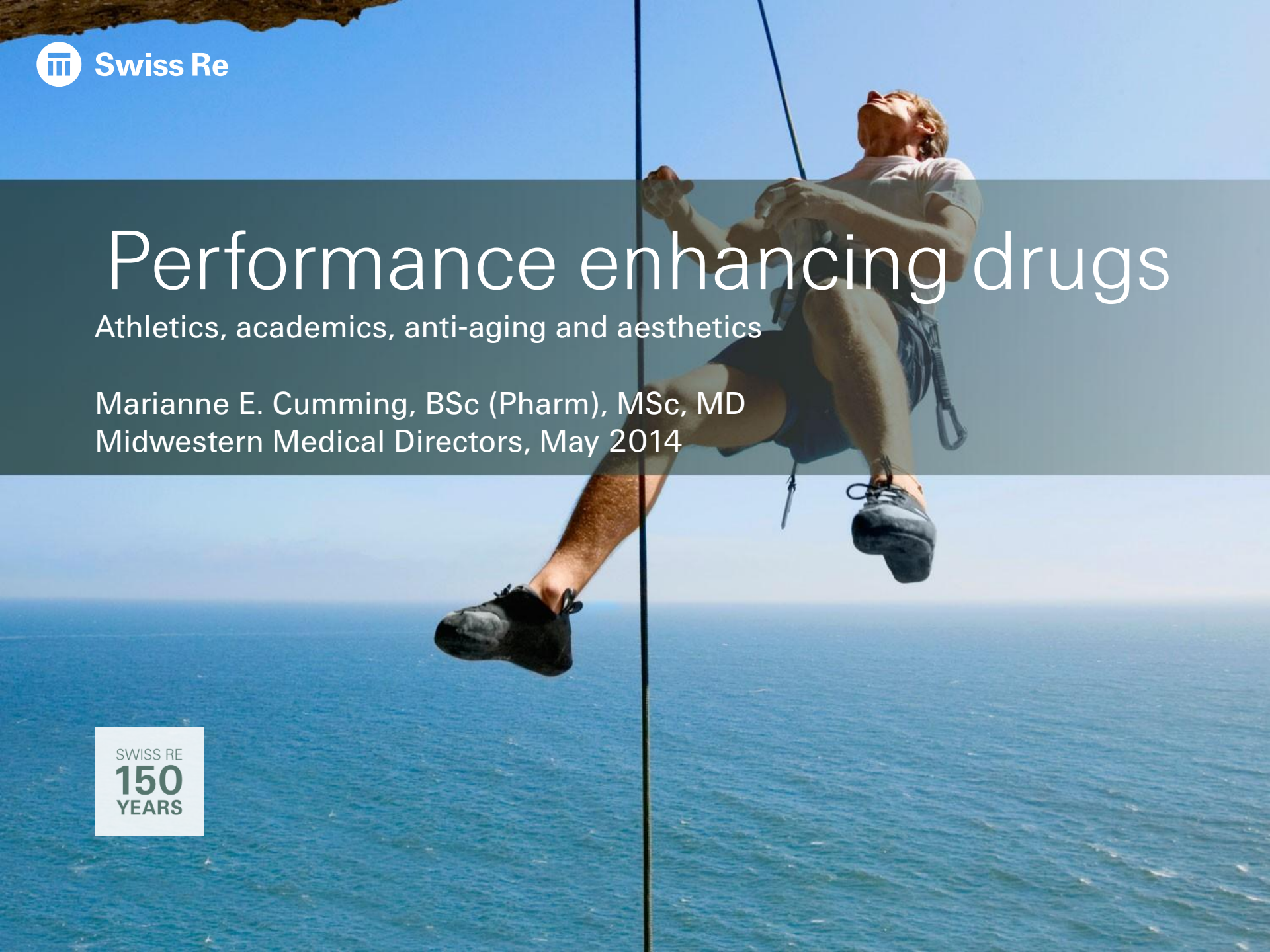


Swiss Re

Performance enhancing drugs

Athletics, academics, anti-aging and aesthetics

Marianne E. Cumming, BSc (Pharm), MSc, MD
Midwestern Medical Directors, May 2014

SWISS RE
150
YEARS

Table of Contents / Agenda

- Performance enhancement: definitions
- User characteristics
- Enhancer characteristics
  - Neuro-enhancers
  - Anabolic-androgenic steroids
  - Other enhancers
- Underwriting considerations

Performance enhancement: definitions

Performance enhancement

- *Performance:*
  - *action or process of carrying out or accomplishing an action, task, or function*
- *Enhance*
  - *intensify, increase, or further improve the quality, value, or extent of*
- Performance-enhancing drug
  - *"any substance taken to perform better athletically"*
  - most commonly associated with elite competitive sports...

