogenous androgen use was urine samples positive for synthetic testosterone compounds at a testosterone to epitestosterone ratio (T/E) >10. In the event of a positive screening result, subsequent targeted testing procedures were conducted.

Questionnaires

Fatigue

To evaluate the level of fatigue in each participant, we used the Shortened Fatigue Questionnaire (SFQ), a reliable and quick clinical questionnaire to assess complaints of bodily fatigue in chronically ill patients (49). The questionnaire consists of the four items 'I feel tired', 'I tire easily', 'I feel fit' and 'I feel physically exhausted'. A 7-point Likert Scale was used to score each item from 1 'no that is not true' to 7 'yes that is true'. With item 3 being reversed, it would give a total score that varied from 4 to 28, with a cut-off score of ≥18 to predict severe fatigue (50).

Depression

To evaluate symptoms of psychological distress, we used the Hopkins Symptom Checklist-10 (HSCL-10) (51). The ten items questionnaire is particularly designed to measure levels of anxiety and depression in the preceding week (52, 53). Each item is scored from 1 to 4, and an average score of ≥1.85 indicates psychological distress. Participants that reported reduced zest for life during the last 14 days *and* exhibited an indifference to death or a recent desire to die, were presented to the suicidal ideation item of the Montgomery and Åsberg Rating Scale (MADRS) (54). The MADRS assesses suicide risk, by rating the question 'have you had any thoughts on suicide or any desires of death in the last three days' on a scale of 0 ("enjoys life or takes it as it comes") to 6 ("explicit plans for suicide when there is an opportunity; active preparations for suicide").

Wellbeing

The WHO-5 is a short self-report questionnaire of current mental wellbeing (55). The WHO-5 includes five non-intrusive questions on the subjective feeling of mental health during the last two weeks: 'I have felt cheerful in good spirits', 'I have felt calm and relaxed', 'I have felt active and vigorous', 'I woke up feeling fresh and rested', 'My daily life has been filled with things that interest me'. It offers six response options ranging from *all the time* (score = 5) to *at no time* (0). Consequently, it gives a raw score ranging from 0 to 25, which is then multiplied by 4 in order to transform the cumulative score into a percentage that spans from 0 to 100, where 0 is indicative of absence of well-being and 100 representing the highest quality of life levels (55).

Sexual function

The assessment of sexual interest and functioning among the participants were based on four questions gathered from a questionnaire established in previous literature (56). First question is designed to

measure level of sexual interest and self-perceived sexual attractiveness whereas the next three questions are measures of sexual function. Each question was scored with a 5-item scale from 1 ‘not at all’ to 5 ‘a great deal’ with question 1 being reversed, giving a total cumulative score between 4 and 20, with higher scores representing more severe degrees of sexual dysfunction.

Safety measures

Exclusion criteria due to safety measures were: prior or present severe mental illness (severe depression with suicidal ideation or attempts, bipolar disorder, or psychosis), prior or present severe cardiovascular diseases (history of thromboembolic incidents or cardiac arrest), prescribed testosterone replacement therapy (TRT) for hypogonadism unrelated to prior AAS use, non-prescribed TRT or PCT, illicit substance use, or previous adverse events to CC. Other safety prerequisites prior to starting intervention included haemoglobin levels <18 g/dl (13.4–17), ALT levels <210 U/L (10–70) and AST levels below <135 U/L (15–45), which corresponds to being less than three times the upper limit of the normal reference for liver aminotransferases. Participants with abnormal levels of haemoglobin or liver aminotransferases at the time of study enrolment were monitored regularly with blood tests until levels reached physiologic levels. Consequently, six participants were given physiological doses of transdermal testosterone as bridge medication due to safety measures prior to starting the intervention. One participant with consistently high haemoglobin levels underwent venesection prior to starting intervention, with 450 ml blood drawn twice a week in two consecutive weeks, resulting in haemoglobin levels dropping from 19.4 to 15.8 g/dl. The initial assessment and follow-up were closely monitored by the study physicians.

Considering the pilot design of the current study and the lack of previous research on off-label PCT-medication, strict safety measures were effectuated during eligibility screening (48). Adverse events were monitored with self-report questionnaires every second week, as well as every fourth week by thorough physical examinations (measurement of weight, height and waist circumference, auscultation of heart and lungs, gynecomastia assessment, oedema assessment and blood pressure measurements), blood tests (haematocrit, haemoglobin, calcium, prolactin, liver and kidney parameters), urine sampling (screening for AAS and substance use) and clinical interviews. The clinical interviews during week 4-16 of the intervention started with an open-ended question regarding well-being, with subsequent recordings of potential side effects, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (57). Any adverse occurrence that would require medical attention at CTCAE level 2 or higher were to be recorded. Any Severe Adverse Events (SAEs) related to the intervention and Suspected Unexpected Severe Adverse Reactions (SUSARs) would be reported to the Norwegian Medicines Agency within 7 days for cases involving fatality or life-threatening situations, and within 15 days for other SUSARs. All participants underwent enhanced eye examinations prior to intervention start and at the end of intervention, to detect any potential vision changes or retinal damages from CC use.

Participants were offered an open direct 24 hours line to the research physicians via phone or email in cases of emergency related to the intervention. In addition, all participants were insured against adverse events attributable to study drug occurring during or after participation, via the Project Leader´s membership in the Norwegian Drug Liability Association. The research physicians meticulously assessed any detected pathological findings related to AAS use, and if found, participants were either referred directly to specialist health services or recommended to contact their GP for further follow-up.

Statistics

All safety evaluation data from physical examinations including laboratory measures are presented in frequency distribution tables for the total sample. Shapiro-Wilk tests and histograms were employed to evaluate normal distribution in the data set. Means and standard deviation (SD) are used to present normally distributed data, and changes in blood measures during intervention are illustrated through one-way repeated measures analysis of variance (ANOVA) with effect size reported as adjusted R^2. Subsequent Bonferroni post hoc tests were applied in cases of significant differences between time points. Prior to conducting ANOVA, sphericity was tested with Mauchly's W tests, and in cases where assumption of sphericity was violated, the Greenhouse-Geisser estimate of sphericity was used for violation correction. Non-normal numerical data are reported as medians and interquartile range (IQR, 25th-75th percentiles). Friedman tests (Chi^2) with Kendall's W (effect size) are employed to assess potential changes in blood measure levels during intervention, along with post hoc Wilcoxon signed-rank tests to assess which time points any significant changes differed. A significance level was set at $p < 0.05$.

In this pilot with ten participants, an illustrative summary of each participant's hypogonadism is presented. Thus, the hormone panels for each participant are presented as individual graphs to depict changes in hormone levels during intervention, shown together with responses from questionnaires to simultaneously portray subjective changes in ASIH-symptoms from week 0 to 16. Logarithmic scales were used in cases where the data from one questionnaire set (WHO-5) deviated substantially from the majority of the dataset. Two sample t-test were used to compare differences in accumulated AAS use (in years) between the "responders" and "non-responders", and a Wilcoxon rank sum test (Mann-Whitney) was used for between-group comparison in age. All statistical analyses, tables and figures were conducted using STATA (version 17.0, StataCorp LLC, Texas, USA).

Ethical considerations

Ethical clearance for the initial study was obtained from the Norwegian Regional Committees for Medical Research Ethics (33872), the Norwegian Medicines Agency (21/18081-9), and the Data Protection Officer at Oslo University Hospital (20/27593). The study adhered to the principles defined in the Declaration of Helsinki. Before joining the intervention, all eligible participants were given

comprehensive verbal and written information about the study, and written informed consent was collected. Due to heightened risk of severe depression with suicidal ideation during AAS cessation (17), all participants were enrolled in SUD treatment at the time of study inclusion and throughout the 16-week intervention. After the end of intervention, participants could continue SUD treatment based on individual needs. At any point before data publication, participants retained the rights to withdraw from the study without losing their access to SUD treatment. All assessments, medications, and follow-ups associated with the study were provided at no cost, however, no additional compensation or remuneration was provided (48).

Results

Demographics and baseline characteristics of the subjects

Demographic data and AAS use characteristics are presented in Table 1. In total, ten participants completed the 16 weeks intervention, with median (IQR) age 32 years (30-45), mean (±SD) debut age for AAS use 20.7±3.8 years and mean (±SD) accumulated use 11.1±4.1 years. All the participants fulfilled the DSM IV-criteria for AAS-dependence (47), had previous attempts of AAS cessation without success and had a desire to quit AAS use on a permanent basis. Five participants had previously been prescribed a combination of antidepressants and anxiolytics, indicating a prior diagnosis of either depression or anxiety, and two received current treatment for ADHD (attention deficit hyperactivity disorder). Seven participants identified bodybuilding to be among their primary recreational activities, and four indicated previous involvement in sports competitions at either national or international level. All participants reported side effects from AAS use, with testicular atrophy (n=10), erectile dysfunction (8), oedema (8), and mood swings (8) being the most common, followed by fatigue (6), depression (6), anxiety (6), reduced libido (6), hyperhidrosis (6), acne (5), striae (4), androgen alopecia (4), and gynecomastia (3).

Safety measures

Safety measures during the intervention were patient reports of adverse events, assessment of suicidal ideation and objective measures that included physical examination and blood tests. Seven participants reported at least one adverse event once or more during the intervention period. The most reported adverse events were headache, dizziness and mood swings, see Table 2. Blurred vision or gynecomastia related to CC were not reported. No serious adverse events were reported or observed.

At baseline, seven participants reported reduced life zest, and three reported both reduced life zest *and* indifference to death or a recent desire to die. Among these three participants, two participants scored

0 on MADRS ("enjoys life") and one participant scored 2 ("weary of life, only fleeting suicidal thoughts"). During week 4, two of the same three from W0 were subjected to MADRS, whereas the first scored 2 ("weary of life, only fleeting suicidal thoughts.") and the other scored 4 ("probably better off dead, suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention"). Over the course of 16-week intervention, there was an apparent reduction in suicidal ideation: no participant exhibited any indifference to death or a recent desire to die at week 8, 12 or 16, and two participants reported reduced life zest at week 16.

Safety parameters including physical examination and blood tests for the total sample are seen in Table 3. There were no pathological findings on heart and lung auscultations prior to or during intervention, oedema of lower extremities was not found and no participants developed gynecomastia. Ophthalmological examinations were normal and unchanged in all participants throughout intervention. Mean systolic blood pressure was high prior to and during the intervention, with 8 out of 10 participants exhibiting hypertensive levels at baseline, defined as a systolic blood pressure of ≥140 and/or or a diastolic pressure ≥90 mm Hg (58). There was a significant reduction in levels of haematocrit and haemoglobin from baseline to the end of intervention. There were intermittent significant changes in renal parameters during the intervention with unclear clinical significance. One participant tested positive for exogenous testosterone in urine at week 16 due to self-initiated TRT by the end of intervention. Two participants were found to have traces of dexamphetamine in urine throughout the intervention due to prescribed ADHD-treatment, and one participant exhibited traces of tramadol and oxycodone due to prescribed pain-relieving treatment for musculoskeletal damage.

