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Hormones and performance-enhancing drugs

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Conflict of Interest



- We have received payments for research projects, lectures, ad hoc consultancy work and related expenses from manufacturers of pharmaceutical products.

Aims

- Discussion on the efficacy and safety of hormones as performance-enhancing drugs
- Identification of men and women that use anabolic steroids and complain of other clinical problems

Structure



- Introduction
- Epidemiology
- Types
- Efficacy
- Safety
- Conclusions

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Questions



- **Efficacy:** Does the use of anabolic steroids increase athletic performance?
- **Safety:** Is the use of anabolic steroids dangerous?

Identical approaches



- **Pharmaceutical industry:** Efficacy and safety
- **Physician:** Efficacy and safety
- **Patient:** Efficacy and safety

Different approaches



- **Trainer and athlete:** Increase of athletic performance
- **Physician:** Safety of athlete - patient
- **Public:** Information on use and potential harm
- **Press:** Presentation of doping cases

Baseline characteristics

- **Providers:** Legitimate pharmaceutical company, strict legislation
- **Co-administration:** Other substances, characterized as drugs
- **Use:** Controlled use (route, dosage, amount)
- **Physician:** Sufficient knowledge of drug effect and safety, evidence from trials

Special characteristics

- **Providers:** Not health professionals - fellow athlete, trainer, sport magazine, Internet
- **Co-administration:** Human chorionic gonadotropin (hCG), aromatase inhibitor, estrogen-receptor antagonist, masking agents
- **Use:** Intermittent use
- **Physician:** No information of use, insufficient knowledge of drug effect and safety, lack of trials

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Prevalence: elite athletes



- United States Anti-Doping Agency (USADA): 12756 screening tests in Olympics Games: 137 possible cases - **prevalence: 1%**.

https://www.usada.org/about/annual-report/2016_annual_report.pdf

- From 26 member of US Weight-Lifting National Team, 10 admitted use of anabolic steroids, and 5 declared that they were able to by-pass the screening procedure of International Olympic Committee - **prevalence: 38%**

Opinions



- When it comes to doping in international competition, it is very likely that almost “everyone's doing it”

Walsh LA. Ballantine Books, 2007

- We should stop trying to catch the cheats, and allow athletes to use whatever substances they like, as they are only harming themselves

Wood RI, et al. Horm Behav 61:147;2012

Prevalence: adolescence



- Study the Center of Disease Control (CDC) on adolescent students using anabolic steroid, over-the-counter - **prevalence: 4%**

Prevalence: overall



- The global lifetime prevalence of anabolic steroid abuse is **6.4% for males** and **1.6% for women**

Structure



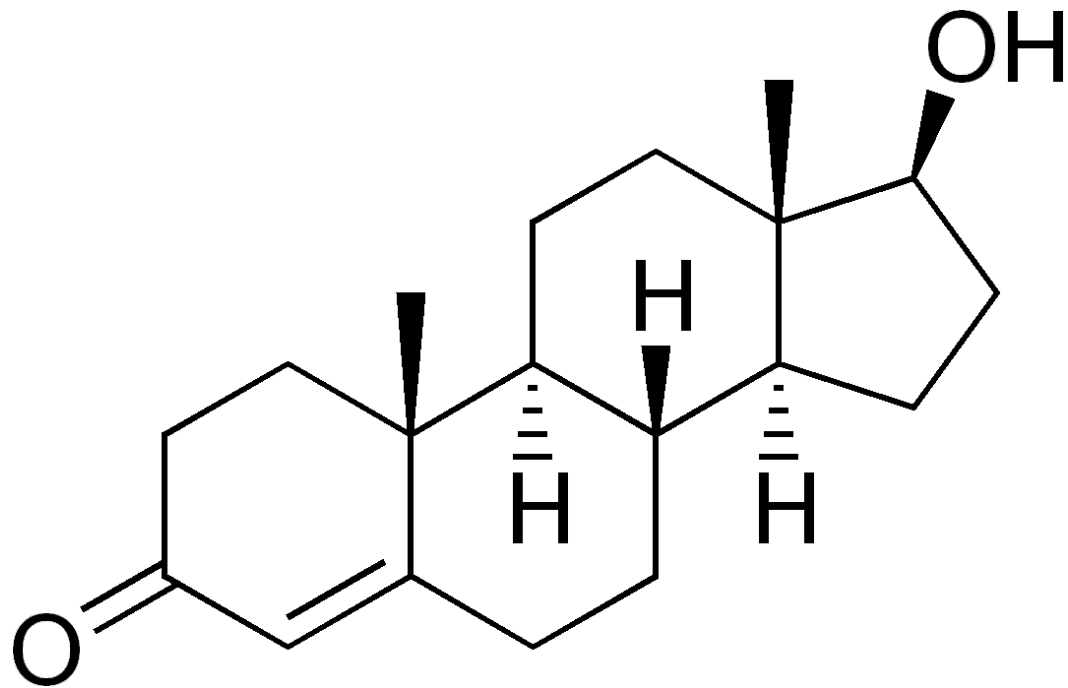
- Introduction
- Epidemiology
- Types
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Structure



- Introduction
- Epidemiology
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Testosterone

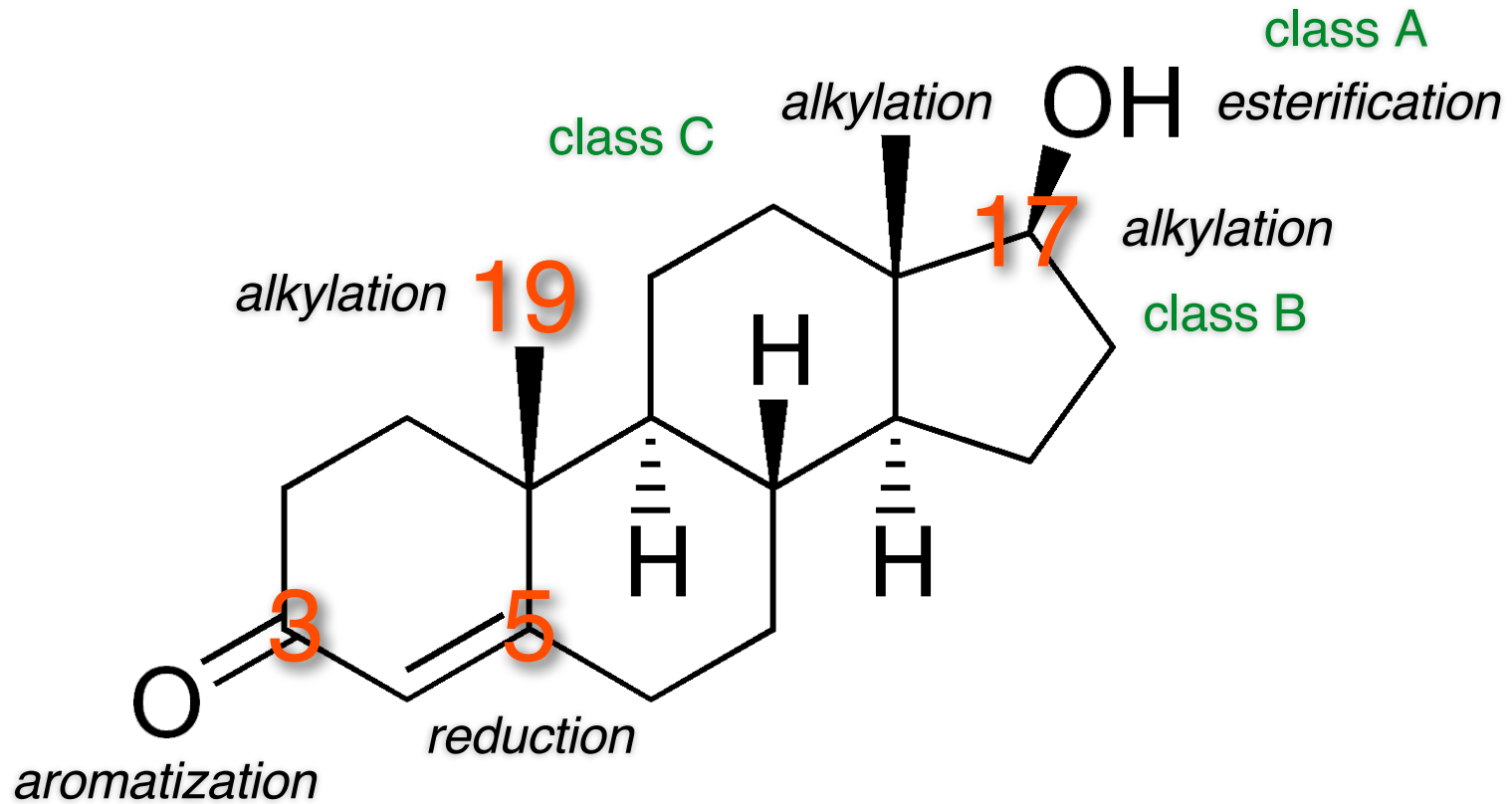


Anabolic steroids



anabolic effect > androgenic effect

Testosterone

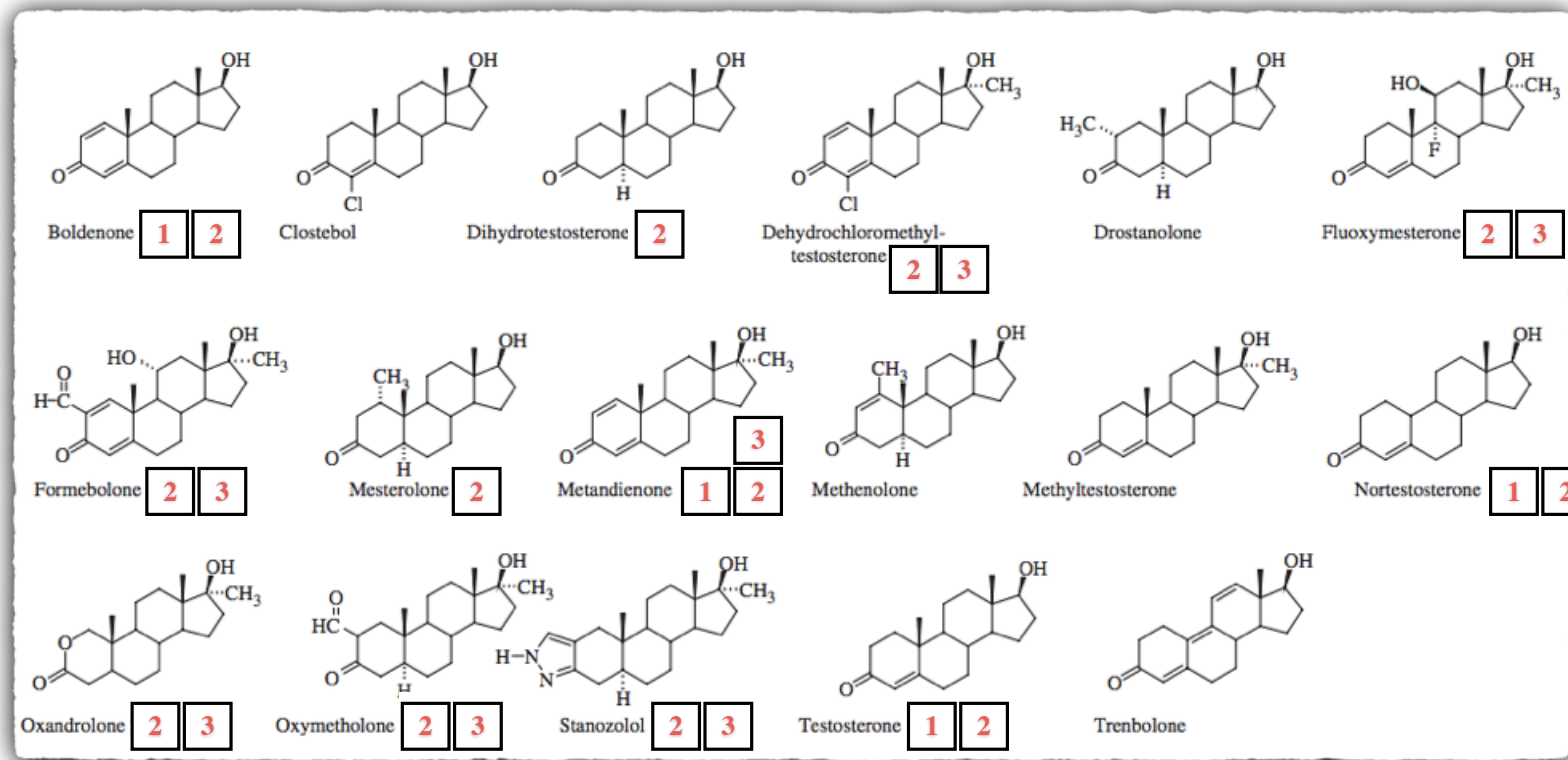


Types of androgens

- **Testosterone esters**
 - enanthate
 - cypionate
- **Synthetic androgens**
 - stanozolol
 - nandrolone
- **Pro-hormones**
 - Δ_4 -androstenedione
 - dehydroepiandrosterone