Performance enhancement: medical models

The foundation of modern pharmacy is medical innovation and drug development within a disease-based model.
Several factors contribute to the increased use of drugs as enhancers

Medicalization common conditions formerly not considered "disease"

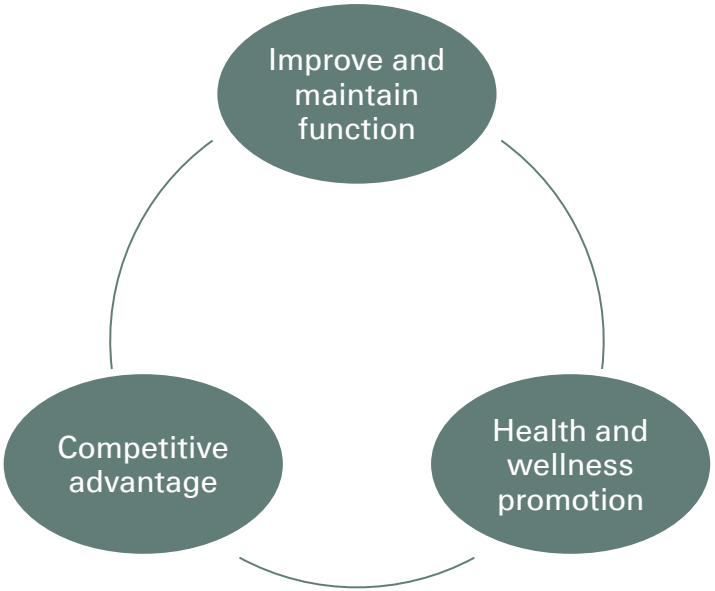
- disease awareness campaigns, direct-to-consumer advertising
- self-directed medical care, "lifestyle drugs"
- accessible health information via internet
- increasing "off-label" prescription drug use

Use of pharmaceuticals in absence of disease or medical condition

- physical enhancement, cognitive enhancement or both
- with or without athleticism
- with or without "performance"
- *("without the work")*

Enhancer benefits: perceptions or deceptions

"Transhumanism":
transform human condition by developing & making available technologies to greatly enhance human intellectual, physical, psychological capabilities



- increase energy, reduce fatigue
- increase endurance
- increase strength
- improve physical performance
- improve physical appearance
- increase muscle mass
- decrease body fat
- improve concentration
- improve cognitive performance
- financial gain
- perceived safety and efficacy
- and so much more..

The wealth of promotional information and the dearth of evidence-based recommendations related to benefits and risks serve to translate wishful thinking into widespread and not always sensible use of 'enhancers'

Enhancers: the insurance applicant

- Increasing acceptance and use in the general population
- Increasing identification in insured groups
  - motivated, successful, competitive
  - well-educated, well-informed
  - health conscious, perceived benefits
  - peer pressure
  - potential financial and career incentives
  - expanded "indications" for enhancer use, the four A's
    - athletics
    - academics
    - anti-aging
    - appearance

Medical enhancing drug: definition

Any substance taken to feel or look better

The list is long; select examples:

Athletics	Academics	Anti-aging	Appearance

• Anabolic steroids
• Testosterone precursors
• Human growth hormone (HGH)
• Human chorionic gonadotropin
• Erythropoietin
• Creatine
• Stimulants
• Opioids
	• Stimulants
	  • Amphetamines
	  • Caffeine
	  • Methylphenidate
	  • Modafinil
	  • Armodafinil
	• Beta-blockers
		• Athletics list
		• Academics list
		• Aromatase inhibitors
		• Metformin
		• Other hormones – thyroid, melatonin
		• Others - statins
			• HGH
			• Androgens
			• Mesotherapy

38 year old male, professional athlete, life insurance applicant

- Highly publicized use of performance-enhancing drugs
- Reported substances include AAS and HGH, dosages unavailable

28 year old female, PhD student, life insurance applicant

- No diagnosed medical condition
- Takes methylphenidate during preparation for examinations
- Prescribed by her regular physician, no evaluation