Feasibility of intervention

Table 4 provides a summary of hormone measures in the total sample during the 16-week intervention. Intervention with CC, transdermal testosterone and hCG showed varying effect on the HPG axis. Overall, there was a significant increase in FSH, LH and SHBG during intervention. Five of the participants developed sufficient HPG axis response to produce endogenous testosterone that either surpassed target TT level of 20 nmol/l during intervention or were within normal range for TT (9-30 nmol/l) at the end of intervention and were classified as 'responders'. The remaining five participants exhibited limited or no response in endogenous testosterone level, classifying them as 'non-responders'. The responder group did not significantly differ from the non-responder group on age (median age 31 years, IQR 30-32, range 26-32 vs median age 45, IQR 32-48, range 30-57, p=0.09) or accumulated use (8.7±2.8 vs 13.5±4 years, p=0.06), see Figure 2 for a boxplot summary.

The self-reported ASIH-related withdrawal symptoms varied greatly between the participants and did not seem to correspond well with endogenous levels of testosterone. Among the participants, 80% of

the responders had well-being scores below the low cut-off (WHO-5), while an equal percentage of non-responders maintained normal WHO-5 scores consistently throughout the entire period. To provide a comprehensive overview, individual hormone panels were graphically presented, illustrating the fluctuations in hormone levels throughout the intervention period, accompanied by questionnaire responses, depicting subjective changes over time in ASIH-symptoms. In Figure 3a-j an overview of each participant's ASIH status is presented. Figure 3a-e represents the five participants with positive response on endogenous testosterone levels (responders), and Figure 3f-j represents the five participants with limited response on endogenous testosterone levels (non-responders).

Participants with positive intervention response on endogenous testosterone levels

Case 1

Case 1 was in his early 30s, had initiated AAS use at 20 years and used AAS for a combined seven years. As seen in Figure 3a, during the first 4-8 weeks of the intervention, TT levels exceeded the target range, prompting the cessation of hormone therapy at week 8. Subsequently, both LH and TT levels decreased but remained within the normal range throughout the rest of the intervention. The participant experienced consistently moderate to high levels of fatigue. Despite an apparent improvement in depression scores, the participant’s quality of life remained subpar, with a score of 36% by week 16.

Case 2

Case 2 was in his early 30s, debuting with AAS at 22 years and reported an accumulated AAS use of 10.5 years. As depicted in Figure 3b, the participant initially exhibited a positive HPG axis response, with both an increase in LH and TT levels that reached target level by weeks 4-8, prompting the termination of intervention. Subsequently, LH and TT levels declined but consistently stayed within the normal reference ranges for the remainder of the intervention. Around week 6, the participant reported elevated levels of fatigue and sexual dysfunction. The quality of life had its highest peak around week 12, before declining to the low initial starting point of 20%.

Case 3

Case 3 was in his early 30s, with AAS debut at 28 years of age and an accumulated AAS use of 4.5 years. As seen in Figure 3c, the participant initially exhibited a low HPG axis response, prompting the inclusion of hCG in the therapy regimen. Nevertheless, by week 8, both LH and T levels had begun to rise and maintained stable for the rest of the intervention. Notable improvements were observed in the participant's experience of withdrawal symptoms during intervention. Particularly noteworthy was the increase in quality of life, which surged from 20% to 84% over the course of 16 weeks.

Case 4

Case 4 was in his early 30s, with AAS debut at 20 years and an accumulated use of 11 years. As illustrated in Figure 3d, the participant reached target TT level by week 8, and maintained normal TT levels between weeks 8 and 16. This was likely attributable to the introduction of hCG from week 4, as LH levels remained undetectable throughout the course of the intervention. The participant consistently endured high levels of fatigue, depression and sexual dysfunction throughout the intervention. Furthermore, quality of life was significantly compromised, reaching a mere 5% by week 16.

Case 5

Case 5 depicts a man in his 20s with an accumulative 10.5 years of AAS use since the age of 15. He had ceased illicit AAS some weeks prior to intervention start. As seen in Figure 3e, the participant developed a rapid HPG axis response following week 4, resulting in an abrupt increase in LH levels beyond the reference range and subsequent TT levels surpassing the lower normal reference. However, a rise in SHBG from week 8 to 16 contributed to a lower FTI. Despite a modest improvement in fatigue levels and quality of life, scores for fatigue, quality of life, depression, and sexual dysfunction all remained at a suboptimal level throughout the intervention.

Participants with limited intervention response on endogenous testosterone levels

Case 6

Case 6 illustrates a man in his mid-40s, with AAS debut at 20 years and accumulated AAS use for 11 years. As depicted in Figure 3f, the participant's TT levels increased slightly during the initial 8 weeks, followed by a gradual decline, and ultimately falling below the reference by the end of the intervention. Notably, an elevation in LH levels between weeks 12 and 16 may suggest the beginning of a potential reactivation of the HPG axis. Throughout the intervention period, quality of life and depression scores remained within the normal range. Sexual dysfunction displayed fluctuations and remained at a notably high symptom-burden by week 16. The participant experienced the highest levels of fatigue between weeks 2 and 6, with scores surpassing the threshold for severe fatigue, but these levels appeared to improve from the beginning of the intervention to its conclusion.

Case 7

Case 7 was in his early 30s, debuted with AAS at 19 years and had an accumulated AAS use for 10 years. As seen in Figure 3g, in the first eight weeks of intervention, a LH increase signified a positive HPG axis response. Despite consistently low TT levels throughout the intervention, the concurrent presence of low SHBG lead to a high FTI, which contradicted the addition of hCG in the treatment regimen. The participant's symptom-burden appeared to reach its peak around week 4. Even though

quality of life improved during intervention, the level of fatigue ended above the threshold for severe fatigue.

Case 8

Case 8 was in his late 40s, with AAS debut at 23 years old and an accumulative use of 20 years. As illustrated in Figure 3h, TT levels gradually increased from the outset, reaching its highest point around week 12, before rapidly declining after the discontinuation of hCG. LH levels remained undetectable for the majority of the intervention. Despite the participant's low TT levels, scores reflecting mental health and quality of life were not notably impacted. The participant's sexual function persisted at a mid to high level, while fatigue levels occasionally exceeded the threshold for severe fatigue.

Case 9

Case 9 was in his early 30s, debuting AAS at 15 years old with an accumulative use of 14.5 years. As seen in Figure 3i, despite the addition of hCG, TT levels remained below the desired range throughout the intervention. The low HPG axis response corresponded well with consistent high scores of fatigue, depression and sexual dysfunction, and a rapid decline in quality of life. However, the rise in LH and the subsequent increase in TT levels from week 12 to 16 might suggest a positive breakthrough in HPG axis response.

Case 10

Case 10 was in his 50s with AAS debut at 24 years old and with an accumulative use of 12 years. As depicted in Figure 3j, the participant consistently demonstrated a diminished HPG axis response, as evidenced by low LH levels throughout the intervention. However, the introduction of hCG appeared to lead to a modest increase in TT levels between weeks 4 and 12. It is important to note how the self-initiation of TRT at the end of the intervention, led to an immediate surge in TT and FTI levels, as well as a drop in SHBG levels, as seen in the 16-week blood test. Despite the low HPG axis response throughout intervention, the participant self-reported a minimal amount of withdrawal symptoms and a high quality of life.

Discussion

This is the first intervention study to explore safety and feasibility of endocrine therapy consisting of 25 mg clomiphene citrate every second day for 16 weeks among AAS-dependent men. Our findings suggest that treatment in the given dosages and period appears to be safe in treating ASIH resulting from long-term continuous AAS use. Although half of the participants also seemed to experience a

HPG axis response, it did not appear to correspond to the burden of ASIH-related withdrawal symptoms. The findings and its clinical implications will be discussed in further detail below.

Safety

In our study, only mild and transient side effects from CC was reported, and no serious adverse events were observed on neither regular physical examinations, eye exams nor blood measures. The findings are in accordance with previous studies of CC (31, 32). In fact, a recent systematic review and meta-analysis found that the majority of studies examining the impact of CC on male hypogonadism, reported no observed adverse events associated with its use (36). Among the few studies that observed side effects (33, 59), the effects were mild, only found in a minority of participants, and similar to the ones reported more frequently among the participants in our study, including headache, mood swings and breast tenderness.

Particular attention was given to assessments of eligibility for receiving endocrine therapy, especially in instances where participants displayed concurrent elevated levels of liver aminotransferases levels or secondary polycythemia due to AAS use, conditions conflicting with the initiation of CC. It was particularly important to ascertain that patients undergoing hormone therapy did not exhibit elevated hemoglobin levels, as this condition may heighten the risk of thromboembolic events, an infrequent but noteworthy adverse outcome associated with CC use (39, 60). In instances of consistently high haemoglobin levels, participants received regular monitoring until their levels returned to normal, and in one specific case, a phlebotomy procedure was performed before starting the intervention. Similar to earlier research (61, 62), there were no observed elevated haematocrit or liver enzyme levels secondary to starting CC treatment. On the contrary, haematocrit and haemoglobin levels, as well as ALT, declined during the intervention, likely due to the concurrent discontinuation of AAS (63). In fact, previous studies have shown that polycythemia (62, 64) and deep vein thrombosis (59) are both more common among patients treated with TRT compared with CC. In certain segments of the intervention, significant fluctuations in renal parameters were observed among the participants. Nevertheless, these fluctuations were not deemed clinically relevant. Despite the ambiguity surrounding clinical significance, a preceding animal study demonstrated nephrotoxic effects from CC administration (65).

For participants awaiting CC treatment due to safety measures, a temporary bridge medication was provided in the form of 50 mg transdermal testosterone applied daily. This measure was introduced to prevent the sudden onset of ASIH symptoms prior to intervention start, as ASIH can lead to severe depression and suicidal ideation (17). There was an apparent improvement in life zest, MADRS-score and suicidal ideation from the beginning of intervention until the end. However, it might prove challenging to distinguish between the impact of time passage and the influence of CC on psychological factors related to ASIH. It is also reasonable to anticipate that the enrollment of

participants and their psychosocial follow-up at the SUD clinic may have had a positive effect on depressive scores and the simultaneous presence of suicidal ideation.