Quiz 1

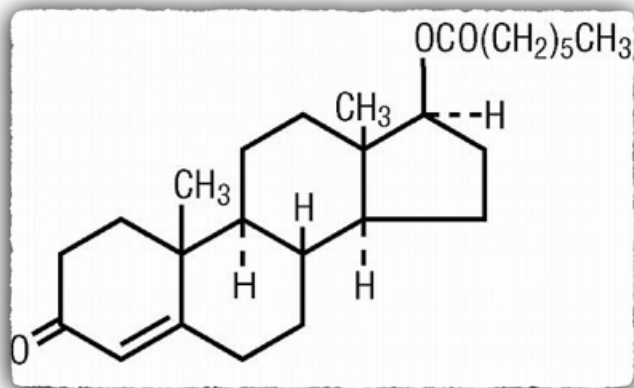
Anabolic steroids metabolism



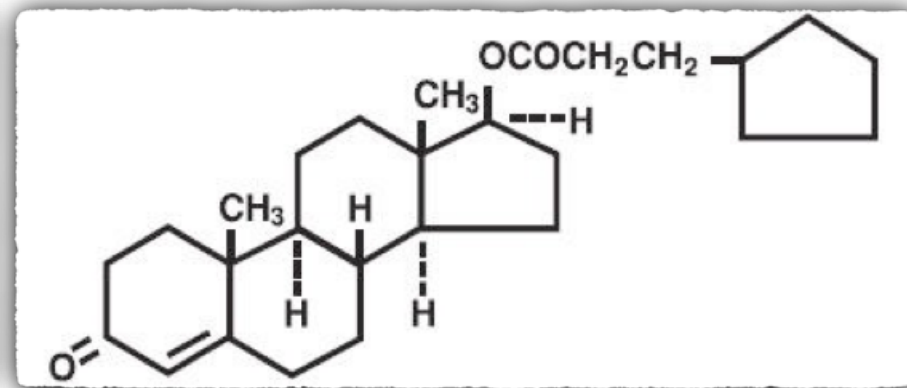
1: Can be aromatised, 2: Are or can be 5 α -reduced, 3: Liver-toxic 17 α -alkylation

Testosterone esters

Characteristics
injectable
long half-life
no hepatotoxicity



Testosterone enanthate



Testosterone cypionate

Testosterone esters

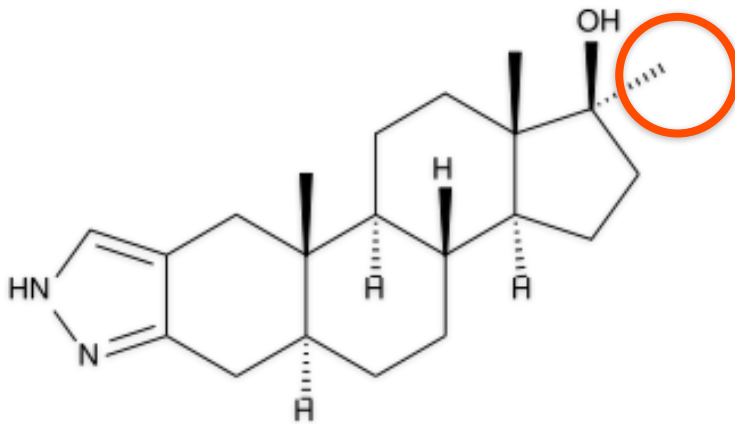


Alkylated derivatives

Characteristics

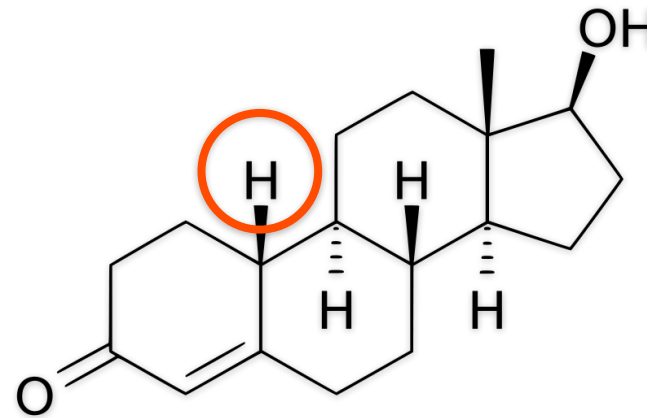
per os
short half-life
hepatotoxicity

17 α -alkylation



Stanozolol

19-derivative



Nandrolone

Alkylated derivatives

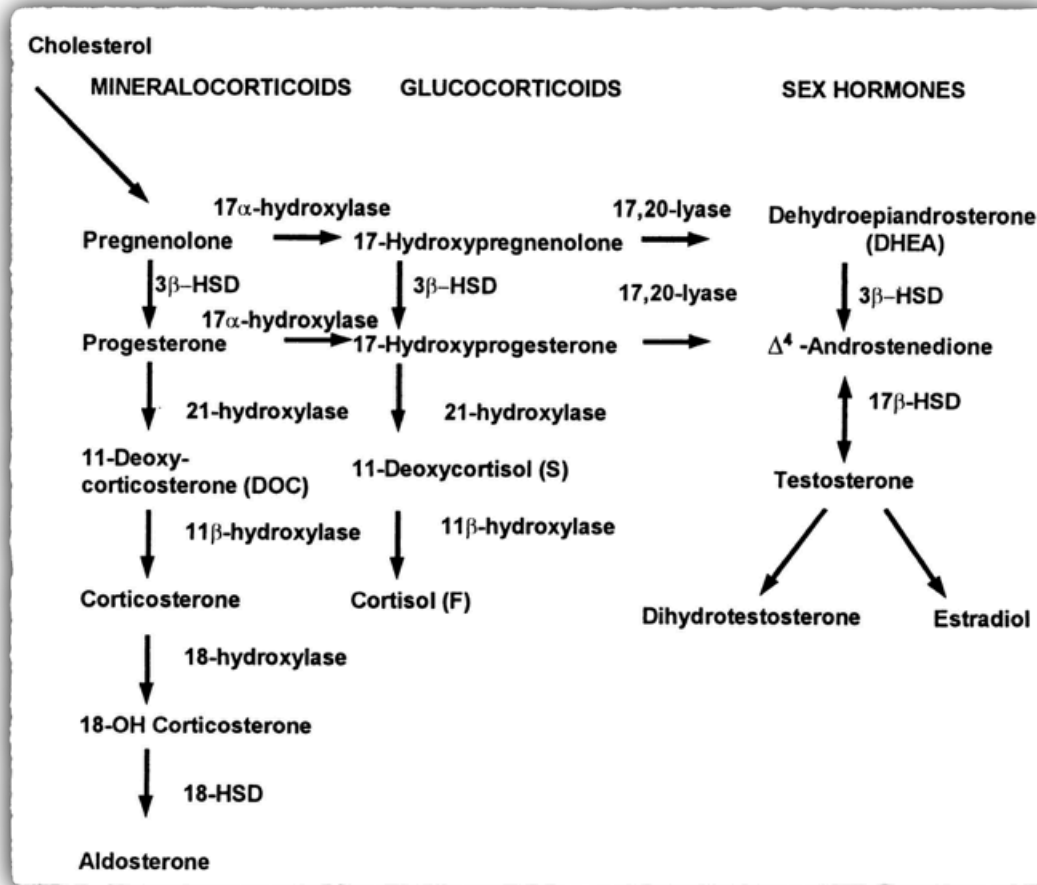


Stanozolol



Nandrolone

Corticosteroid biosynthesis



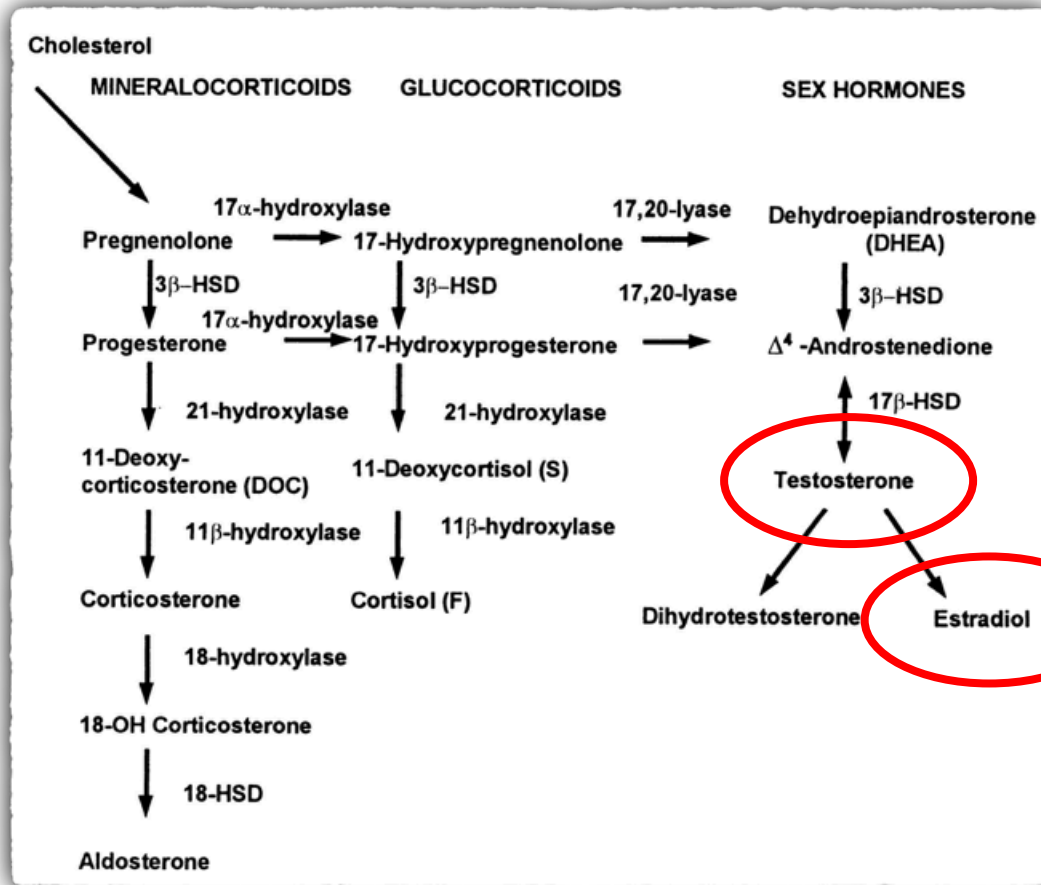
Androstenedione



- Randomized, placebo-controlled trial
- Androstenedione 100 mg tds or placebo for 4 weeks
- No increase in testosterone
- Increase in estradiol