58 year old male, successful entrepreneur, life insurance applicant

- Fit, healthy, active, no medical conditions although recent diagnosis "adult growth hormone deficiency"
- Rx: testosterone, somatotropin (Norditropin), DHEA, finasteride (Propecia), Marine Fish oil, Men's multivitamin
- Prior omega-3, lycopene, coenzyme Q10, melatonin, indole-3-carbinol, glucosamine chondroitin, methylsulfonylmethane (DMSO, MSM)

Performance enhancement: user characteristics

The performer

Athletic	likely younger, generally healthy, recreational and professional sports
	supra-physiologic dosages, poly-pharmacy, legal and/or illegal sources, variable monitoring, possible non-disclosure
	co-existing psychiatric diagnosis or substance (alcohol, tobacco, opioids, other) misuse, risk-taking behaviors (accidents, violence, illegal activity), sport-related risk
Academic	all ages, likely younger and healthy, possibly higher education level
	variable monitoring, legitimate manufacture, poly-pharmacy less likely, possible non-disclosure
	co-existing psychiatric or substance misuse
Aesthetic	all ages; likely older, possibly higher socio-economic, education level
	poly-pharmacy, legal sources, good access to care and monitoring, disclosure Rx more likely
	co-existing medical (or psychiatric) conditions

Athletics: long history of enhancer use

Enhancers: highly prevalent throughout the history of modern sport with no end in sight

early 1900s - Strychnine, caffeine, cocaine, alcohol
1928 – International track and field association, first doping ban
1960 - Olympic cyclist amphetamine-related death prompted drug testing
1966 - Cycling and football/soccer (FIFA) first drug testing
1967 - International Olympic Committee first list prohibited substances
1972 – First full scale drug testing program; stimulants, opioids
1976 - Anabolic steroids added to the list, reliable detection method developed
1999 – World Anti-doping Agency (WADA), independent, international agency , unified standards and coordinated efforts, list >100 banned substances
2000 – United States Anti-doping Agency (USADA), Olympic, Paralympic, Pan American , Parapan American sport

Risk profile: male college athletes using performance enhancers

TABLE 1. Substance-use behaviors and risk profiles of male student athletes who did or did not report past-year performance-enhancing substance (PES) use

Variable	Non-PES users (n = 160)	PES users (n = 73)
Alcohol-use behaviors, mean (SD)		
Frequency of use in past year[a]	2.7 (1.3)	3.9 (1.0)§
Frequency of ≥5 drinks in one sitting in past year	23.8 (31.8)	69.2 (49.7)§
No. of drinks on the heaviest drinking day in past year	11.2 (6.8)	17.5 (7.2)†
Prevalence of past-year drug use, % yes		
Cigarettes	6%	21%†
Smokeless tobacco	11%	46%§
Marijuana	22%	70%§
Cocaine	3%	32%§
Psychedelics	3%	29%§
Prescription drugs without a medical prescription	6%	40%§
Consequences of use		
Alcohol problems	2.5 (3.0)	5.6 (4.0)§
Drug problems[b]	13%	52%§

- 234 college male athletes
  - PED users (n=73) in past year (stimulants, hormone precursors, supplements) more likely to report problem alcohol and drug use compared to nonusers (n=160)
  - *Buckman et al, J Stud Alc Drugs 2009*

Professional athletes: compared to insured groups

- Pro athletes
  - ages 20-40, 1970-2000
  - baseball, basketball, football, hockey
  - violent deaths more common
    - *most were motor vehicle accidents*
  - medical deaths less common
  - few "high profile" athletes
  - more deaths in off-season
  - overall, no significant difference in athlete mortality vs other insured young males
  - *Pinkham, Contingencies 2001*

Differences in cause of death between professional athletes and insured groups of similar-aged males

Ages 20-29

	Pro Athlete	Lincoln RE 95-99	SOA 85-90
Accidents	73.0%	42.2%	31.1%
Suicide	8.1%	11.8%	12.7%
Homicide	5.4%	18.7%	5.6%
Circulatory	8.1%	5.9%	18.1%
Neoplasms	5.4%	4.8%	14.1%
Other Medical	0.0%	16.6%	18.4%

Ages 30-39

	Pro Athlete	Lincoln RE 95-99	SOA 85-90
Accidents	84.6%	27.5%	19.2%
Suicide	7.7%	10.6%	9.6%
Homicide	0.0%	6.7%	3.7%
Circulatory	0.0%	18.0%	28.4%
Neoplasms	7.7%	15.9%	20.5%
Other Medical	0.0%	21.3%	18.5%