Feasibility of intervention

We hypothesized that endocrine therapy with clomiphene citrate, transdermal testosterone and hCG might restore the HPG axis even after the initial shutdown induced by long-term AAS use. CC has been found effective in improving serum LH and testosterone levels, alleviating symptoms of hypogonadism, and addressing infertility in men with hypogonadism caused by factors other than AAS use (31-33, 36). In addition, recent observational findings have shown than men who self-initiate PCT following AAS cessation have significantly higher levels of endogenous testosterone compared to those who do not (66), and self-report 60% less withdrawal symptoms including 50% less suicidal thoughts (67). In our study, average levels of FSH, LH and SHBG significantly increased during the intervention, and half of the participants reached physiological TT levels within 16 weeks. However, since active AAS use effectively decreases gonadotropin and SHBG levels (68), some observed effects may have arisen merely due to AAS cessation and the subsequent restoration of the HPG axis due to time passage, rather than being attributable to the CC intervention itself. Nonetheless, in a cohort of males with cycling AAS use, it was observed that FSH and SHBG levels were lower three months after a cycle compared to during the active cycle (22). Prior to intervention start, a standard prerequisite was that participants had ceased AAS usage at least four weeks prior to inclusion and exhibit baseline testosterone levels below 25 nmol/l. As a consequence, some participants began intervention with TT levels within the physiological range or even at mid-high levels, while others initiated CC with levels below 9 nmol/l. This disparity in baseline TT levels may have influenced the outcomes of the endogenous hormonal response. While all participants experienced decreased LH levels following recent AAS cessation, variations were observed in their baseline LH levels. Notably, some studies have found a better CC response among men with low baseline LH levels (69), whereas others have not found any correlation (70).

We propose some theories to why men withdrawing from AAS respond more effectively to endocrine therapy than others. Firstly, it is plausible to assume that a younger age may be indicative of a more adaptable HPG axis (71). Notably, three out of the five non-responders in our sample were above 40 years old. Secondly, it is likely that accumulated years of AAS use might have an impact on the HPG axis (72), with the presumption that individuals with the lengthiest duration of use may experience the most unfavorable outcomes, as previously demonstrated for recovery rates of spermatogenesis after AAS cessation (23). Notably, among the five participants with limited endogenous testosterone response to the treatment, the average accumulated duration of use was 13.5 years, whereas those with a positive response had accumulated use of 8.7 years. Of note, to distinguish responders from non-responders, we established a specific target testosterone level. As a result, one participant (Case 6) was

classified as a non-responder despite observing some effects on the HPG axis. Lastly, the participants involved in this pilot were individuals with a history of long-term, continuous AAS use. The majority were engaged in bodybuilding, with several reporting prior participation at a competitive level – a factor that has recently been associated with extended and recurrent AAS usage (73). In addition, all participants had made multiple prior unsuccessful attempts to cease use. This aspect is integral to AAS dependence (20) and distinguishes this group from men with short-term AAS use or intermittent cycling use with breaks between them, who may be more inclined to experience positive treatment effects from similar interventions (22, 66).

Besides the CC response on serum testosterone levels, the subjective response and symptoms of hypogonadism is equally important when defining hypogonadism (74). Improvement on symptoms of hypogonadism while treated with CC has previously been difficult to predict and measure on a sole questionnaire, as hypogonadism is considered a multifactorial diagnosis (36). Interestingly, an improvement in ASIH withdrawal symptoms did not align with the levels of endogenous testosterone. In fact, four out of five participants classified as "responders" scored below the cut-off for low well-being (WHO-5), whereas four out of five "non-responders" maintained normal WHO-5 scores throughout the entire period. Men with a history of long-term AAS use have recently been reported to experience a sustained reduction in their quality of life two years after cessation (27), despite reports that endogenous testosterone levels return to normal after 3-18 months (22, 23, 68). Nevertheless, it is noteworthy that the studies demonstrating HPG recovery within a year of AAS cessation predominantly involve men engaging in cycling intermittent use or with fewer years of accumulated AAS use. Concurrently, some men with former use continue to experience persistent erectile dysfunction even after testosterone levels have normalized (25). Erectile dysfunction often emerges in post-cycle periods and may be a source of mental distress, impacting overall quality of life (75). In fact, as many as eight of 10 participants reported erectile dysfunction as an adverse effect from AAS use. However, the impact of CC on sexual function in our sample remains questionable, as levels of sexual dysfunction did not seem to change markedly from baseline to week 16 in most participants. Considering the generally high levels of mental distress and fatigue in our study group during the intervention, these findings suggest that factors beyond endogenous testosterone levels may contribute to the manifestation of suspected ASIH withdrawal symptoms. For instance, it has previously been shown that adverse childhood experiences increase the risk of later AAS use (76). A higher incidence of depression, anxiety, suicidal attempts and substance use have been found among people who use AAS(77), as well as a higher use incidence of antidepressants, anxiolytics and antipsychotics (78). In another study, troubled childhood histories and ongoing social disadvantages was more prevalent among people who use AAS, with reports of compromised parent relationships including physical or mental abuse, concentration problems, and learning difficulties (79). Finally, a recent study

demonstrated higher levels of psychopathology in men with long-term AAS use compared to weightlifting controls (80).

The optimal dosage of CC to induce a sufficient treatment response in men with ASIH remains unclear. Prior studies of CC treating hypogonadism unrelated to AAS, have extended treatment durations up to 1, 2 and 3 years and beyond, with dosages exceeding the ones used in our study (31-33). While some studies have adjusted the CC doses based on each patient's preference and the severity of hypogonadism symptoms (70), others advocate adopting the identical dose employed in our study (25 mg CC every other day) (36). Insufficient response after 16 weeks of CC intervention might indicate persisting hypogonadotropic hypogonadism, as previously recorded in some former AAS-using men (81). In such instances, CC or similar medications may be less effective. The effectiveness of CC treatment in men with hypogonadism unrelated to AAS use has been found depend largely on the patient's age (70), with younger age increasing likelihood of both higher serum T levels and quality of life (59). Factors contributing to persistent ASIH are not well studied; however, the causative factor might be multifactorial, influenced by age, AAS debut age, consumption of multiple AAS at high doses and cumulative exposure to supraphysiological levels of AAS over time (15, 25, 81-83).

In relation to hCG, which was co-administered with CC during the intervention based on indications, a distinct advantage is in its direct impact on the testes, eliciting a prompt response compared to indirect medications such as CC, which depend on the pituitary synthesis of LH (30). Moreover, hCG, in contrast to TRT, does not negatively impact spermatogenesis, emphasizing its important role in the treatment of male fertility (29). In addition, monotherapy with hCG has shown to have a notable positive effect on both serum testosterone levels and symptoms of hypogonadism (84). This implies that it could function as a substitute for TRT in treating individuals with former long-term AAS use and persistent ASIH, particularly when a current fertility desire is involved. However, limitations such as cost, subcutaneous administration, and a relatively short half-life generally preclude hCG's widespread use as the primary therapy for male hypogonadism (30).

Although TRT among AAS-dependent men might be considered controversial as the HPG axis tends to normalize within a year after AAS cessation (22, 68), it remains the primary treatment choice for men with hypogonadism (74, 85). However, numerous benefits of CC compared with hCG and TRT can be highlighted, such as its cost-effectiveness, non-invasiveness and fertility-preserving properties (68). The median age in our sample was 32 years, whereas six out of ten participants reporting not having children at time of inclusion. It is therefore reason to believe that considerations of future fertility may have influenced their motivations to quit AAS. Ultimately, monotherapy with CC has been deemed to be equally as efficacious, when compared with either hCG alone or in combination with CC, in restoring testosterone levels in late-onset hypogonadism not related to AAS use (84). The

optimal therapeutic model for treating ASIH may need adjustments or open up for individually tailored dosing regimens to ensure a satisfactory HPG axis response. As of today, only a minority of endocrinologists feel confident in treating ASIH (86, 87), yet there is a likelihood that they will confront a rising incidence of ASIH cases in the foreseeable future (88). Further research, particularly randomized clinical trials, is needed to establish the concept and refine the treatment model. If endocrine therapy proves feasible in helping individuals with AAS dependence, it could potentially lead to novel treatment guidelines for this population, addressing a significant current public health concern.

Strengths and Limitations

The study has several strengths and limitations. A notable strength is its pioneering status in this area, paving the way for future randomized clinical trials. Adhering to ethical guidelines, the study provided extensive support and monitoring for participants, and it unfolded in a real-world setting within the Norwegian healthcare system. Importantly, there were no missing data for blood tests, physical examinations or self-report questionnaire sheets. However, the study also faces limitations. The limited number of participants impacted the statistical power, potentially influencing the clinical significance. The recruitment process in this pilot study encountered various challenges, as elaborated in a methodological paper (48), leading to a final count of eligible participants that was below the initially targeted range of 25–30. Enrolled participants, predominantly characterized by long-term AAS usage, exhibited significant heterogeneity; however, specific modifications to individual treatments were not implemented, potentially influencing the responses to treatment. It is challenging to differentiate reported adverse effects from other concurrent psychological or somatic comorbidities. At the same time, it is difficult to discern feasibility of the intervention, the passage of time on the HPG axis, and the influence of SUD treatment. In most cases, the participants self-reported withdrawal symptoms before receiving blood test results, but this was not always feasible, and responses to prior tests could have influenced subsequent questionnaire self-reports. Ultimately, this paper exclusively focuses on the 16-week intervention period, making it challenging to ascertain whether the HPG axis response remained consistent after discontinuing CC among the participants.

Conclusions

Treatment with CC, transdermal testosterone and hCG in the given dosages and period appear to be safe in treating ASIH from long-term continuous AAS use. The proposed endocrine therapy lead to sufficient HPG axis response to produce endogenous testosterone within the normal range in half of the sample. The achieved testosterone levels by the intervention did not correspond well with the symptoms of hypogonadism. CC could potentially be considered a safer alternative to the standard

TRT for men with ASIH, in particular in young men with a future fertility aspect. However, studies randomising more subjects and controls to different treatment regimens should be performed before this novel treatment for men with AAS dependence is established as a routine.

Acknowledgements

The authors are thankful to the study participants for their valuable contributions to the research project.

Funding

This work was supported by the South-Eastern Norway Regional Health Authority under Grant No. 2020090 to Ingrid Amalia Havnes and internal research grants from Oslo University Hospital to Ingrid Amalia Havnes and Hans Christian Bordado Henriksen.

Data Availability

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Disclosure statement

No potential conflict of interest was reported by the authors.

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TABLES

Table 1 Demographics and basal characteristics related to AAS use (n = 10) prior to intervention start

	All (n = 10)	Range
Age (years)	32 (30-45)	26-57
BMI (kg/m^2)	26.5 (26-28.7)	24.2-37.5
Education (years)	14.5±2.6	10-18
Current student (yes/no)	4	
Current employment (yes/no)	9	
Have children (yes/no)	4	
Currently smoking (yes/no)	2	
Alcohol consumption (yes/no)	5	
Former use of antidepressants (yes/no)	6	
Former use of anxiolytics (yes/no)	5	
Current use of ADHD medication (yes/no)	2	
Former illicit substance use (yes/no)	4	
AAS debut age	20.7±3.8	15-28
Accumulated AAS use (years)	11.1±4.1	4.5-20
Number of combined AAS used at time of inclusion	2.5±1.3	1-4
Weekly dose (mg) at time of inclusion	855±651	300-2000
Engaged in bodybuilding	7	
Engaged in fitness	5	
Engaged in combat sports	7	

Note: Data are presented as n, mean±SD or medians (IQR). AAS = anabolic-androgenic steroids, BMI = body mass index, ADHD = attention deficit hyperactivity disorder

Table 2 CC adverse events in all participants during intervention (n = 10)

	Week 4	Week 8	Week 12	Week 16
Any CC adverse event	7	6	3	3
Headache	3	3	1	1
Dizziness	3	2	2	2
Mood swings	2	1	1	2
Depression	3	1	0	1
Flushing	1	0	0	0
Breast tenderness	1	1	1	1
Abdominal pain	0	1	0	0
Bloating	1	1	2	1
Nausea or vomiting	1	1	1	2
Anorexia	1	0	1	0
Diarrhoea	1	0	0	0
Other non-serious adverse events†	3	3	2	3

Note: Data are presented as n. Adverse events for W0 were not recorded. † sleep disorder, androgen alopecia, increased sweating and constipation.