Brown GA, et al. J Clin Endocrinol Metab 85:4074, 2000

Corticosteroid biosynthesis



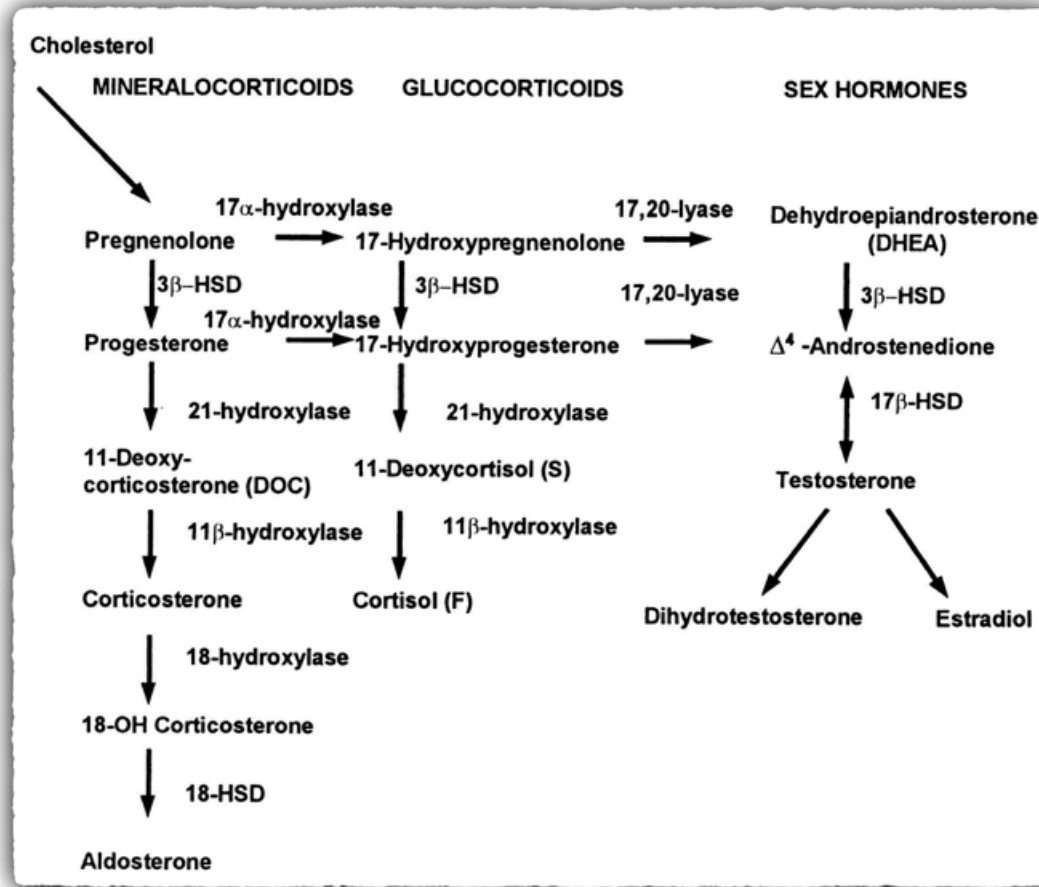
Dehydroepiandrosterone



- Randomized, placebo-controlled trial
- Androstenedione 100 mg od or dehydroepiandrosterone 100 mg od or placebo
- No difference on muscle mass or strength

Wallace MB, et al. Med Sci Sports Exerc 31:1788, 1999

Corticosteroid biosynthesis



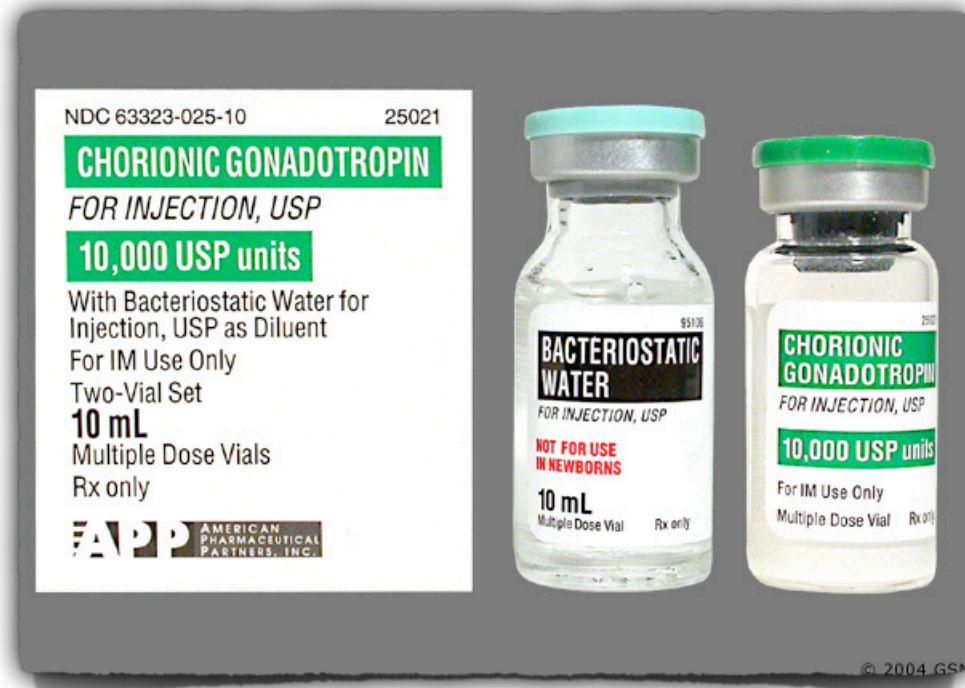
10

20

100

90 - 250

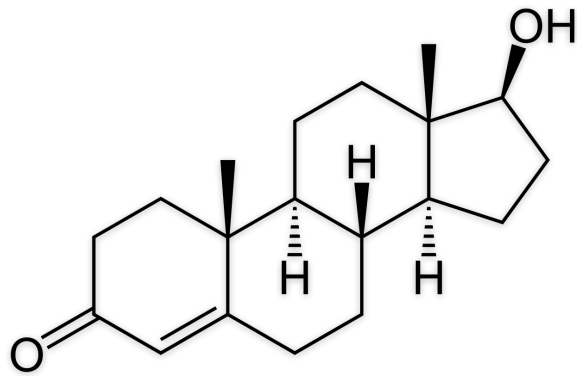
Chorionic gonadotropin



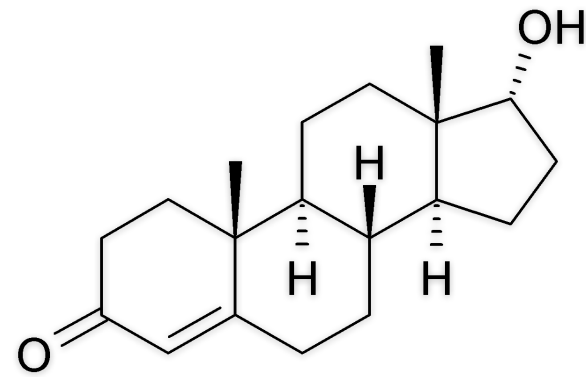
- Production of natural testosterone
- Normal ratio of testosterone : epitestosterone

Testosterone epimers

normal ratio 1:1
upper limit 4:1



Testosterone



Epitestosterone

Changes in endogenous testosterone



- Testosterone concentrations through menstrual cycle
- Cardiovascular exercise and resistance training transiently increase testosterone concentrations in men and women
- Pre-competition: the “challenge hypothesis”
- Post-competition: in men, testosterone commonly increases following victory and decreases following loss
- Testosterone concentrations can change up to 100% post-competition

Tamoxifen



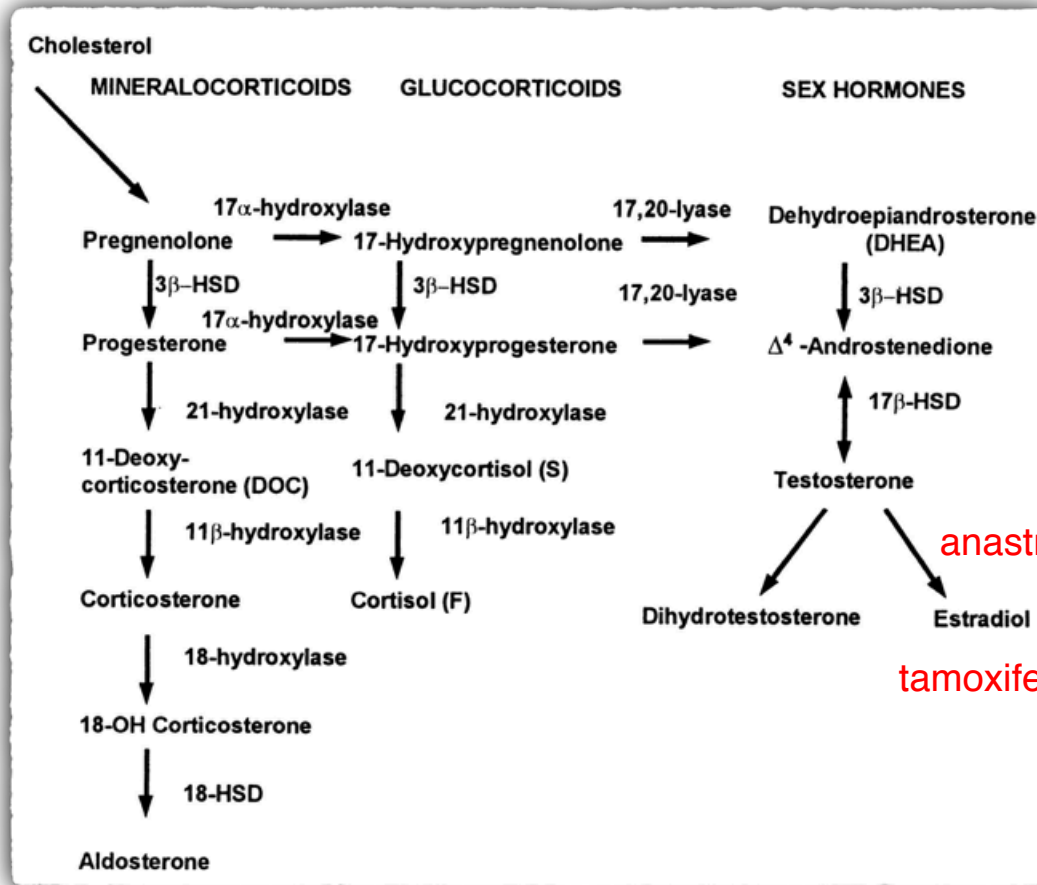
- Anti-estrogen
- Block estrogen effects

Anastrozole



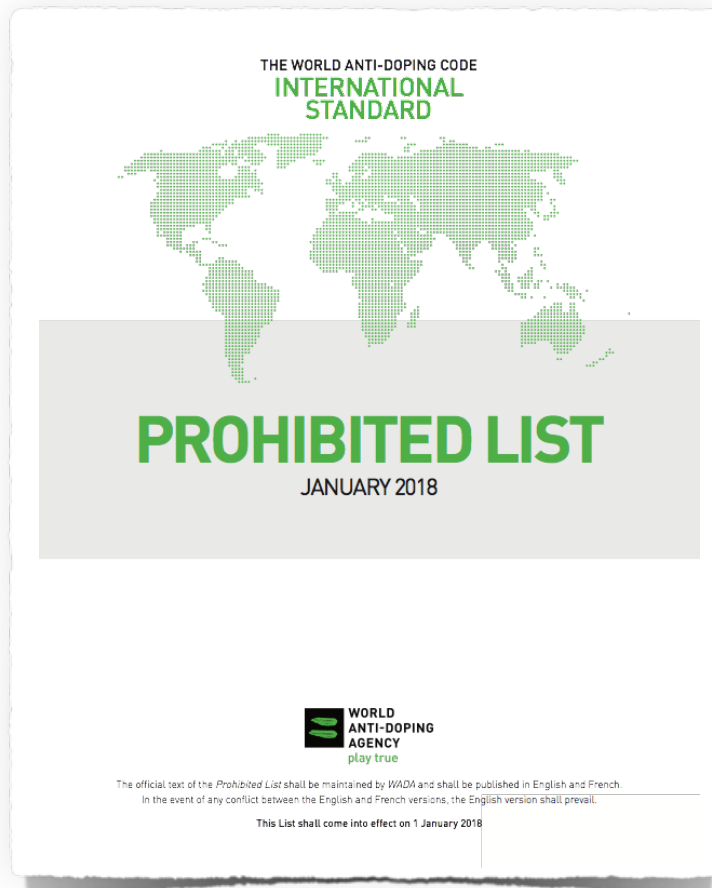
- Aromatase inhibitor
- Increase in testosterone
- Decrease in estrogens

Corticosteroid biosynthesis



Quiz 2

WADA 2018



SUBSTANCES & METHODS PROHIBITED AT ALL TIMES

(IN- AND OUT-OF-COMPETITION)

IN ACCORDANCE WITH ARTICLE 4.2.2 OF THE WORLD ANTI-DOPING CODE, ALL PROHIBITED SUBSTANCES SHALL BE CONSIDERED AS "SPECIFIED SUBSTANCES" EXCEPT SUBSTANCES IN CLASSES S1, S2, S4.4, S4.5, S6.A, AND PROHIBITED METHODS M1, M2 AND M3.