Performance enhancement: enhancer characteristics

Enhancer risk: drug or supplement itself

Enhancer types, names, dosages

- multiple -vs. single - enhancers common
- intentional or inadvertent nondisclosure possible
- dosage may vary from therapeutic recommendations
- route of administration: potentially unsafe practices
- legal vs. illegal enhancer
- FDA regulation as drug or supplement – or not at all

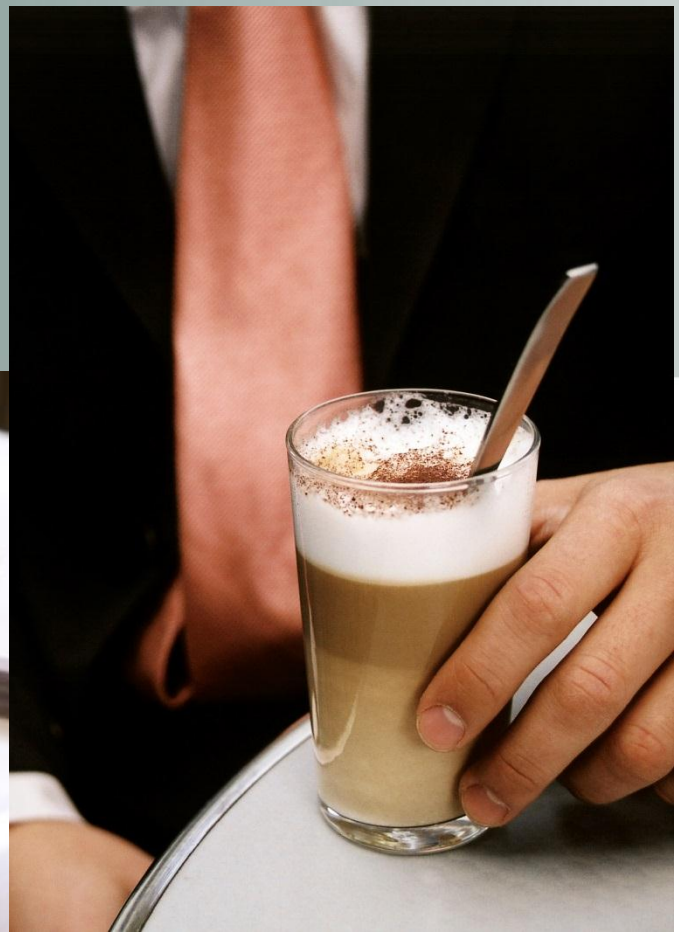
Prescriber details

- attending physician(s), or alternate prescriber/supplier
- legitimate or illegitimate prescriber
- may or may not be available in APS

Source

- attending physician: adequate follow-up, identification adverse effects more likely
- trainer, internet or other sales: adequate follow-up less likely
- enhancer: legitimate Rx with proper manufacture and quality controls, with FDA regulation; vs. other sources less reliable manufacture, potential contaminants, possibly less rigorous regulation as dietary supplement

Neuro-enhancers



The universal enhancer: caffeine - health benefits and risks

Potential benefits

- increased mental alertness, energy, ability to concentrate
- enhanced athletic performance
- analgesia
- possible decreased risk: type 2 diabetes, Parkinson's, Alzheimer's, liver cirrhosis, myocardial infarction (low dose)
- possible decreased risk: liver, endometrial cancer, (breast cancer uncertain)
- possible decreased all-cause mortality risk
- *Nehlig 2010, Lopez-Garcia et al, 2008*

Potential risks

- short-term: headache, anxiety, tremors, insomnia
- long-term: anxiety (GAD, panic disorder), depression, antisocial behavior, substance misuse
- cardiac: coronary or arrhythmic events, acute BP elevation
- increased fracture risk, lower BMD
- increased risk lung and bladder cancer (confounded by smoking)
- withdrawal: headache, fatigue, nausea, irritability, depression; *≥100mg/d, peak 1-2d, duration≤9 days*

World Anti-Doping Agency (WADA): 2004, caffeine removed from banned list, previous limit >12mcg/mL (8C coffee) until research demonstrated this amount more likely detrimental to performance

Cognitive enhancers (CEs)

Smart drugs, nootropics

Cognition- or neuro-enhancers

Academic doping

Cosmetic neurology

Psycho-stimulants

"Brain gain"

Academic doping or Viagra for the brain?