Table 3 Safety parameters in all participants during intervention (n = 10)

Physical examination		Week 0	Week 4	Week 8	Week 12	Week 16	F-value/Chi^2	p-value	Kendall's W/ Adjusted R^2
Weight (kg)		87.5 (81-91)	87 (80-88)	86.5 (80-88)	87.5 (80-90)	84 (80-89)	4.10	0.39	0.10
BMI		27 (26-29)	26 (26-28)	27 (25-28)	26 (26-28)	26 (25-28)	2.62	0.62	0.07
Waist circumference (cm)		89 (86-91)	88 (87-90)	90 (87-93)	91 (87-93)	91 (89-94)	7.38	0.11	0.18
Systolic blood pressure		157±13	161±19	154±17	154±19	150±18	5.20	0.27	0.13
Diastolic blood pressure		89±6	85±15	86±9	87±10	86±13	0.41	0.80	0.57
Pulse		68±15	68±16	64±17	65±18	69±15	5.34	0.25	0.13
AAS urine		0	0	0	0	1	-	-	
Psychoactive substances urine		3	3	3	3	3	-	-	
Blood panel	**Reference range**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**F-value/Chi^2**	**p-value**	**Kendall's W/ Adjusted R^2**
P-haematocrit†	0.40-0.50	0.49±0.04	0.49±0.03	0.48±0.03	0.46±0.02	0.46±0.04	5.16	**0.002***	0.65
P-haemoglobin, g/dL‡	13.4-17.0	16.4±1.4	16.4±1.1	15.9±1.2	15.7±0.9	15.5±1.1	5.59	**0.001***	0.73
P-ALT, U/L§	10-70	61 (34-77)	44±16.6	40±13.5	38±12.9	41±13.3	13.16	**0.01***	0.33
P-AST, U/L	15-45	40 (20-44)	38±16.6	34±13.4	42±27.7	34±14.6	4.16	0.38	0.10
P-ALP, U/L	35-105	64±14.4	63±13.5	63±16.0	65±17.0	67±21.5	0.58	0.55	0.81
P-calcium, mmol/L	2.20-2.55	2.37±0.09	2.36±0.09	2.35±0.09	2.32±0.07	2.34±0.10	1.28	0.30	0.60
P-creatinine, µmol/L¶	60-105	92±11.9	100±9.6	93±9.6	91±6.3	92±11.3	3.95	**0.009***	0.68
eGFR, mL/min/1,73m2 #	> 60	94 ±15.6	86±12.1	94±12.7	94±10.7	95±12.4	3.73	**0.01***	0.73
P-prolactin, x10E-3 IU/L	90-325	175 (120-230)	195 (150-227)	143 (128-195)	185±39.7	167 (129-280)	3.68	0.45	0.09

Notes: Data are presented as mean±SD and medians (IQR). Degrees of freedom (ANOVA) for all measures = 4. BMI = body mass index, P = plasma, ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate.

*$p < 0.05$ indicates statistical significance.

†$p < 0.05$, Bonferroni's post hoc: W16 vs W0 (p=0.018) and W16 vs W4 (p=0.007).

‡$p < 0.05$, Bonferroni's post hoc: W12 vs W0 (p=0.04), W12 vs W4 (p=0.03), W16 vs W0 (p=0.01) and W16 vs W4 (p=0.01)

§ $p < 0.05$, Wilcoxon signed-rank post hoc: W16 vs W0 (p = 0.03)

¶ $p < 0.05$, Bonferroni's post hoc: W4 vs W0 (p=0.03), W12 vs W4 (p=0.02) and W16 vs W4 (p=0.03).

# $p < 0.05$, Bonferroni's post hoc: W12 vs W4 (p=0.04) and W16 vs W4 (p=0.03).

Table 4 Hormone parameters in the total sample during intervention (n = 10)

Blood panel	Reference range	Week 0	Week 4	Week 8	Week 12	Week 16	Chi^2	p-value
P-FSH, U/L†	1.4-12.0	0 (0-1)	1.2 (0-2.6)	2.7 (0.9-2.7)	2 (0.4-3.5)	3.2 (2.7-3-6)	20.43	**0.0001***
P-LH, U/L‡	1.8-12.0	0.2 (0-0.5)	1.4 (0-3.9)	4.8 (0.7-11.1)	3.1 (0-5.5)	4.9 (3.6-5.8)	12.54	**0.006***
P-SHBG, nmol/L§	18-54	18±5.6	26 (17-29)	25 (22-31)	31 (24-34)	32±14.9	18.87	**0.0003***
P-TT, nmol/L	9.0-30.0	15.1±9.9	7.4 (4.2-10.4)	15.1±8.7	12.6±5.2	15.3 (6.8-24.6)	3.24	0.36
P-FTI		9.3±5.7	3.1 (2.2-7.1)	6.3±3.4	4.5±1.4	3.8±2.3	3.0	0.39
P-oestradiol, nmol/L	0.06-0.14	0 (0-0.12)	0 (0-0.09)	0.1 (0-0.16)	0.11 (0-0.13)	0.09 (0-0.11)	5.40	0.14

Notes: Data are presented as mean±SD and medians (IQR). FSH and LH levels < 1 U/L and oestradiol levels < 0.09 nmol/L (i.e. undetectable levels) were marked as 0. There was 1 missing from W16 (n = 9) for sex hormone parameters including FSH, LH, SHBG, TT, FTI and oestradiol. P = plasma, FSH = follicle-stimulating hormone, LH = luteinizing hormone, SHBG = sex hormone binding globulin, TT = total testosterone, FTI = free testosterone index.

*$p < 0.05$ indicates statistical significance.

†$p < 0.05$, Wilcoxon signed-rank post hoc: W4 vs W0 ($p = 0.01$), W8 vs W0 ($p=0.006$), W12 vs W0 ($p=0.006$) and W16 vs W0 ($p=0.009$)

‡$p < 0.05$, Wilcoxon signed-rank post hoc: W4 vs W0 ($p = 0.03$), W8 vs W0 ($p=0.01$), W12 vs W0 ($p=0.02$) and W16 vs W0 ($p=0.02$)

§$p < 0.05$, Wilcoxon signed-rank post hoc: W4 vs W0 ($p = 0.02$), W8 vs W0 ($p=0.006$), W12 vs W0 ($p=0.005$) and W16 vs W0 ($p=0.01$)

FIGURES

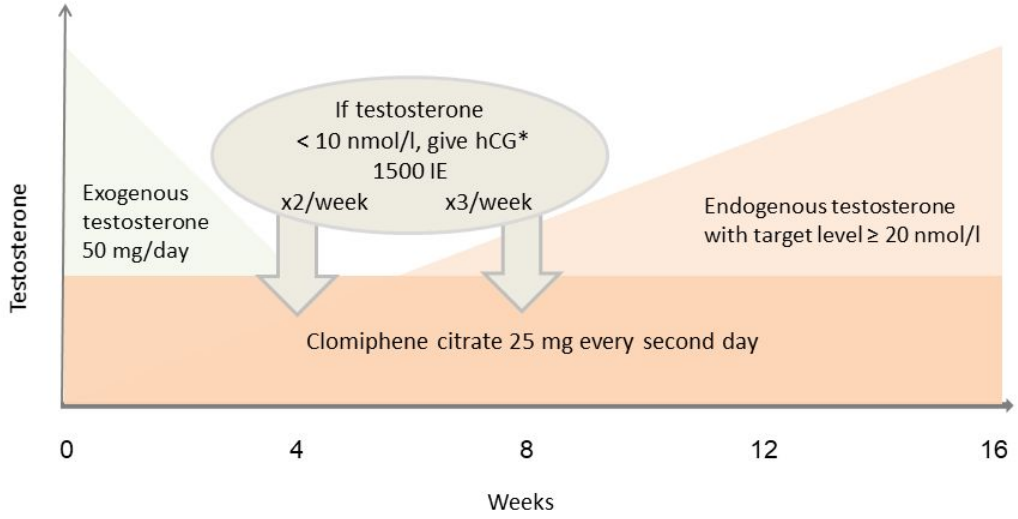


Figure 1: The endocrine therapy model with 16 weeks intervention. hCG = human chorionic gonadotropin.