PROHIBITED SUBSTANCES

S0 NON-APPROVED SUBSTANCES

Any pharmacological substance which is not addressed by any of the subsequent sections of the List and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under pre-clinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times.

S1 ANABOLIC AGENTS

Anabolic agents are prohibited.

1. ANABOLIC ANDROGENIC STEROIDS (AAS)

a. Exogenous* AAS, including:

1-Androstenediol [5 α -androst-1-ene-3 β ,17 β -diol];
1-Androstenedione [5 α -androst-1-ene-3,17-dione];
1-Androsterone [3 α -hydroxy-5 α -androst-1-ene-17-one];
1-Testosterone [17 β -hydroxy-5 α -androst-1-en-3-one];
4-Hydroxytestosterone [4,17 β -dihydroxyandrost-4-en-3-one];
Bolandiol [estr-4-ene-3 β ,17 β -diol];
Bolasterone;
Calusterone;
Clostebol;
Danazol [(1,2)oxazolo(4',5':2,3)pregna-4-en-20-yn-17a-ol];
Dehydrochloromethyltestosterone [4-chloro-17 β -hydroxy-17a-methylandrosta-1,4-dien-3-one];
Desoxymethyltestosterone [17a-methyl-5 α -androst-2-en-17 β -ol];
Drostanolone;
Ethylestrenol [19-norpregna-4-en-17a-ol];
Fluoxymesterone;
Formebolone;
Furazabol [17a-methyl (1,2,5)oxadiazolo(3',4':2,3)-5 α -androst-17 β -ol];
Oestrinone;

Mestanolone;
Mesterolone;
Metandienone [17 β -hydroxy-17a-methylandrosta-1,4-dien-3-one];
Metenolone;
Methandiolol;
Methasterone [17 β -hydroxy-2a,17a-dimethyl-5 α -androst-3-one];
Methylenolone [17 β -hydroxy-17a-methyl-4,9-dien-3-one];
Methyl-1-testosterone [17 β -hydroxy-17a-methyl-5 α -androst-1-en-3-one];
Methylnortestosterone [17 β -hydroxy-17a-methyl-4-en-3-one];
Methyltestosterone;
Mebolone [methylmethylenolone, 17 β -hydroxy-17a-methyl-4,9,11-trien-3-one];
Mibolerone;
Norbolatone;
Norclostebolol;
Norethandrolone;
Oxabolone;
Oxandrolone;
Oxymesterone;
Oxymetholone;
Prostanozolol [(1 β)-(tetrahydropyran-2-yl)oxy]-1H-pyrazolo(3,4-d:2,3)-5 α -androstane];
Quinbolone;
Stanozolol;
Stenbolone;
Tetrahydrogestrinone [17-hydroxy-18a-homo-19-nor-17a-pregna-4,9,11-trien-3-one];
Trenbolone [17 β -hydroxyestr-4,9,11-trien-3-one];
and other substances with a similar chemical structure or similar biological effect(s).

2

b. Endogenous** AAS when administered exogenously:

19-Norandrostenediol [estr-4-ene-3,17-diol];
19-Norandrostenedione [estr-4-ene-3,17-dione];
Androstanoione [5 α -dihydrotestosterone, 17 β -hydroxy-5 α -androst-3-one];
Androstenediol [androst-5-ene-3 β ,17 β -diol];
Androstenedione [androst-4-ene-3,17-dione];
Boldenone;
Boldione [androsta-1,4-diene-3,17-dione];
Nandrolone [19-nortestosterone];
Prasterone [dehydroepiandrosterone, DHEA, 3 β -hydroxyandrost-5-en-17-one];
Testosterone;

and their metabolites and isomers, including but not limited to:

3 β -Hydroxy-5 α -androst-17-one;
5 α -Androst-2-ene-17-one;
5 α -Androstane-3 α ,17 α -diol;
5 α -Androstane-3 α ,17 β -diol;
5 α -Androstane-3 β ,17 α -diol;
5 α -Androstane-3 β ,17 β -diol;
5 β -Androstane-3 α ,17 β -diol;
7 α -Hydroxy-DHEA;
7 β -Hydroxy-DHEA;
4-Androstenediol [androst-4-ene-3 β ,17 β -diol];
5-Androstenedione [androst-5-ene-3,17-dione];
7-Keto-DHEA;
19-Norandrosterone;
19-Noretiocholanolone;
Androst-4-ene-3 α ,17 α -diol;
Androst-4-ene-3 α ,17 β -diol;
Androst-4-ene-3 β ,17 α -diol;
Androst-5-ene-3 α ,17 α -diol;
Androst-5-ene-3 α ,17 β -diol;
Androst-5-ene-3 β ,17 α -diol;
Androsterone;
Epi-dihydrotestosterone;
Epitestosterone;
Etiocholanolone.

2. OTHER ANABOLIC AGENTS

Including, but not limited to:

Clenbuterol, selective androgen receptor modulators (SARMs, e.g. andarine, LGD-4033, ostarine and RAD140), tibolone, zeranol and zolasterol.

For purposes of this section:

* "exogenous" refers to a substance which is not ordinarily produced by the body naturally.

** "endogenous" refers to a substance which is ordinarily produced by the body naturally.

S2 PEPTIDE HORMONES, GROWTH FACTORS, RELATED SUBSTANCES, AND MIMETICS

The following substances, and other substances with similar chemical structure or similar biological effects, are prohibited:

1. Erythropoietins (EPO) and agents affecting erythropoiesis, including, but not limited to:

1.1 Erythropoietin-Receptor Agonists, e.g.
Darbepoietins (dEPO);
Erythropoietins (EPO);
EPO based constructs (EPO-Fc, methoxy polyethylene glycol-epoetin beta [CERA]);
EPO-mimetic agents and their constructs (e.g. CNTO-530, peginesatid).

1.2 Hypoxia-inducible factor (HIF) activating agents, e.g.
Argon;
Cobalt;
Molidustat;
Roxadustat (FG-4592);
Xenon.

1.3 GATA inhibitors, e.g.
K-11706.

1.4 TGF-beta (TGF- β) inhibitors, e.g.
Luspatercept;
Sotatercept.

3

1.5 Innate repair receptor agonists, e.g.
Asialo EPO;
Carbonylated EPO [CEPO].

2. Peptide Hormones and Hormone Modulators.

2.1 Chorionic Gonadotrophin [CG] and Luteinizing Hormone [LH] and their releasing factors, e.g. Buserelin, deslorelin, gonadorelin, goserelin, leuprorelin, nafarelin and triptorelin, in males;

2.2 Corticotrophins and their releasing factors, e.g. Corticotrocin;

2.3 Growth Hormone [GH], its fragments and releasing factors, including, but not limited to: Growth Hormone fragments, e.g. AOD-9604 and GHG 176-191; Growth Hormone Releasing Hormone [GHRH] and its analogues, e.g. CJC-1293, CJC-1295, sermorelin and tesamorelin; Growth Hormone Secretagogues [GHS], e.g. ghrelin and ghrelin mimetics, e.g. anamorelin, ipamorelin and tabimorelin; GH-Releasing Peptides [GHRPs], e.g. alexamorelin, GHRP-1, GHRP-2 [pralmorelin], GHRP-3, GHRP-4, GHRP-5, GHRP-6, and hexarelin.

3. Growth Factors and Growth Factor Modulators, including, but not limited to:

Fibroblast Growth Factors [FGFs];

Hepatocyte Growth Factor [HGF];

Insulin-like Growth Factor-1 [IGF-1] and its analogues;

Mechano Growth Factors [MGFs];

Platelet-Derived Growth Factor [PDGF];

Thymosin- β_4 and its derivatives e.g. TB-500;

Vascular-Endothelial Growth Factor [VEGF].

Additional growth factors or growth factor modulators affecting muscle, tendon or ligament protein synthesis/ degradation, vascularisation, energy utilization, regenerative capacity or fibre type switching.

S3 BETA-2 AGONISTS

All selective and non-selective beta-2 agonists, including all optical isomers, are prohibited.

Formoterol;
Formoterol;
Nigamamine;
Indacaterol;
Olodaterol;
Procaterol;
Reproterol;
Salbutamol;
Salmeterol;
Terbutaline;
Tulobuterol;
Vilanterol.

Except:

- Inhaled salbutamol: maximum 1600 micrograms over 24 hours in divided doses not to exceed 800 micrograms over 12 hours starting from any dose;
- Inhaled formoterol: maximum delivered dose of 54 micrograms over 24 hours;
- Inhaled salmeterol: maximum 200 micrograms over 24 hours.

The presence in urine of salbutamol in excess of 1000 ng/mL, or formoterol in excess of 40 ng/mL, is not consistent with therapeutic use of the substance and will be considered as an *Adverse Analytical Finding [AAF]* unless the *Athlete* proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of a therapeutic dose [by inhalation] up to the maximum dose indicated above.

S4 HORMONE AND METABOLIC MODULATORS

The following hormone and metabolic modulators are prohibited:

- 1.** Aromatase inhibitors including, but not limited to:
4-Androstene-3,6,17-trione [4-oxo].
Aminoglutethimide;
Anastrozole;
Androsta-1,4,6-triene-3,17-dione [androsteratrienedione].

Androsta-3,5-diene-7,17-dione [arimistane].

Exemestane;

Formestane;

Letrozole;

Testolactone.

2. Selective estrogen receptor modulators [SERMs]

including, but not limited to:

Raloxifene;

Tamoxifen;

Toremifene.

3. Other anti-estrogenic substances including, but not limited to:

Ciomefene;

Cyclofenil;

Fulvestrant.

4. Agents modifying myostatin function(s) including, but not limited, to: myostatin inhibitors.

5. Metabolic modulators:

5.1 Activators of the AMP-activated protein kinase [AMPK], e.g. AICAR, SR9009; and Peroxisome Proliferator Activated Receptor δ [PPAR δ] agonists, e.g. 2-[2-methyl-4-[[4-methyl-2-[[4-(trifluoromethyl) phenyl]thiazol-5-yl]methyl]thiophenoxy] acetic acid [GW1516, GW501516].

5.2 Insulins and insulin-mimetics;

5.3 Meldonium;

5.4 Trimetazidine.

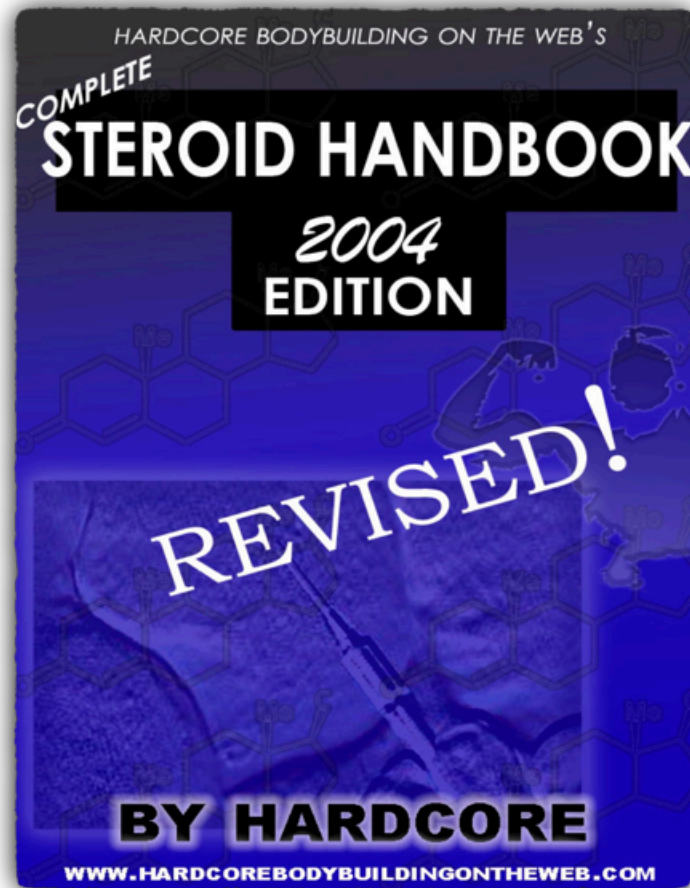
S5 DIURETICS AND MASKING AGENTS

The following diuretics and masking agents are prohibited, as are other substances with a similar chemical structure to those listed below:

Including, but not limited to:

- Desmopressin; probenecid; plasma expanders, e.g. intravenous administration of albumin, dextran, hydroxyethyl starch and mannitol.
- Acetazolamide; amiloride; bumetanide; canrenone; chlorthalidone; etacrynic acid; furosemide; indapamide; metolazone; spironolactone; thiazides, e.g. bendroflumethiazide, chlorothalidate and hydrochlorothiazide; triamterene and vaptans, e.g. tolvaptan.