The history of recreational drug use and pharmacological enhancement can provide insight into these uses of neuropharmaceuticals

Smart drugs: stimulants: amphetamines, methylphenidate, and more

- Medical and non-medical uses for 100+ years
  - athletic competition
  - military - enhanced alertness
  - depression
  - attention-deficit hyperactivity disorder (ADHD)
- More recently
  - extensive off-label use in healthy individuals:
    - increased alertness, energy or concentration
    - academic and business settings
- Stimulants: amphetamine, methylphenidate, modafanil
  - Increasing prevalence in normal healthy individuals: 5% to 35%
  - Improved cognitive abilities: most consistent in clinical populations
  - Mixed results in healthy individuals:
    - some studies - enhancement with improved memory and executive functioning
    - others - report impairment or detrimental effects
      - *Smith and Farah, 2011*

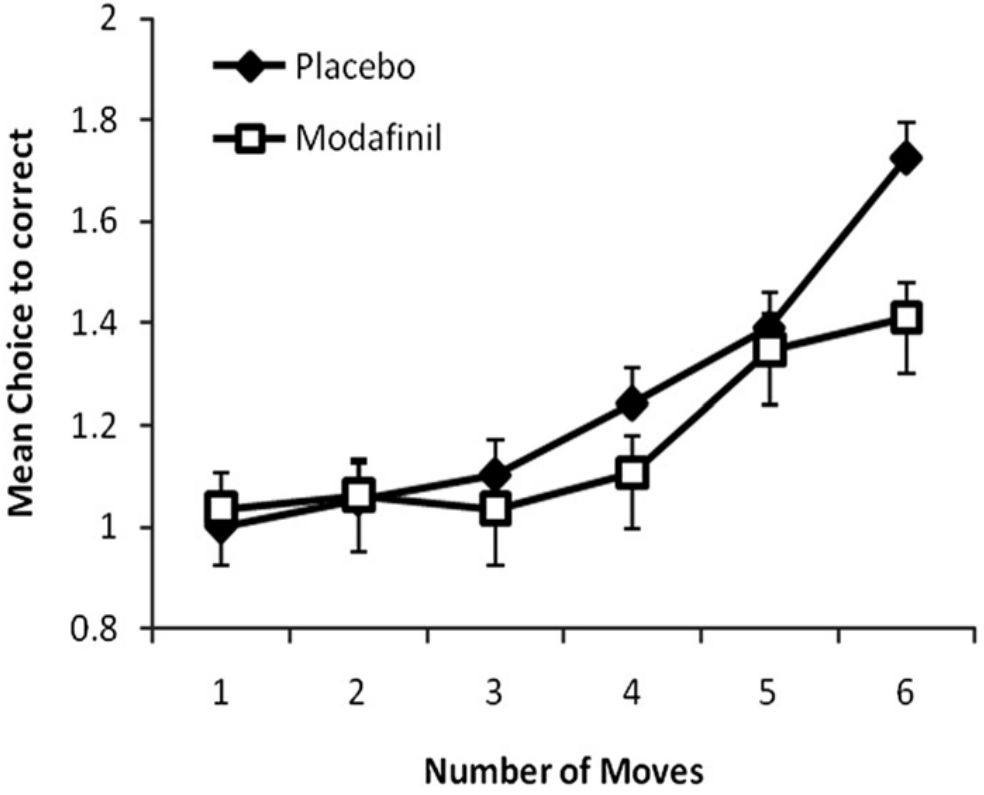
Cognitive enhancers

Stimulants	Cognitive benefits	Adverse effects

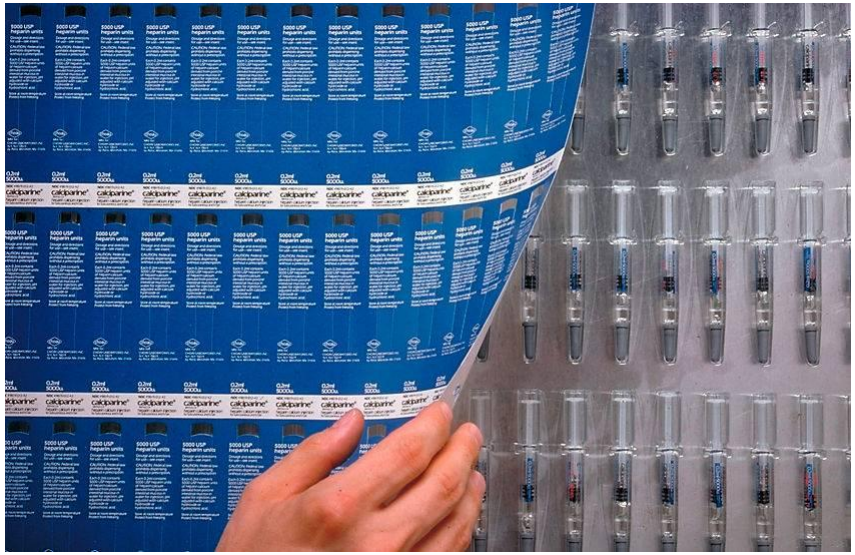
• caffeine
• cocaine
• amphetamine, dextro-amphetamine (Adderal, Dexedrine)
• methylphenidate (Ritalin, Concerta)
• modafinil (Provigil)
• armodafinil (Nuvigil)
• lisdexamfetamine (Vyvanse)
• dimethylphenidate Focalin
• ephedrine *(2004 ban)*
	• improvement in:
	  • learning
	  • executive function
	  • working memory
	  • attention
	  • concentration
	  • energy
	  • speed
	  • endurance
	  • motivation
		• insomnia, nervousness, anorexia, psychosis (rare
		• tachycardia, hypertension, ischemic or hemorrhagic stroke, arrhythmias, myocardial infarction
		• vocal and motor tics, tremors, seizures, hyperthermia
		• addiction potential

Modafinil

- Approved: excessive daytime sleepiness associated with narcolepsy, sleep apnea
- Non-medical use in military and increasing use in academic, business settings
- Studies demonstrate cognitive benefits in healthy individuals
- May be better tolerated than amphetamines
  - *Repantis et al 2010, Müller et al 2013*



Anabolic-androgenic steroids

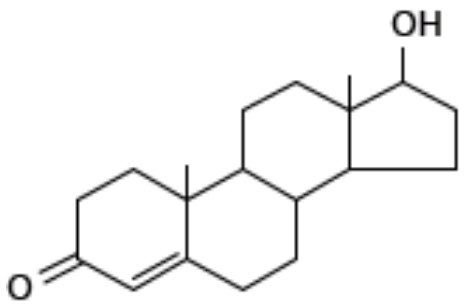


Anabolic-androgenic steroids