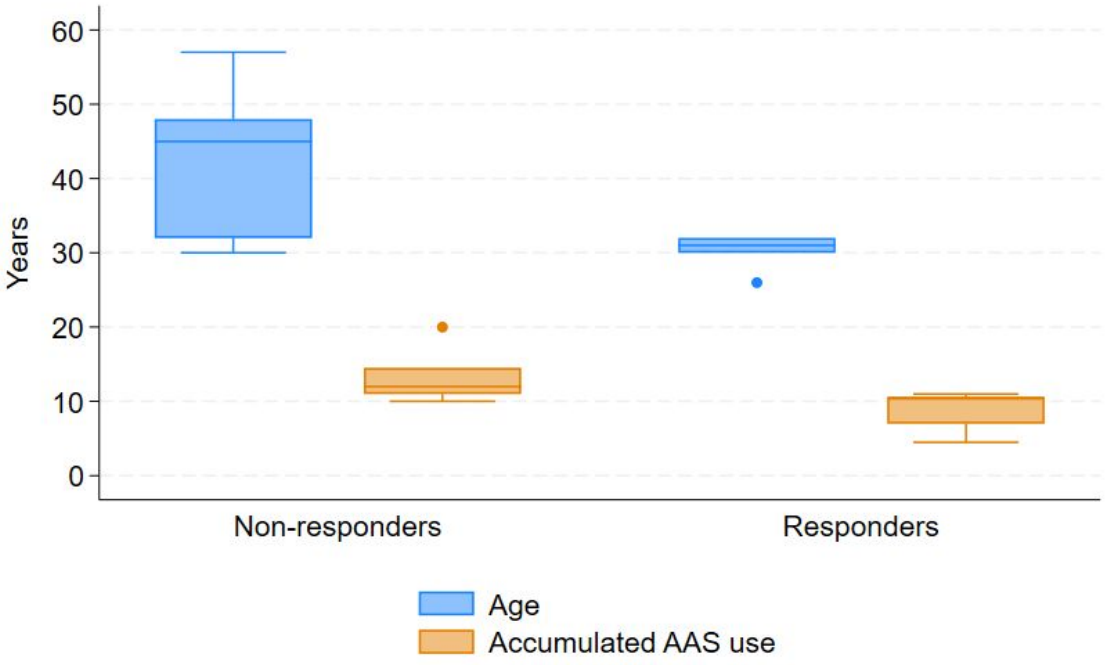
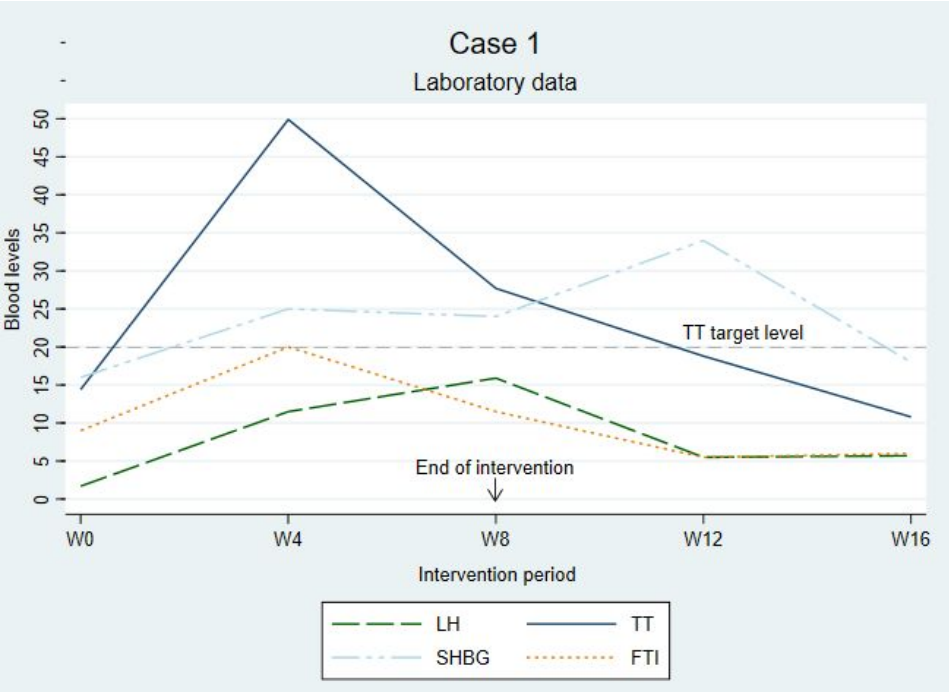


Figure 2: Box plots representing age and accumulated AAS use (in years) for responders and non-responders to endocrine treatment. The box portion is defined by the 25th and 75th percentile with outliers shown as circles. The median is represented as a horizontal line within the box portion.

CASE 1



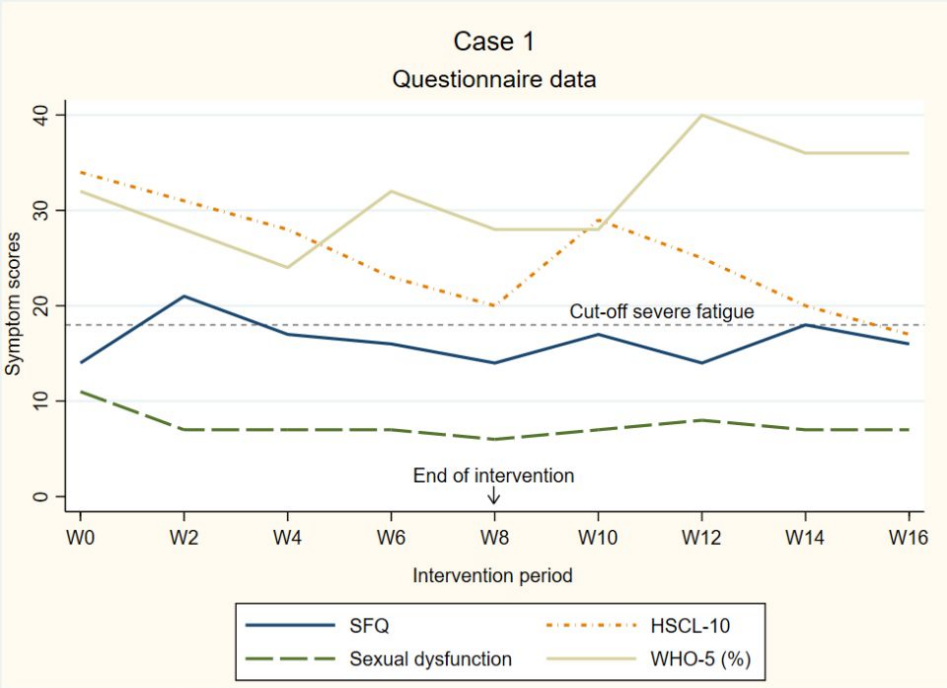
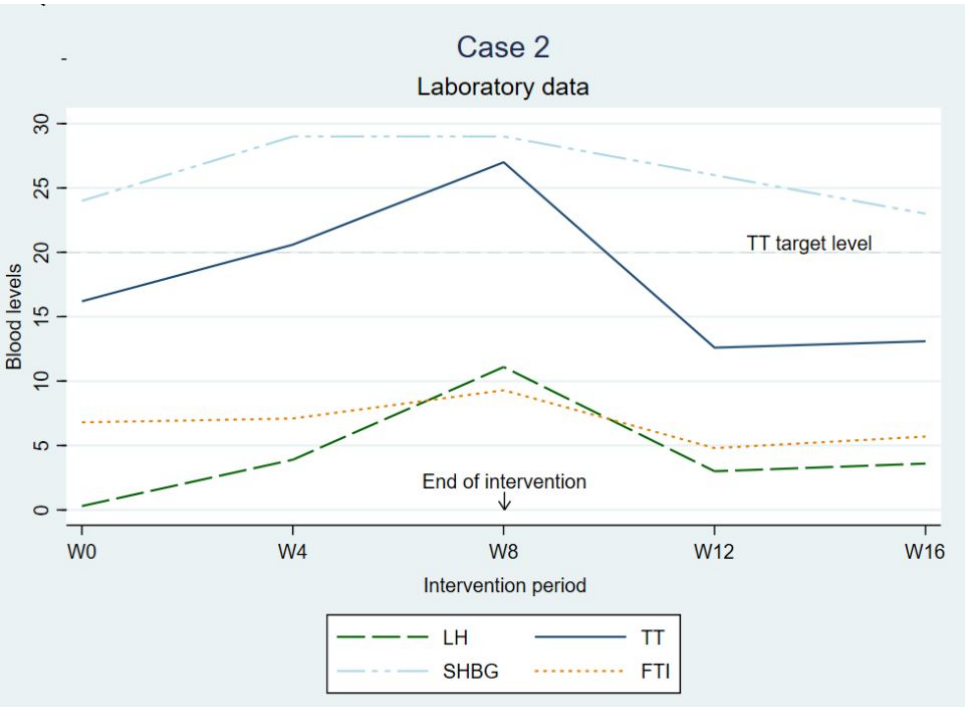


Figure 3a: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 1. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher values indicate sexual dysfunction). W = week, LH = luteinizing hormone, SHBG = sex hormone binding globulin, TT = total testosterone, FTI = free testosterone index, SFQ = Shortened fatigue questionnaire, HSCL = Hopkins Symptom Checklist, WHO = World Health Organisation-Five Well-Being Index.

CASE 2



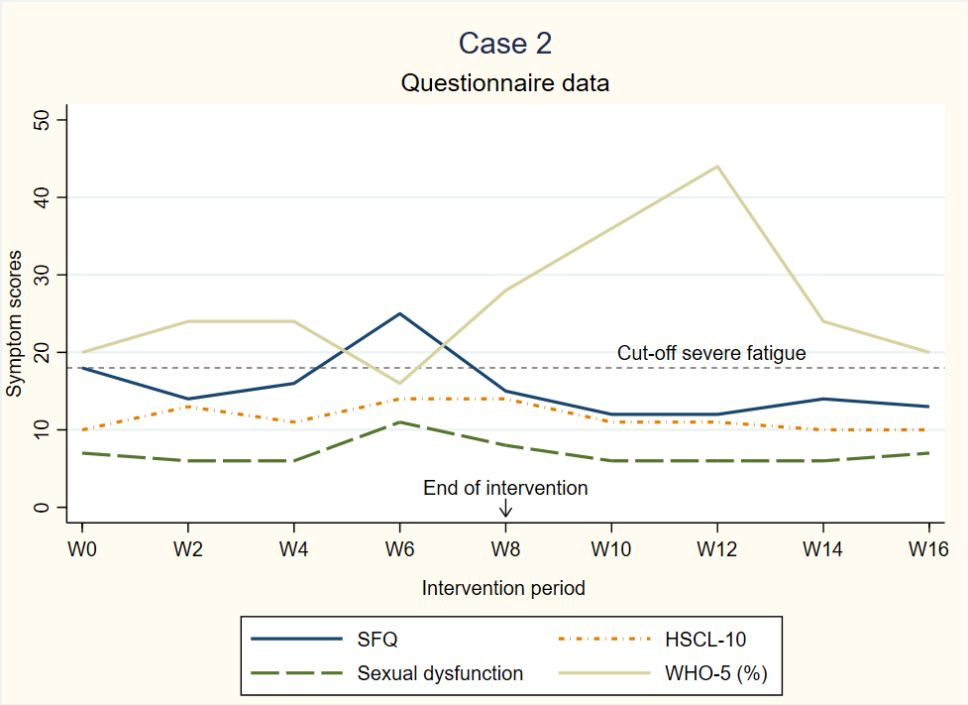
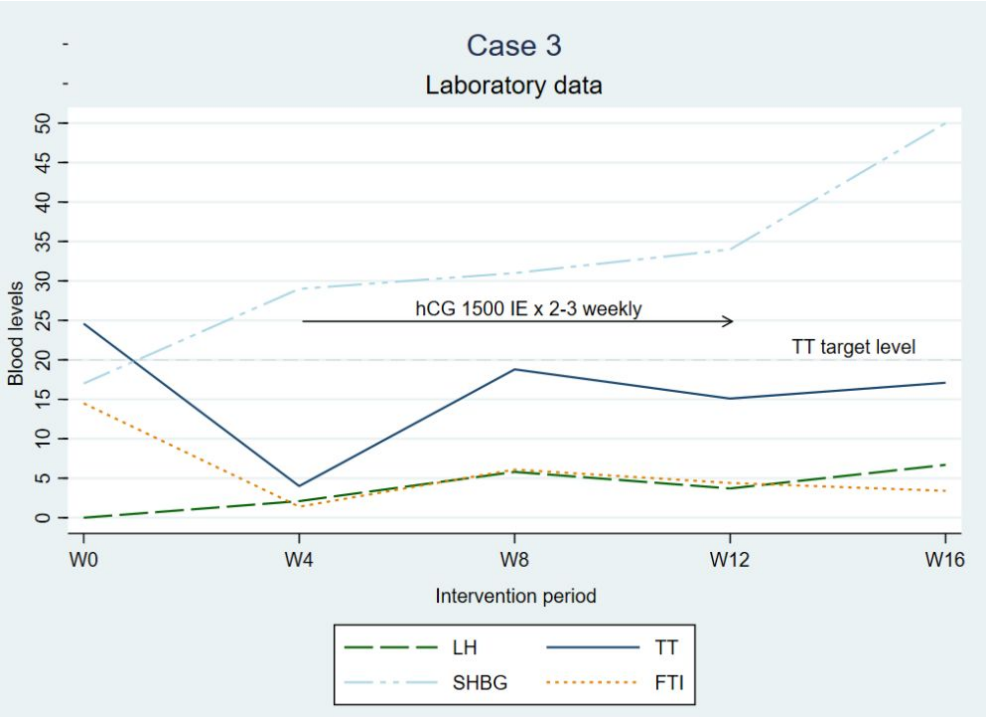