Effect ranking



Effect ranking

Drug	Strength Gains	Mass & Weight Gain	Fat Burning	Test Stimulation	Contest Prep	Appetite Suppression	Use as an Anti-Estrogen	Side Effects	Cost	Keep Gains?
Aldactone	-	-	-	-	9	-	-	8	4	-
Anadrol	10	10	-	-	5	-	-	9	5	1
Anavar	7	4	-	-	6	2	-	1	9	9
Andriol	2	2	-	-	-	-	-	1	7	8
Arimidex	-	-	-	-	9	-	10	3	9	-
Catapres	2	2	-	-	-	-	-	8	6	-
Cheque Drops	2	-	-	-	-	-	-	10	8	-
Clenbuterol	1	1	5	-	9	8	-	3	2	1
Clomid	1	-	-	8	8	-	7	3	6	1
Cyclofenil	1	1	-	7	5	-	6	2	3	1

PROHIBITED METHODS

M1 MANIPULATION OF BLOOD AND BLOOD COMPONENTS

The following are prohibited:

1. The Administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood, or red blood cell products of any origin into the circulatory system.
2. Artificially enhancing the uptake, transport or delivery of oxygen.
Including, but not limited to:
Perfluorochemicals; etafroxiral (RSR13) and modified haemoglobin products, e.g. haemoglobin-based blood substitutes and microencapsulated haemoglobin products, excluding supplemental oxygen by inhalation.
3. Any form of intravascular manipulation of the blood or blood components by physical or chemical means.

M2 CHEMICAL AND PHYSICAL MANIPULATION

The following are prohibited:

1. Tampering, or Attempting to Tamper, to alter the integrity and validity of Samples collected during Doping Control.
Including, but not limited to:
Urine substitution and/or adulteration, e.g. proteases.
2. Intravenous infusions and/or injections of more than a total of 100 mL per 12 hour period except for those legitimately received in the course of hospital treatments, surgical procedures or clinical diagnostic investigations.

M3 GENE DOPING

The following, with the potential to enhance sport performance, are prohibited:

1. The use of polymers of nucleic acids or nucleic acid analogues.
2. The use of gene editing agents designed to alter genome sequences and/or the transcriptional or epigenetic regulation of gene expression.
3. The use of normal or genetically modified cells.

SUBSTANCES & METHODS PROHIBITED IN-COMPETITION

IN ADDITION TO THE CATEGORIES S0 TO S5 AND M1 TO M3 DEFINED ABOVE, THE FOLLOWING CATEGORIES ARE PROHIBITED IN-COMPETITION:

PROHIBITED SUBSTANCES

S6 STIMULANTS

All stimulants, including all optical isomers, e.g. *d*- and *l*- where relevant, are prohibited.

Stimulants include:

a: Non-Specified Stimulants:

Adrafinil;
Amfepramone;
Amfetamine;
Amfetaminil;
Amiphenazole;
Benfluorex;
Benzylpiperazine;
Bromantan;
Clobenzorex;
Cocaine;
Cropropamide;
Crotetamide;
Fencamine;
Fenetyline;
Fenfuramine;
Fenproporex;
Fonturacetam [4-phenylpiracetam (carphedon)];
Furfenorex;
Lisdexamfetamine;
Mefenorex;
Mephentermine;
Mesocarb;
Metamfetamine[*d*-];
p-methylamfetamine;
Modafinil;
Norfenfuramine;
Phendimetrazine;
Phentermine;
Prenylamine;
Propiintane.

A stimulant not expressly listed in this section is a Specified Substance.

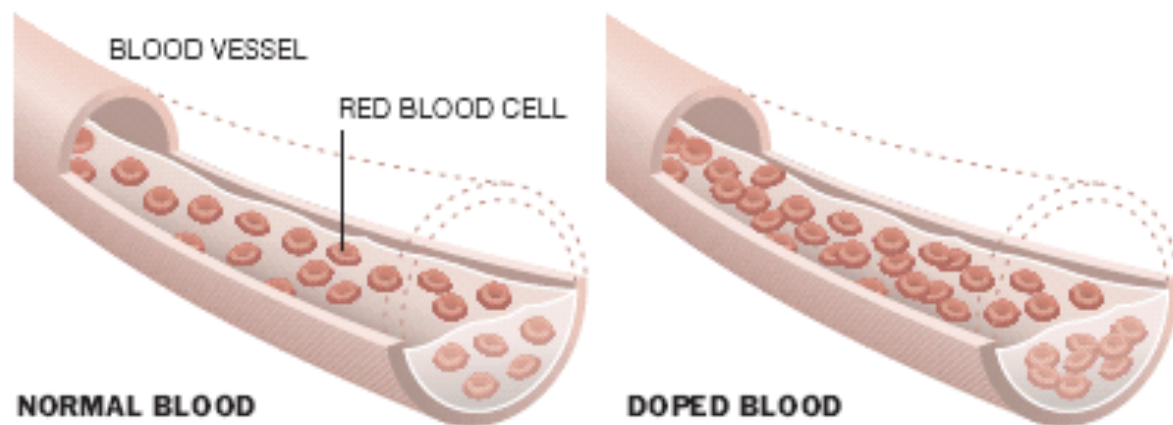
b: Specified Stimulants.

Including, but not limited to:

1,3-Dimethylbutylamine;
4-Methylhexan-2-amine (methylhexanamine);
Benzfetamine;
Cathine**;
Cathinone and its analogues, e.g. mephedrone, methedrone, and α -pyrrolidinovalexerophenone;
Dimethylamfetamine;
Ephedrine***;
Epinephrine**** (adrenaline);
Etamivan;
Etilamfetamine;
Etiliefrine;
Famprofazone;
Fenbutrazole;
Fencamfamin;
Heptaminol;
Hydroxylamfetamine (parahydroxylamfetamine);
Isometheptene;
Levmetamfetamine;
Meclofenoxate;
Methylenedioxyamfetamine;
Methylphenidine***;
Methylphenidate;
Nikethamide;
Norfenefrine;
Octopamine;
Oxlofrine (methylsynephrine);
Pemoline;
Pentetrazol;
Phenethylamine and its derivatives;
Phenmetrazine;
Phenpromethamine;
Propylhexedrine;
Pseudoephedrine****;

How Blood Doping Works

Elevated levels of red blood cells found in an athlete's bloodstream can be a sign of blood doping.



NORMAL BLOOD

The blood of a typical adult male is made up of 40 to 50 percent red blood cells, which carry oxygen to tissues. Typical levels for women are 35 to 45 percent.

DOPED BLOOD

Red blood cells (from a donor or previously removed from the athlete) or the hormone erythropoietin (EPO) are injected. The increase in red cells allows muscles to work longer and harder without cramping.

Sources: Harrison's Principles of Internal Medicine; Quest Diagnostic Laboratories

PROHIBITED METHODS

M1 MANIPULATION OF BLOOD AND BLOOD COMPONENTS

The following are prohibited:

1. The Administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood, or red blood cell products of any origin into the circulatory system.
2. Artificially enhancing the uptake, transport or delivery of oxygen.
Including, but not limited to:
Perfluorochemicals; etafroxiral (RSR13) and modified haemoglobin products, e.g. haemoglobin-based blood substitutes and microencapsulated haemoglobin products, excluding supplemental oxygen by inhalation.
3. Any form of intravascular manipulation of the blood or blood components by physical or chemical means.

M2 CHEMICAL AND PHYSICAL MANIPULATION

The following are prohibited:

1. Integrity and validity of Samples collected during Doping Control.
Including, but not limited to:
Urine substitution and/or adulteration, e.g. proteases.
2. Intravenous infusions and/or injections of more than a total of 100 mL per 12 hour period except for those legitimately received in the course of hospital treatments, surgical procedures or clinical diagnostic investigations.

M3 GENE DOPING

The following, with the potential to enhance sport performance, are prohibited:

1. The use of polymers of nucleic acids or nucleic acid analogues.
2. The use of gene editing agents designed to alter genome sequences and/or the transcriptional or epigenetic regulation of gene expression.
3. The use of normal or genetically modified cells.

SUBSTANCES & METHODS PROHIBITED IN-COMPETITION

IN ADDITION TO THE CATEGORIES S0 TO S5 AND M1 TO M3 DEFINED ABOVE, THE FOLLOWING CATEGORIES ARE PROHIBITED IN-COMPETITION:

PROHIBITED SUBSTANCES

S6 STIMULANTS

All stimulants, including all optical isomers, e.g. *d*- and *l*- where relevant, are prohibited.

Stimulants include:

a: Non-Specified Stimulants:

Adrafinil;
Amfepramone;
Amfetamine;
Amfetaminil;
Amiphenazole;
Benfluorex;
Benzylpiperazine;
Bromantan;
Clobenzorex;
Cocaine;
Cropropamide;
Crotetamide;
Fencamine;
Fenetyline;
Fenfuramine;
Fenproporex;
Fonturacetam [4-phenylpiracetam (carphedon)];
Furfenorex;
Lisdexamfetamine;
Mefenorex;
Mephentermine;
Mesocarb;
Metamfetamine[*d*-];
p-methylamfetamine;
Modafinil;
Norfenfuramine;
Phendimetrazine;
Phentermine;
Prenylamine;
Propiltane.

A stimulant not expressly listed in this section is a Specified Substance.

b: Specified Stimulants.

Including, but not limited to:

1,3-Dimethylbutylamine;
4-Methylhexan-2-amine (methylhexanamine);
Benzfetamine;
Cathine**;
Cathinone and its analogues, e.g. mephedrone, methedrone, and α -pyrrolidinovalexerophenone;
Dimethylamfetamine;
Ephedrine***;
Epinephrine**** (adrenaline);
Etamivan;
Etilamfetamine;
Etiliefrine;
Famprofazone;
Fenbutrazole;
Fencamfamin;
Heptaminol;
Hydroxylamfetamine (parahydroxylamfetamine);
Isometheptene;
Levmetamfetamine;
Meclofenoxate;
Methylenedioxyamfetamine;
Methylphenidine***;
Methylphenidate;
Nikethamide;
Norfenefrine;
Octopamine;
Oxlofrine (methylsynephrine);
Pemoline;
Pentetrazol;
Phenethylamine and its derivatives;
Phenmetrazine;
Phenpromethamine;
Propylhexedrine;
Pseudoephedrine****;

TestClear

*Powdered Human
Urine*



*Not Synthetic, Real Human Urine

PROHIBITED METHODS

M1 MANIPULATION OF BLOOD AND BLOOD COMPONENTS

The following are prohibited:

1. The Administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood, or red blood cell products of any origin into the circulatory system.
2. Artificially enhancing the uptake, transport or delivery of oxygen.
Including, but not limited to:
Perfluorochemicals; etafroxiral (RSR13) and modified haemoglobin products, e.g. haemoglobin-based blood substitutes and microencapsulated haemoglobin products, excluding supplemental oxygen by inhalation.
3. Any form of intravascular manipulation of the blood or blood components by physical or chemical means.