Figure 3b: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 2. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 3



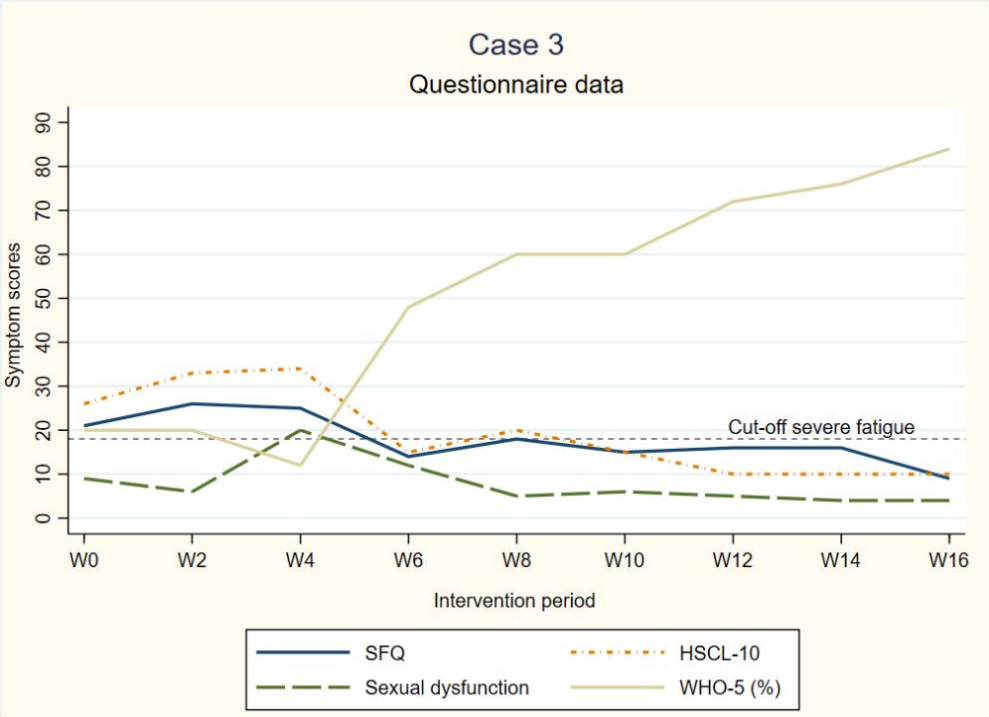


Figure 3c: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 3. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 4

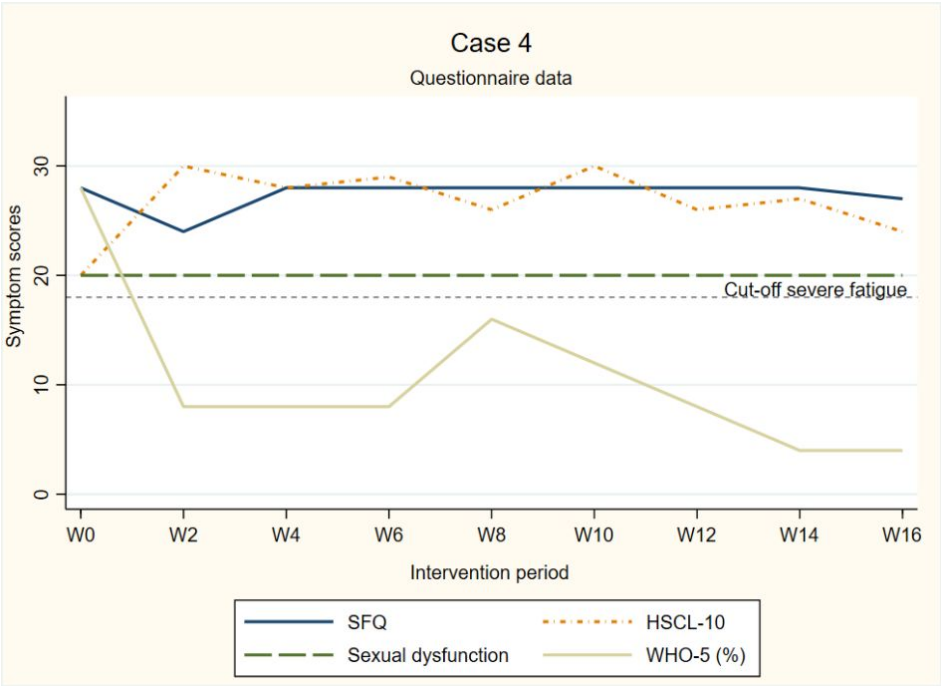
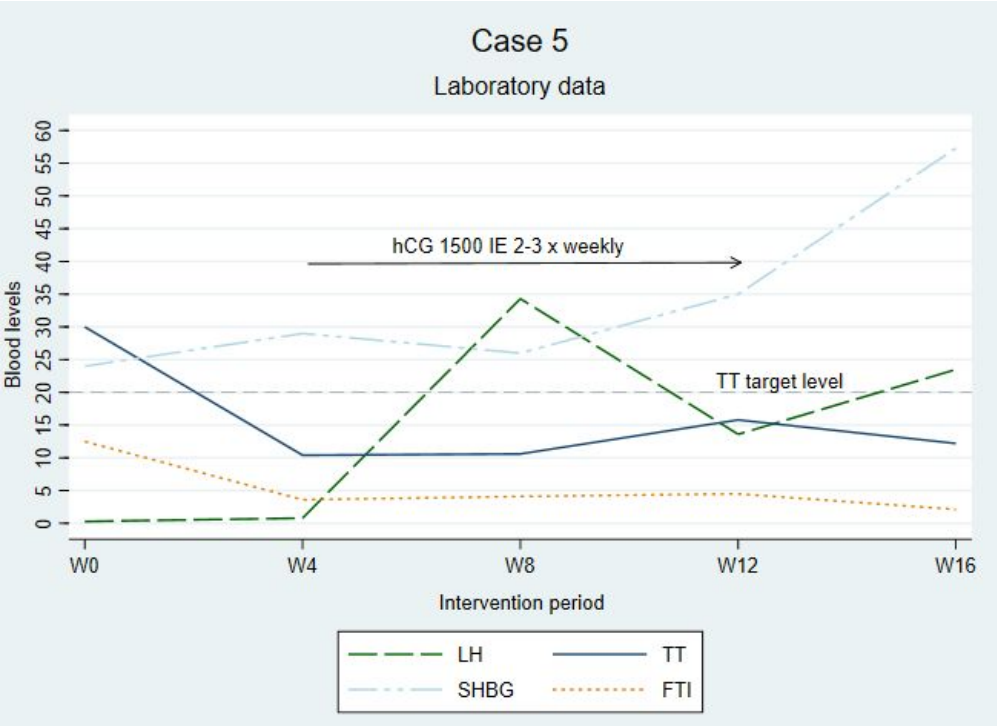


Figure 3d: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 4. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 5



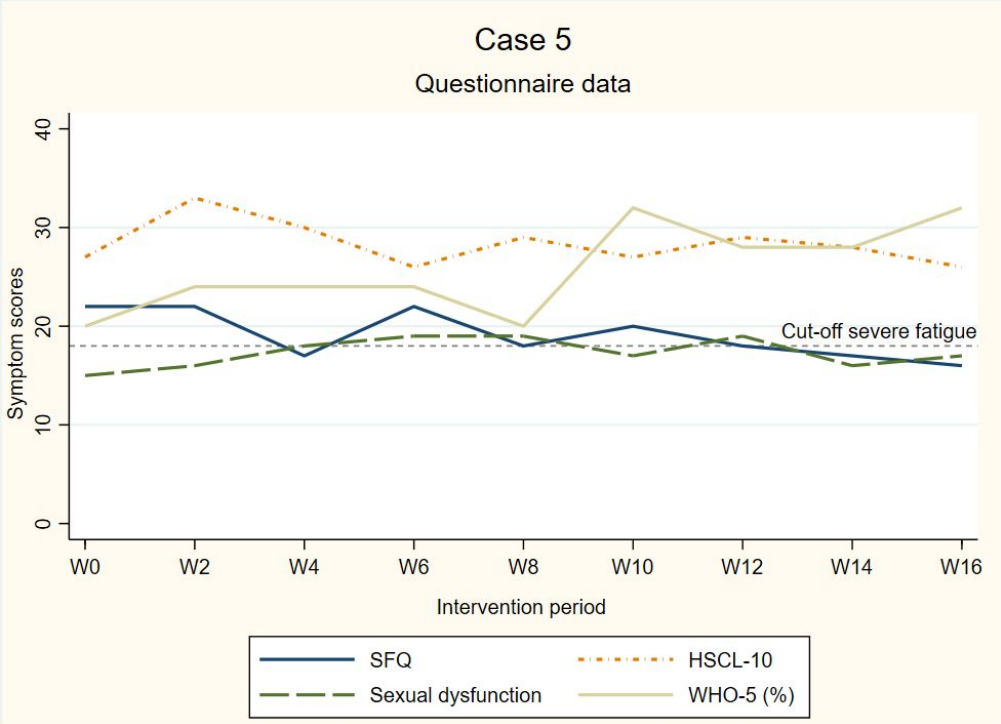
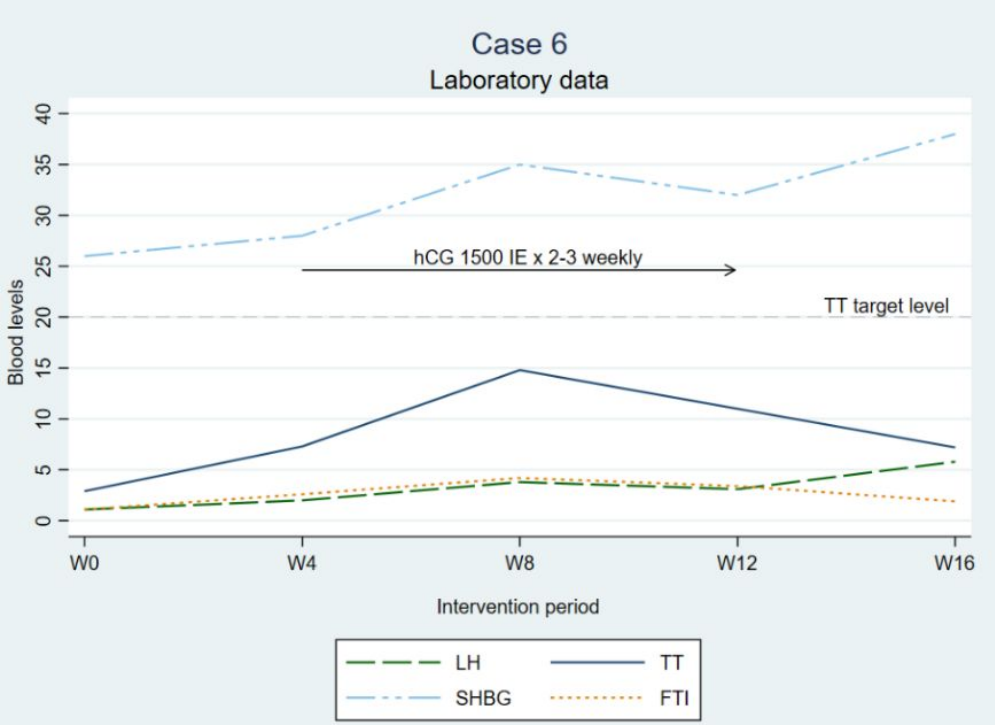


Figure 3e: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 5. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 6



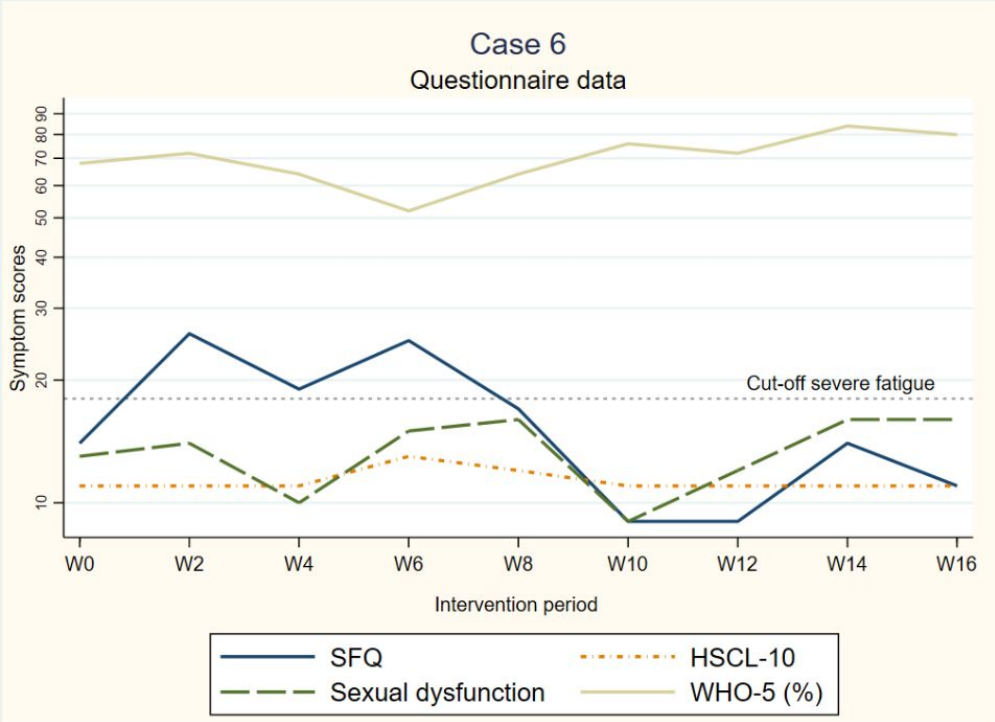
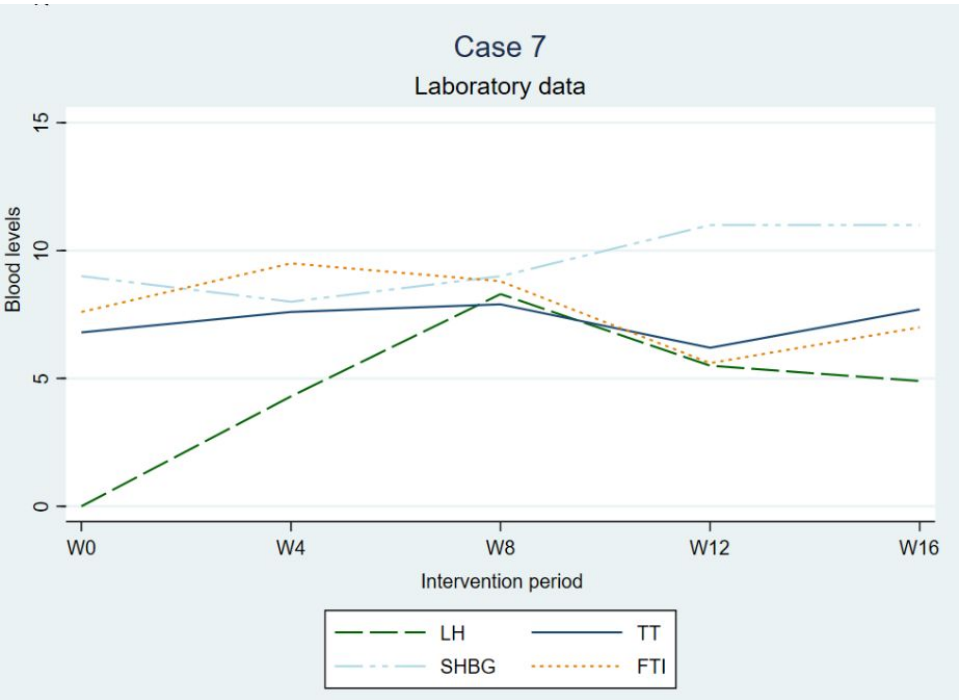


Figure 3f: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 6. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 7



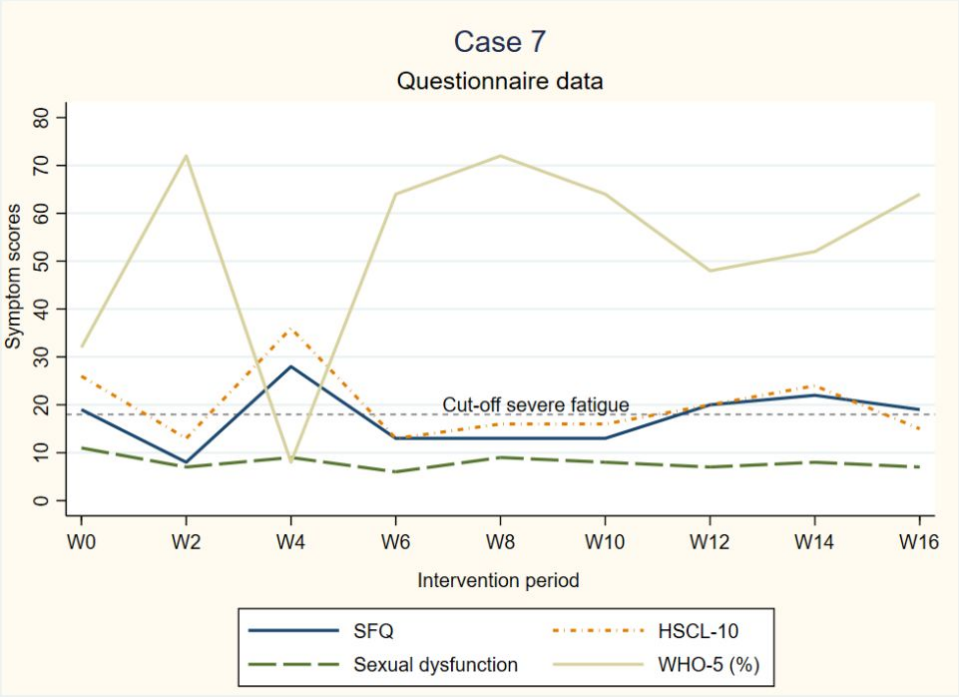
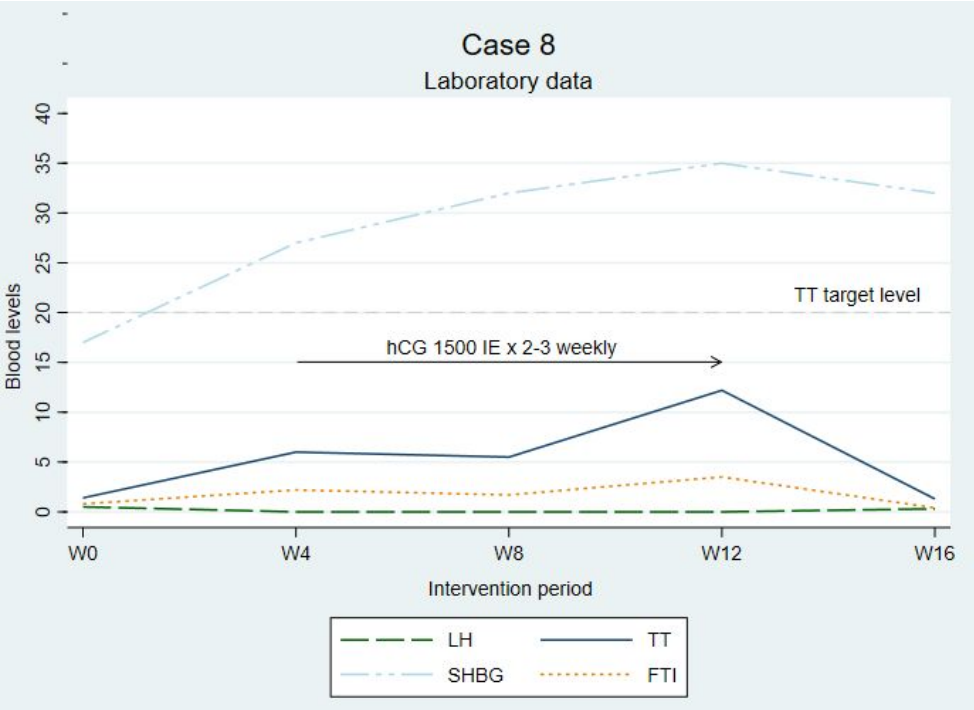


Figure 3g: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 7. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 8