M2 CHEMICAL AND PHYSICAL MANIPULATION

The following are prohibited:

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Clobenzorex;
Cocaine;
Cropropamide;
Crotetamide;
Fencamine;
Fenetyline;
Fenfuramine;
Fenproporex;
Fonturacetam [4-phenylpiracetam (carphedon)];
Furfenorex;
Lisdexamfetamine;
Mefenorex;
Mephentermine;
Mesocarb;
Metamfetamine[*d*-];
p-methylamfetamine;
Modafinil;
Norfenfuramine;
Phendimetrazine;
Phentermine;
Prenylamine;
Propiintane.

A stimulant not expressly listed in this section is a Specified Substance.

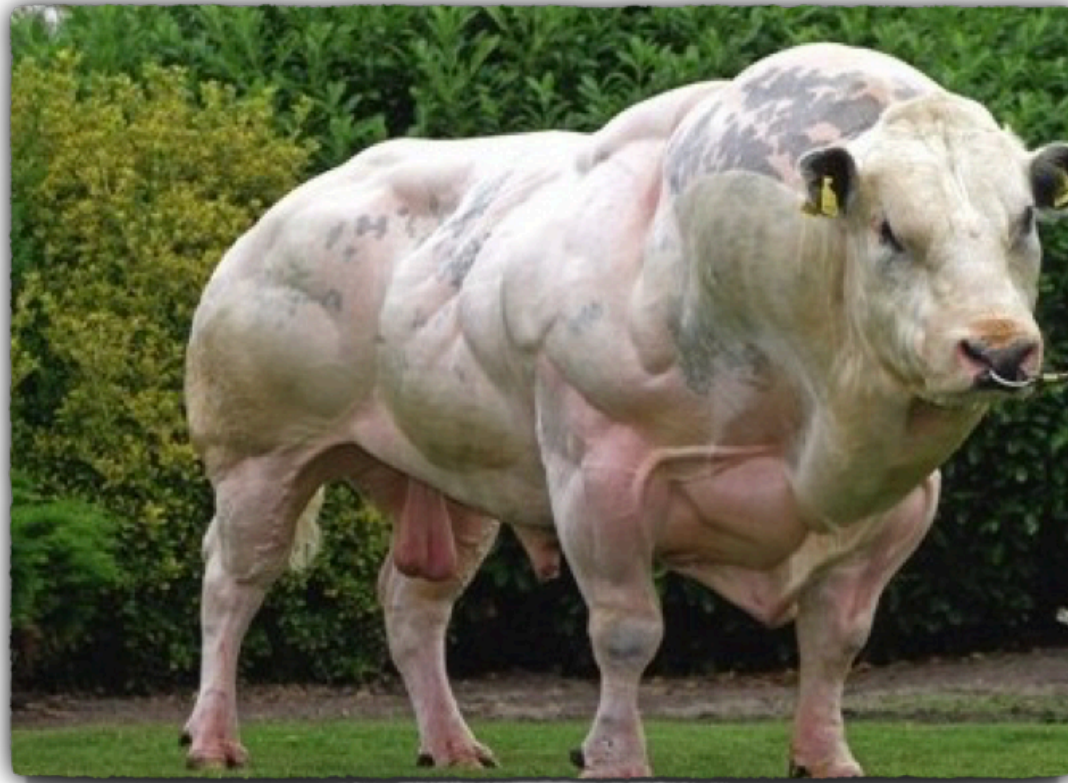
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Oxlofrine (methylsynephrine);
Pemoline;
Pentetrazol;
Phenethylamine and its derivatives;
Phenmetrazine;
Phenpromethamine;
Propylhexedrine;
Pseudoephedrine****;



Belgian Bull



PROHIBITED METHODS

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Crotetamide;
Fencamine;
Fenetyline;
Fenfuramine;
Fenproporex;
Fonturacetam [4-phenylpiracetam (carphedon)];
Furfenorex;
Lisdexamfetamine;
Mefenorex;
Mephentermine;
Mesocarb;
Metamfetamine[*D*];
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Modafinil;
Norfenfuramine;
Phendimetrazine;
Phentermine;
Prenylamine;
Propiltane.

A stimulant not expressly listed in this section is a Specified Substance.

b. Specified Stimulants.

Including, but not limited to:

1,3-Dimethylbutylamine;
4-Methylhexan-2-amine (methylhexanamine);
Benzfetamine;
Cathine**;
Cathinone and its analogues, e.g. mephedrone, methedrone, and α -pyrrolidinovalexerophenone;
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Famprofazone;
Fenbutrazole;
Fencamfamin;
Heptaminol;
Hydroxylamfetamine (parahydroxylamfetamine);
Isometheptene;
Levmetamfetamine;
Meclofenoxate;
Methylenedioxyamfetamine;
Methylphenidine***;
Methylphenidate;
Nikethamide;
Norfenefrine;
Octopamine;
Oxlofrine (methylsynephrine);
Pemoline;
Pentetrazol;
Phenethylamine and its derivatives;
Phenmetrazine;
Phenpromethamine;
Propylhexedrine;
Pseudoephedrine****;

Selegiline;
Sibutramine;
Strychnine;
Tenamfetamine (methylenedioxyamphetamine);
Tuaminoheptane;

and other substances with a similar chemical structure or similar biological effect[s].

Except:

- Clonidine;
- Imidazole derivatives for topical/ophthalmic use and those stimulants included in the 2018 Monitoring Program*.
- * Bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradrol, and synephrine: These substances are included in the 2018 Monitoring Program, and are not considered Prohibited Substances.
- ** Cathine: Prohibited when its concentration in urine is greater than 5 micrograms per milliliter.
- *** Ephedrine and methylephedrine: Prohibited when the concentration of either in urine is greater than 10 micrograms per milliliter.
- **** Epinephrine (adrenaline): Not prohibited in local administration, e.g. nasal, ophthalmologic, or co-administration with local anaesthetic agents.
- ***** Pseudoephedrine: Prohibited when its concentration in urine is greater than 150 micrograms per milliliter.

S7 NARCOTICS

The following narcotics are prohibited:

Buprenorphine;
Dextromoramide;
Diamorphine (heroin);
Fentanyl and its derivatives;
Hydromorphone;
Methadone;
Morphine;
Nicomorphine;
Oxycodone;
Oxymorphone;
Pentazocine;
Pethidine.

S8 CANNABINOIDS

The following cannabinoids are prohibited:

- Natural cannabinoids, e.g. cannabis, hashish and marijuana,
- Synthetic cannabinoids e.g. Δ^9 -tetrahydrocannabinol (THC) and other cannabimimetics.

Except:

- Cannabidiol.

S9 GLUCOCORTICOIDS

All glucocorticoids are prohibited when administered by oral, intravenous, intramuscular or rectal routes.

Including but not limited to:

Betamethasone;
Budesonide;
Cortisone;
Deflazacort;
Dexamethasone;
Fluticasone;
Hydrocortisone;
Methylprednisolone;
Prednisolone;
Prednisone;
Triamcinolone.

**SUBSTANCES PROHIBITED
IN PARTICULAR SPORTS**

P1 BETA-BLOCKERS

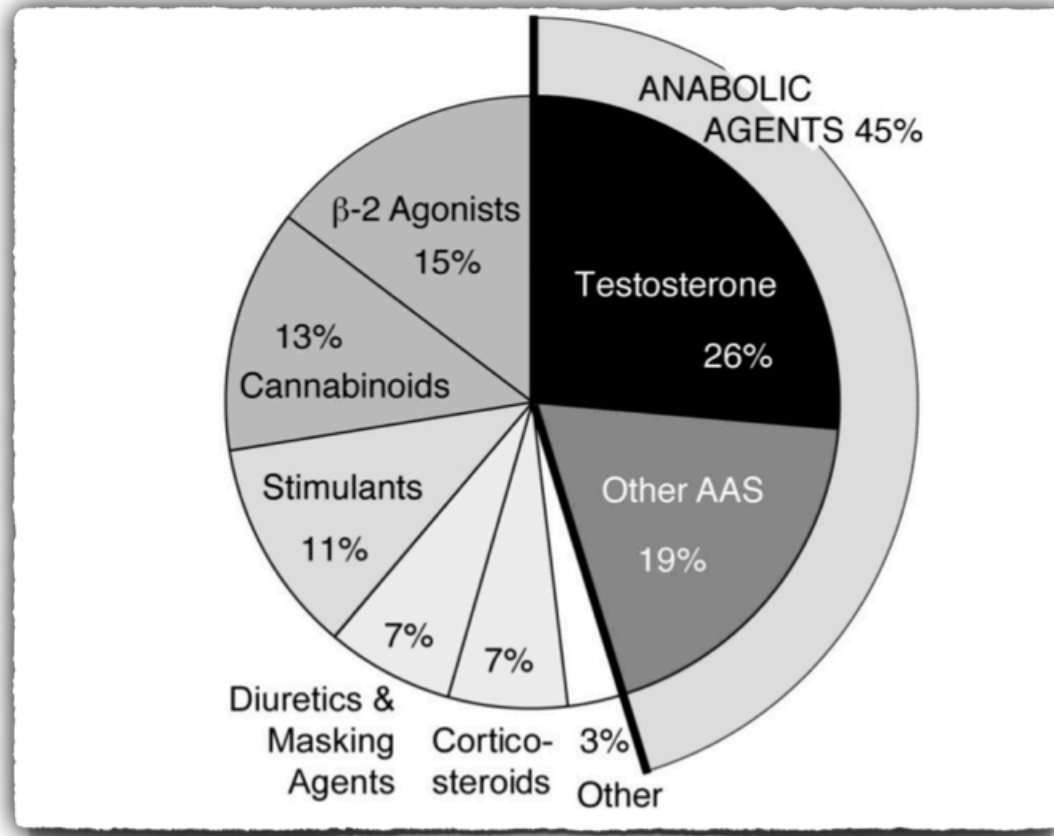
Beta-blockers are prohibited *In-Competition* only, in where indicated.

- Archery (WA)*
- Automobile (FIA)
- Billiards (all disciplines) (WCBS)
- Darts (WDF)
- Golf (IGF)
- Shooting (ISSF, IPC)*
- Skiing/Snowboarding (FIS) in ski jumping, freestyle aerials/halfpipe and snowboard halfpipe/big air
- Underwater sports (CMAS) in constant-weight apnoea with or without fins, dynamic apnoea with and without fins, free immersion apnoea, Jump Blue apnoea, spearfishing, static apnoea, target shooting, and variable

including, but not limited to:

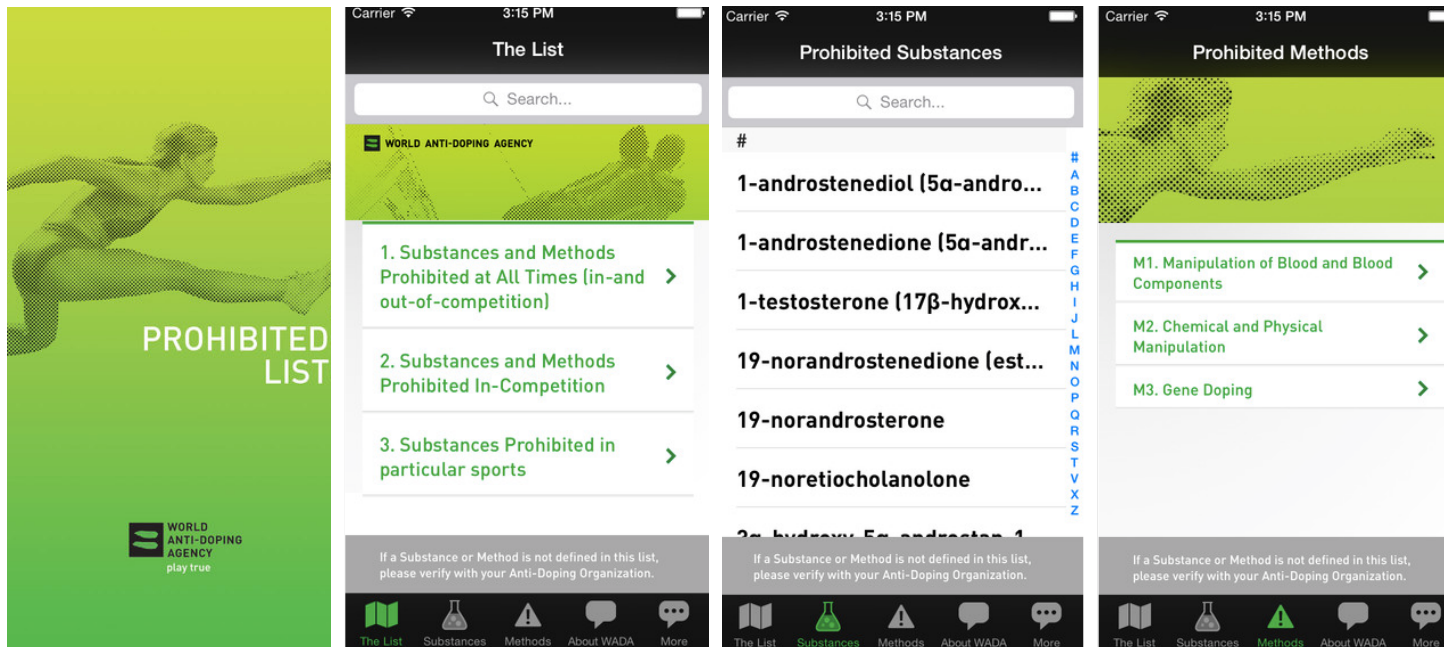
Acebutolol;	Labetalol;
Alprenolol;	Levobunolol;
Atenolol;	Metipranolol;
Betaxolol;	Metoprolol;
Bisoprolol;	Nadolol;
Bunolol;	Oxprenolol;
Carteolol;	Pindolol;
Carvedilol;	Propranolol;
Celiprolol;	Sotalol;
Esmolol;	Timolol.