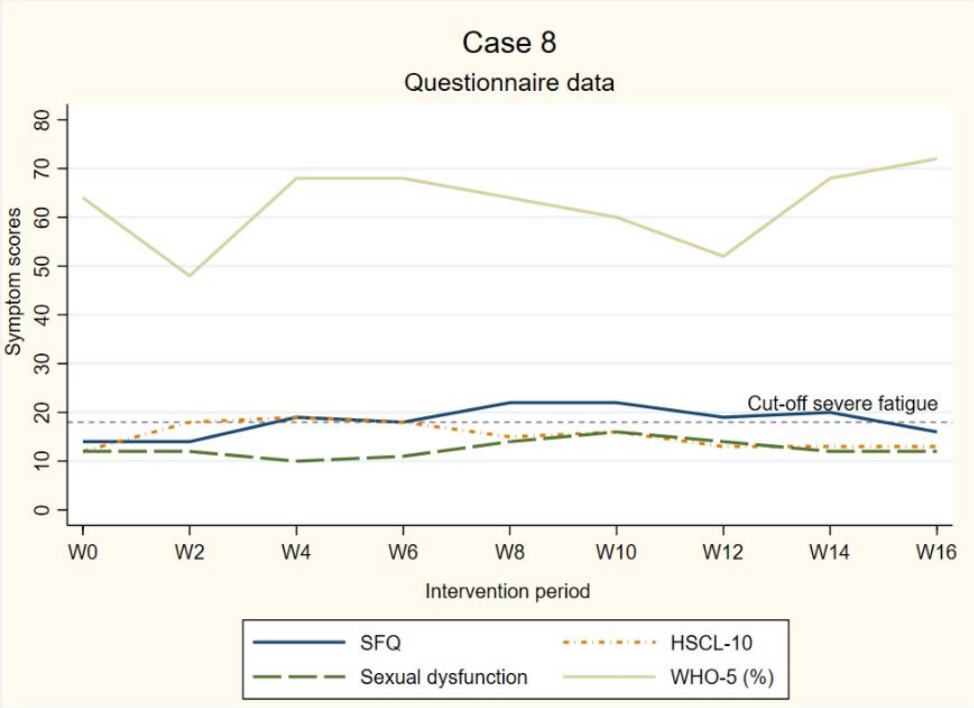
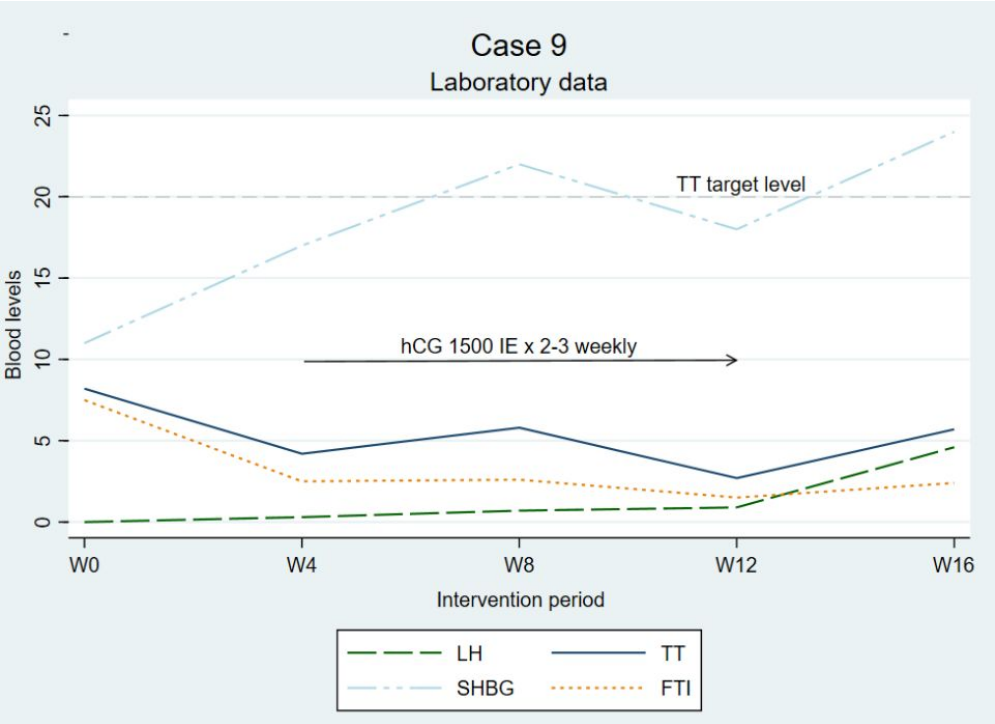


Figure 3h: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 8. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 9



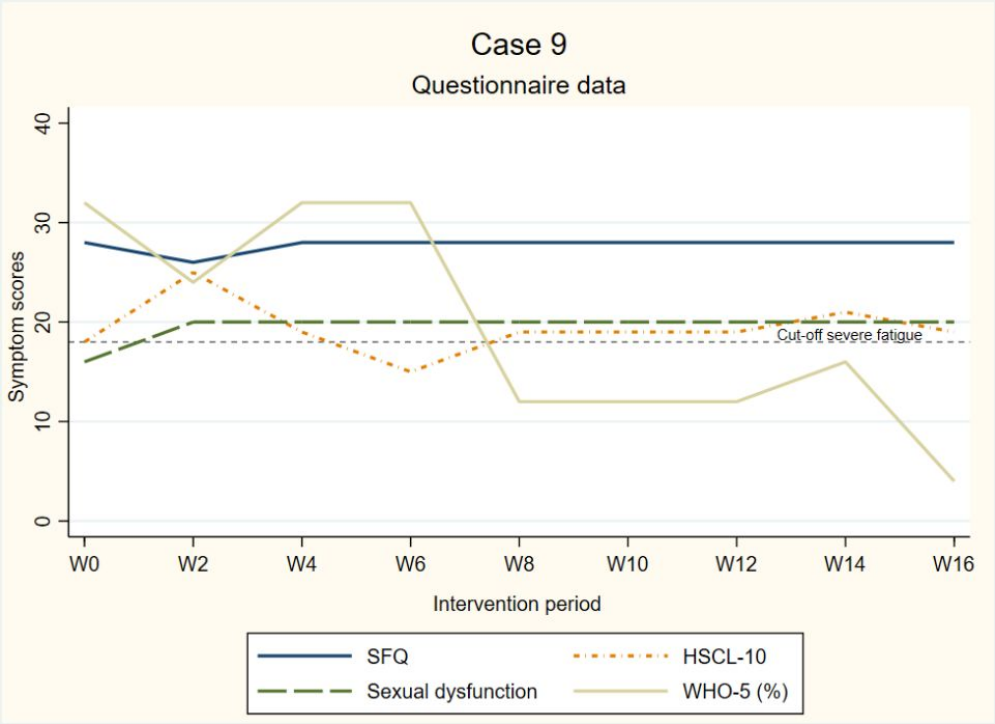


Figure 3i: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 9. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).

CASE 10

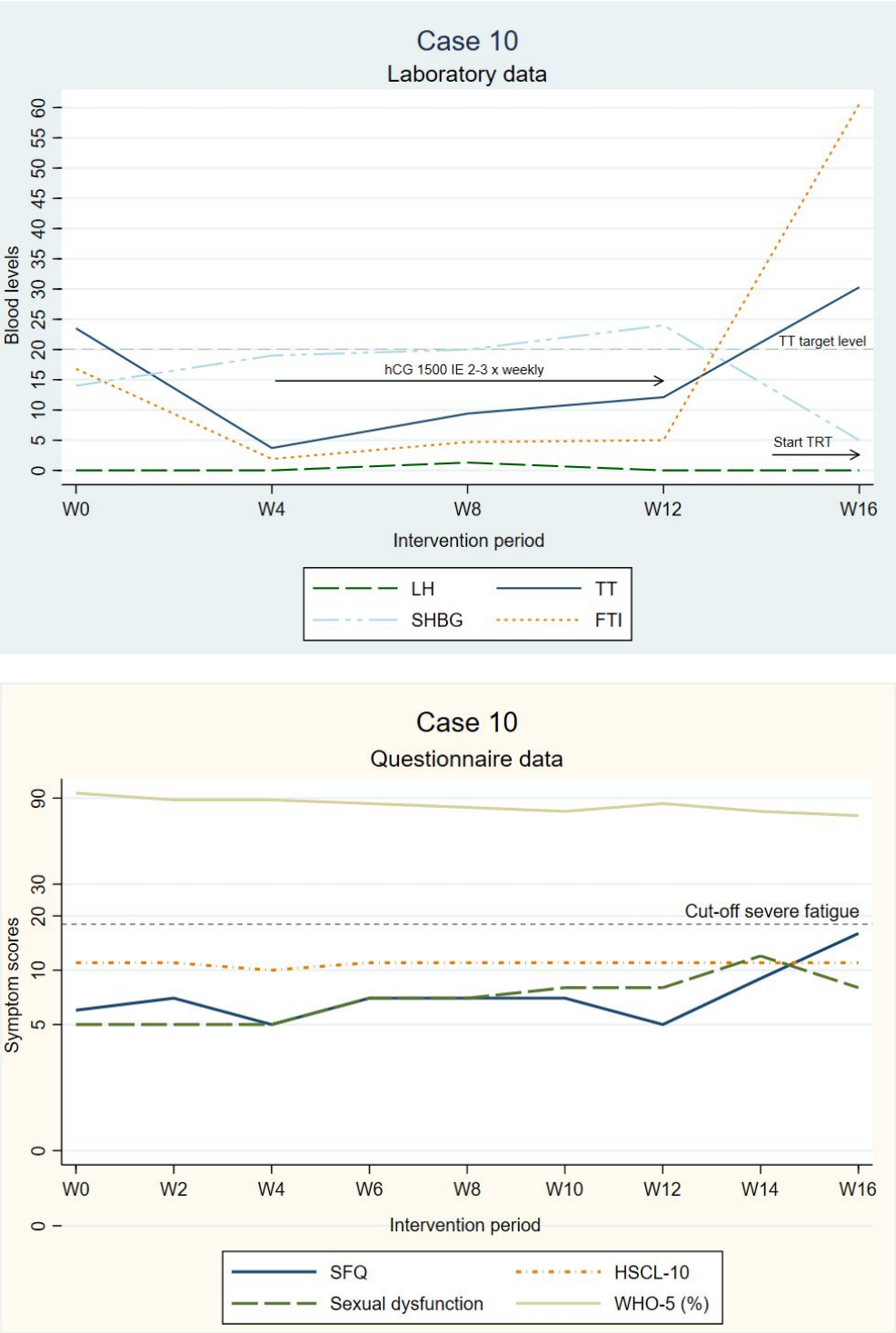


Figure 3j: HPG axis response to the 16-week long intervention and self-reported ASIH-related withdrawal-symptoms in Case 10. Reference ranges: LH 1,8-12 IU/L, TT: 9-30 nmol/L, SHBG 18-54 nmol/L, FTI 1,5-7,3, SFQ 4-28 (18 is cut-off for severe fatigue), HSCL-10: 10-40 (≥18.5 is cut-off for higher mental distress), WHO-5: 0-100% (≤50 indicates poor well-being), sexual function: 4-20 (where higher value indicate sexual dysfunction).