WADA 2016 positive tests



WADA, 2016

WADA application 2018



WADA application



Quiz 3

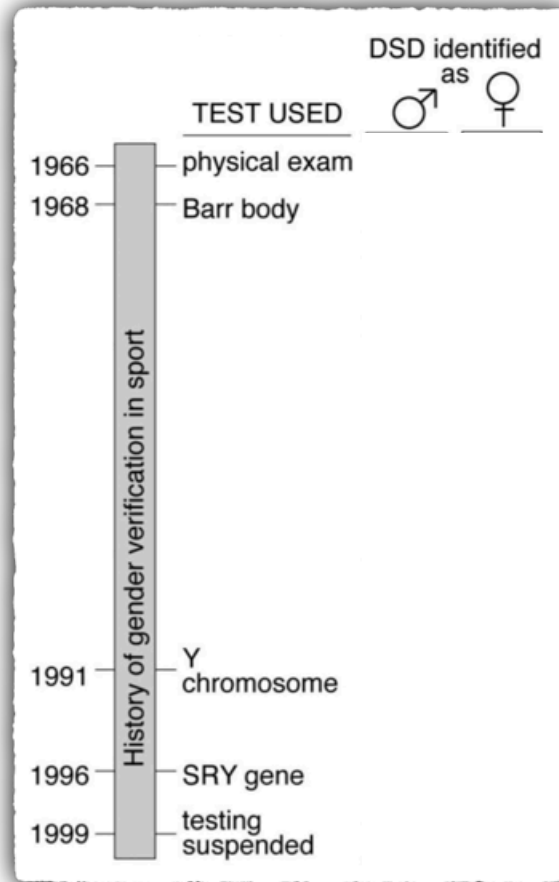
Disorders of Sexual Development

Disorder

- Turner syndrome
- Klinefelter syndrome
- True hermaphrodite
- Mixed gonadal dysgenesis
- Congenital Adrenal Hyperplasia
- Complete AIS
- Partial AIS
- 5 α -reductase inhibition
- Transsexual

Quiz 4

Time-line of gender verification testing



AIS: androgen insensitivity syndrome

CAH: congenital adrenal hyperplasia

XXY: Klinefelter's syndrome

Structure



- Introduction
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- Types
- Efficacy
- Safety
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The New England Journal of Medicine

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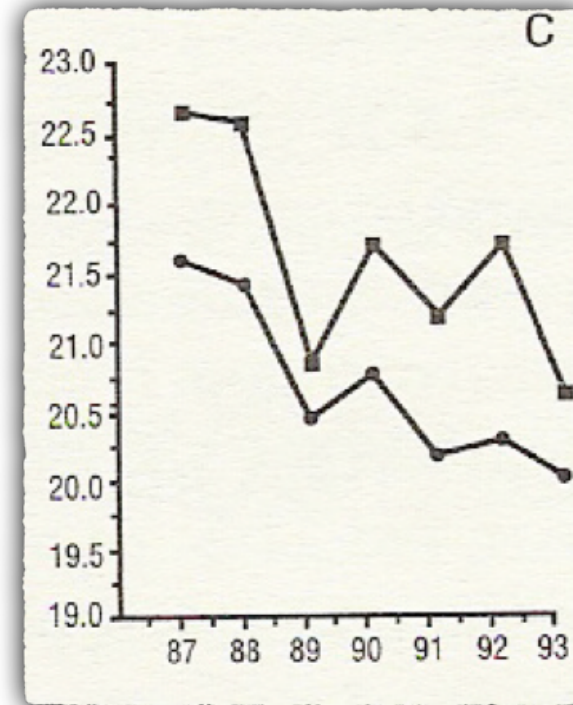
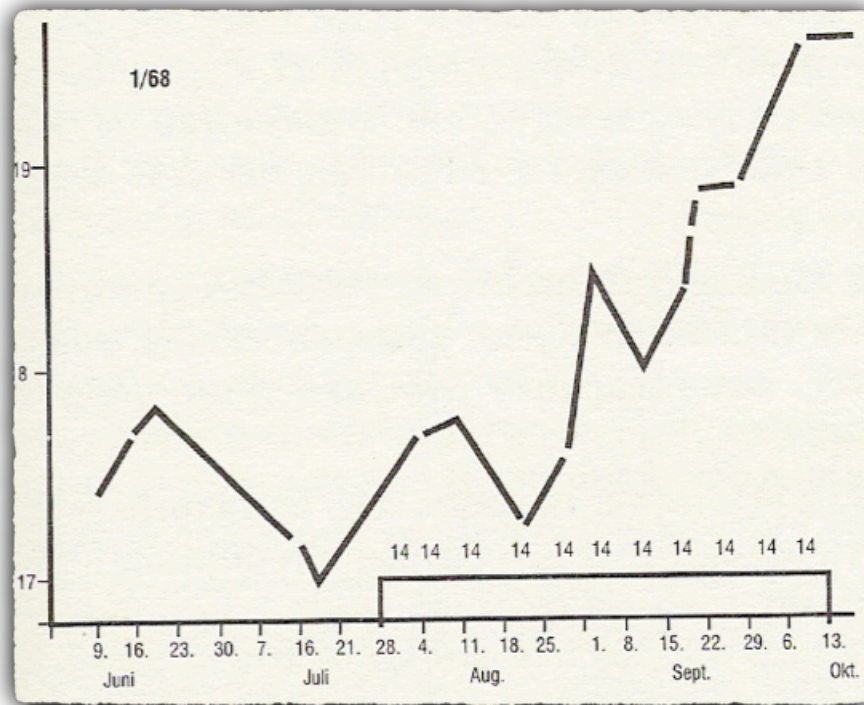
THE EFFECTS OF SUPRAPHYSIOLOGIC DOSES OF TESTOSTERONE ON MUSCLE SIZE AND STRENGTH IN NORMAL MEN

SHALENDER BHASIN, M.D., THOMAS W. STORER, Ph.D., NANCY BERMAN, Ph.D., CARLOS CALLEGARI, M.D.,
BRENDA CLEVINGER, B.A., JEFFREY PHILLIPS, M.D., THOMAS J. BUNNELL, B.A., RAY TRICKER, Ph.D., AIDA SHIRAZI, R.Ph.,
AND RICHARD CASABURI, Ph.D., M.D.

Efficacy study

- **Double-blind, placebo-controlled trial**
- Four groups of men (n = 43):
 - physical exercise & testosterone 600 mg / w
 - physical exercise & placebo
 - no physical exercise & testosterone 600 mg / w
 - no physical exercise & placebo
- Increase in mass muscle and strength with the use of testosterone, especially in combination with physical exercise

Efficacy



Doping Victims' Association

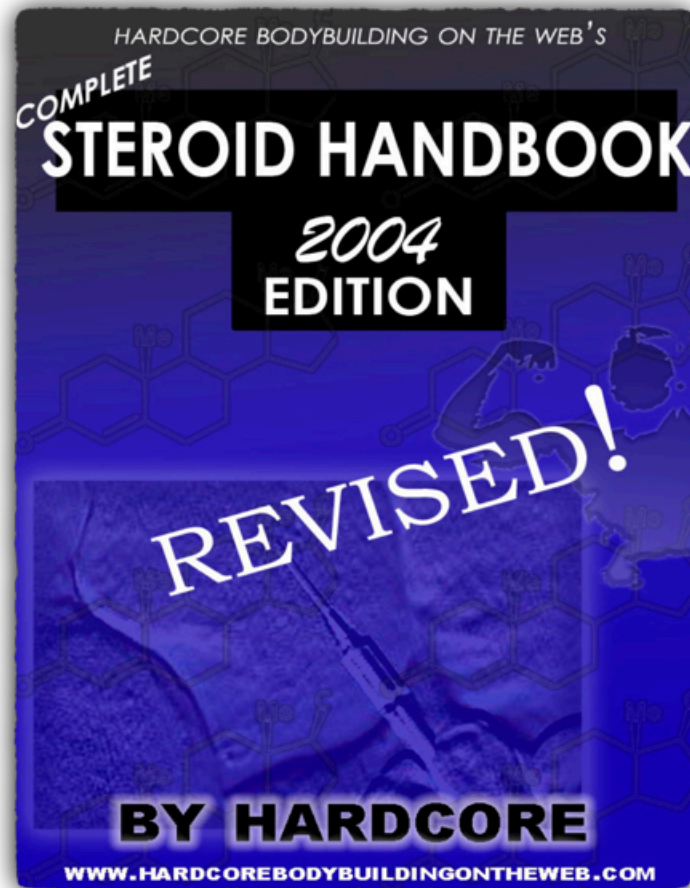


- **Doping-Opfer-Hilfe e.V.**
- **700 of the about 10,000 former GDR high-performance athletes involved in the systematic governmental doping programme based on the anabolic steroid oral turinabol (dehydro-chlormethyl-testosterone) in the 1970s and 1980s.**

Ways of administration

- **Stacking**
 - **Taking two or more anabolic steroids together, mixing oral and/or intramuscular routes**
- **Pyramiding**
 - **At the beginning of a cycle low doses of the stacked substances are administered and the dose is gradually increased for 6 - 12 weeks**
 - **In the second half of the cycle, the doses are slowly decreased to zero**

Effect ranking



Effect ranking

Drug	Strength Gains	Mass & Weight Gain	Fat Burning	Test Stimulation	Contest Prep	Appetite Suppression	Use as an Anti-Estrogen	Side Effects	Cost	Keep Gains?
Aldactone	-	-	-	-	9	-	-	8	4	-
Anadrol	10	10	-	-	5	-	-	9	5	1
Anavar	7	4	-	-	6	2	-	1	9	9
Andriol	2	2	-	-	-	-	-	1	7	8
Arimidex	-	-	-	-	9	-	10	3	9	-
Catapres	2	2	-	-	-	-	-	8	6	-
Cheque Drops	2	-	-	-	-	-	-	10	8	-
Clenbuterol	1	1	5	-	9	8	-	3	2	1
Clomid	1	-	-	8	8	-	7	3	6	1
Cyclofenil	1	1	-	7	5	-	6	2	3	1

Detection times

18 months	Nandrolone Decanoate (Deca Durabolin)
12 months	Nandrolone Phenylpropionate
5 months	Boldenone Undecylate (Equipose) Methenolone Enanthate (Primobolan) Trenbolone (Finaject) Trenbolone Acetate Injectable Methandienone (Dianabol)
3 months	Testosterone-mix (Sustanon & Omnadren) Testosterone Enanthate Testosterone Cypionate
2 months	Oxymetholone (Anadrol & Anapolan) Fluoxymesterone (Halotestin) Injectable Stanozolol (Winstrol) Formebolone Drostanolone Propionate (Masteron)
5 weeks	Methandienone (Dianabol) Mesterolone (Proviron) Ethylestrenole Noretadrolone (Nilevar)
3 weeks	Oxandrolone (Anavar) Oral Stanozolol (Winstrol)
2 weeks	Testosterone Propionate
1 weeks	Testosterone Undecanoate (Andriol)
4 days	Clenbuterol Ephedrine Hydrochloride

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Adverse effects

- **Non-specific**
 - common in all androgens
- **Specific**
 - androgen-specific
 - metabolite-specific / derivate-specific
 - sex-specific

Anabolic steroids adverse effects

Haematopoiesis and coagulation

- Erythrocytes
- Haemoglobin
- Haematocrit
- Polycythaemia
- Hypercoagulability
- Venous thromboembolism
- Arterial thromboembolism
- Stroke / Apoplexy

Musculo-skeletal system

- Premature epiphyseal closure (in adolescents)
- Rhabdomyolysis
- Tendon ruptures (?)
- Ligamentous injuries
- Disc herniation

Cardiovascular system

- HDL ↓ LDL ↑, ApoA1 ↓
- Coronary heart disease
- Myocardial infarction
- Hypertension (?)
- Abnormal ECG (QRS > 114 ms)
- Arrhythmia
- Left ventricular hypertrophy
- Hypertrophic cardiomyopathy
- Dilative cardiomyopathy
- Heart failure
- Sudden cardiac death

Liver

- Cholestasis /Hyperbilirubinaemia
- Steatosis
- Peliosis
- Adenomas
- Hepatocellular carcinoma
- Liver coma

Kidney

- Creatinine ↑, cystatin c ↑
- Glomerulosclerosis
- Cholemic nephrosis
- Renal failure

Psyche and behavior

- Irritability
- Nervousness, unrest
- Aggressiveness
- Reckless behavior
- Self-aggressiveness
- AAS dependence
- AAS withdrawal syndrome
- Depression
- Suicide thoughts

Skin^a

- Acne
- Striae distensae
- Profuse sweating
- Alopecia
- Hirsutism

Male reproductive functions^a

- Decreased testis volume
- Suppressed spermatogenesis
- Infertility
- Loss of libido
- Erectile dysfunction
- Gynaecomastia
- Anabolic steroid induced Hypogonadism (ASIH)

Female reproductive functions^a

- Anovulation
- Amenorrhoea
- Dysmenorrhoea
- Infertility
- Breast atrophy
- Dysphonia
- Deepening of voice

Adverse effects

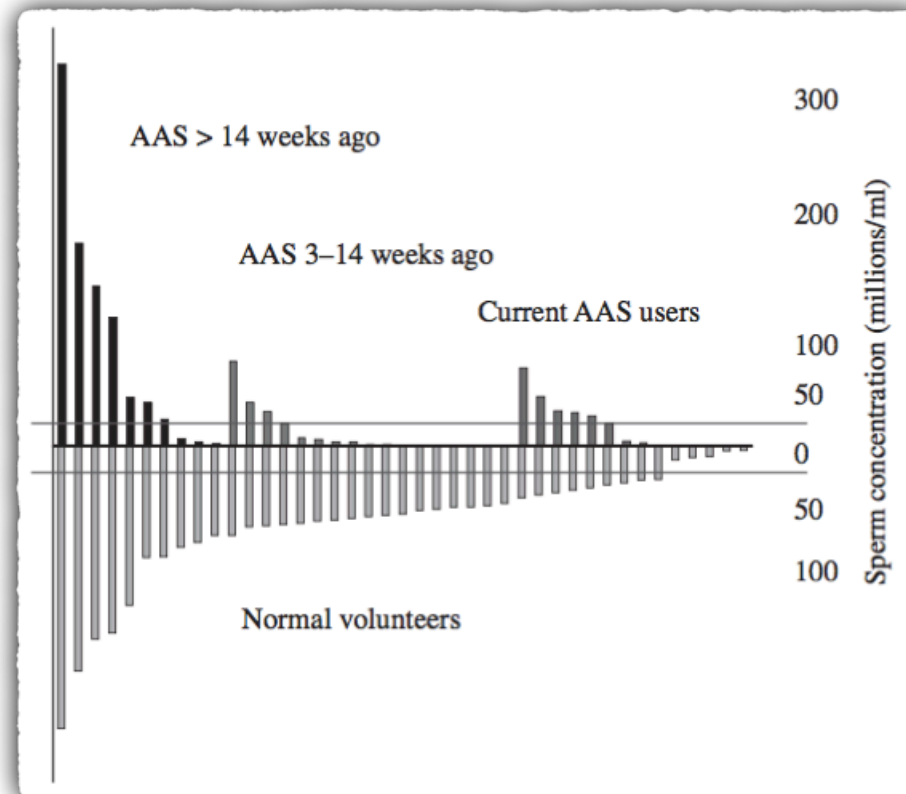
- Inhibition of testicular function
- Gynecomastia
- Polycythemia
- Hepatotoxicity
- Mood disturbances
- Disturbances of cardiac function
- Dyslipidemia
- Activation of coagulation cascade
- Virilization
- Inhibition of linear growth
- Infections

Inhibition of testicular function



- Suppression of gonadotropin secretion
 - suppression of endogenous testosterone secretion
 - suppression of spermatogenesis
 - decrease in testicular size
- Reversible effect in 3-4 months

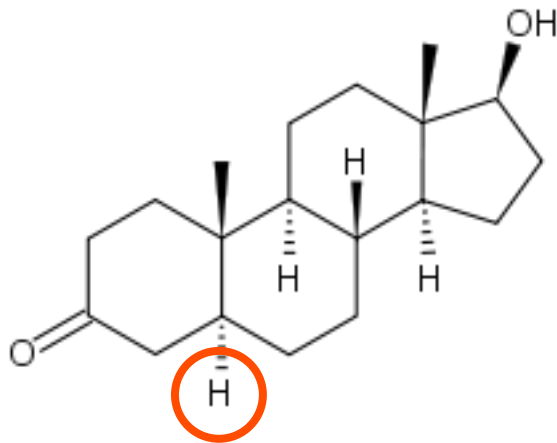
Anabolic steroids on sperm



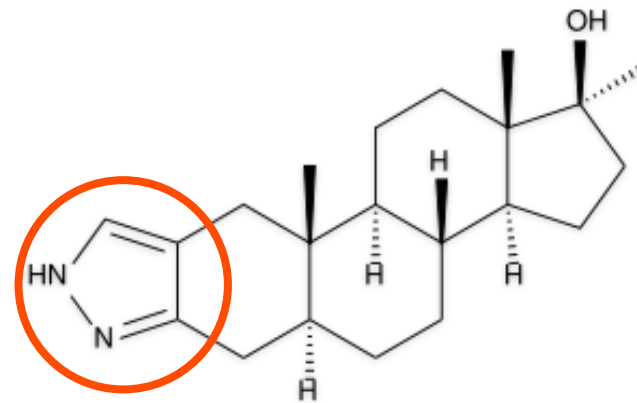
Knuth UA, et al. Fertil Steril 52:1041, 1989

Gynecomastia

- Conversion of testosterone to estradiol



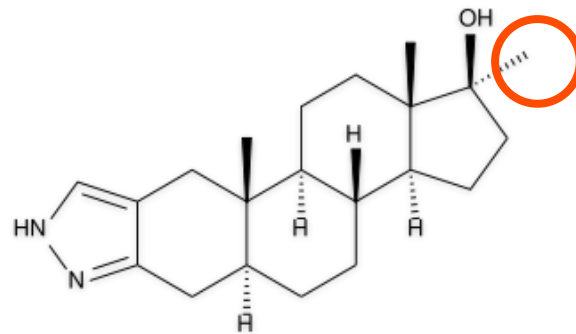
Dihydrotestosterone



Stanozolol

Hepatotoxicity

- Increase in liver enzymes
- Cholestatic jaundice
- Hepatic peliosis
- Hepatoma



Stanozolol

Mood disturbances



- Questionnaire in men, users and non-users of anabolic steroids (n = 160)
- Users had increased incidence of:
 - depression
 - aggressive behavior
- Symptoms were more severe during the periods of androgen intake

Disturbances of cardiac function

- Sudden death
 - cardiac hypertrophy, myocarditis

Hausmann R, et al. Int J Legal Med 111:261, 1998

- **Randomized, placebo-controlled trial**
- Body-building athletes (n = 8)
- Nandrolone or or placebo for 8 weeks
- No differences on ultrasonographic parameters

Hartgens F, et al. Int J Sports Med 24:344, 2003

Anabolic steroids adverse effects

Table 2. Common cardiovascular complications caused by the most frequently used doping substances.

	AMI	CAD	Cardiomyopathy	Arrhythmias	Hypertension	SCD
AAS	√	√	√	√	√	√
Other anabolic agents (clenbuterol)	√	√	√	√	√	√
hGH			√	√	√	√
EPO	√		√	√	√	√
Beta-2 agonists	√		√	√		√
Diuretics				√		
Amphetamines	√	√	√	√	√	√
Ephedrine	√	√	√	√	√	√
Cocaine	√	√	√	√	√	√
Narcotics				√		√
Cannabinoids	√	√		√	√	√

√ indicates an effect. AMI – acute myocardial infarction; CAD – coronary artery disease; SCD – sudden cardiac death; AAS – anabolic androgenic steroids; hGH – growth hormone; EPO – erythropoietin.

Dyslipidemia

- **Effect of 17 α -alcyliated derivatives**
 - decrease in HDL-cholesterol
 - increase LDL-cholesterol

Activation of coagulation cascade

- **Weight-lifting athletes, users to non-users of anabolic steroids (n = 49)**
- **In users as compared to non-users:**
 - increase in thrombin-antithrombin complex
 - increase in plasma prothrombin concentrations
 - increase in antithrombin III concentrations
 - increase in protein S concentrations
 - decrease in tPA and PAI-1 concentrations

Inhibition of linear growth

- **Early epiphyseal closure**
- **Trial of adolescent player of american football (n = 873)**
 - **anabolic drug users: 6%**
 - **use before the age of 15 years: 50%**
 - **use before the age of 10 years: 15%**

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Aims



- Discussion on the efficacy and safety of hormones as performance-enhancing drugs
- Identification of men and women that use anabolic steroids and complain of other clinical problems

Anabolic steroids



- Special characteristics
- Epidemiology
- Types
- Efficacy
- Safety

Suspicion of use

Man

- Competitive sport
- Small testes
- Azoospermia
- High hematocrit
- Low SHBG

Woman

- Competitive sport
- Hirsutism
- Acne
- Androgenic alopecia

Gym program

metandienone Testers nandrolone tamoxifen

	anabol	testoviron	deca	nolvadex	LIVE 52
1η εβδομαδα	14 2 ¹¹⁰⁰ 2	100 100	200 200		
2η εβδομαδα	21 3 ²¹⁰⁰ 4	250 250	400 400		
3η εβδομαδα	28 4 ²⁸⁰⁰ 6	250 250	400 400		
4η εβδομαδα	35 5 ³⁵⁰⁰ 8	250 250	400 400		
5η εβδομαδα	35 5 ³⁵⁰⁰ 8	250 250	400 400	1 η ημερα	1 η ημερα
6η εβδομαδα	28 4 ²⁸⁰⁰ 6	250 250	400 400	1 η ημερα	1 η ημερα
7η εβδομαδα	21 3 ²¹⁰⁰ 4	250 250	400 400	1 η ημερα	1 η ημερα
8η εβδομαδα	14 2 ¹⁴⁰⁰ 2	100 100	200 200	1 η ημερα	1 η ημερα
	280 χαπια	1700mg	2800mg	28 χαπια	
βιταμινες:	EVIOL E	5 τη μερα	56 x 5 =	280	600 = 30
	NEUROBION	5 τη μερα		280	600 = 30
	B SIX	4 τη μερα	56 x 4	224	480 = 48 καρτ.
	CEBION	3 τη μερα	56 x 3	168	360 = 36 καρτ.

Anabolic steroids



The dark side



The bright side



- **Steroid biochemistry**
- **Andrology - testosterone and sperm**
- **Adolescent Medicine**
- **Disorders of Sexual Development**
- **Cardiovascular system**
- **SERMs, aromatase inhibitors**
- **Beta-agonists and Beta-blockers**
- **Belgian bulls**

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