- US Anti-Doping Agency (USADA), 2009, 26/8000 tests positive
- US surveys, androgens:
  - 1% population uses androgens
  - 80% users recreational athletes or body builders
  - adolescent users: 3.6% high school students, mostly boys
  - more common
    - cycling, baseball, weightlifting
    - with personal or family history of drug misuse
- Survey: 500 anabolic-androgenic steroid users:
  - 78% - non-competitive body builders or non-athletes
  - 60% - >1000 mg testosterone or equivalent per week
  - 99% - self injected
  - 25% - also used growth hormone
  - 95% - polypharmacy
  - 100% - reported adverse effects
  - *Parkinson AB, Evans NA, 2006*

Anabolic-androgenic steroids and other hormones

Testosterone



- Testosterone, and its derivatives:
  - increase muscle mass and strength
- Anabolic steroids
  - synthetic derivatives of testosterone
- Testosterone precursors
  - androstenediol, androstenedione and dehydroepiandrosterone (DHEA)
- Human chorionic gonadotropin (hCG)
  - stimulates testosterone production
- Tetrahydrogestrinone (THG)
  - potent androgen "designer steroid", developed to escape urine testing detection

Anabolic-androgenic steroids

Testosterone and derivatives

- Injectable androgens
  - testosterone enanthate (Delatestryl), cyprionate (Depo-testosterone), nandrolone
- Oral androgens
  - danazol, fluoxymesterone, methandrostenolone, methyltestosterone, oxandrolone, oxymetholone, stanozol, testolactone
- Transdermal testosterone
  - Gels - Androgel, Fortesta, Testim
  - Patches –Androderm, Andropatch, (Testoderm)
  - Spray - Axiron
- Buccal testosterone – Striant
- Pellets – Testopel implants

Adverse effects

- liver – abnormal LFTs, hepatitis, tumors *(17-alpha alkylated)*
- abnormal lipids, erythrocytosis
- decreased glucose tolerance
- increased CV disease
- infections - septic arthritis, hepatitis, HIV
- males - testicular atrophy, oligo-spermia, gynecomastia; females – irreversible virilization
- males – prostate cancer
- adolescents – premature growth cessation, epiphyseal closure
- Psychiatric – emotional lability, mania, depression, aggression
- Tendon rupture

BMJ, January 10, 2014

Getting your "T" up

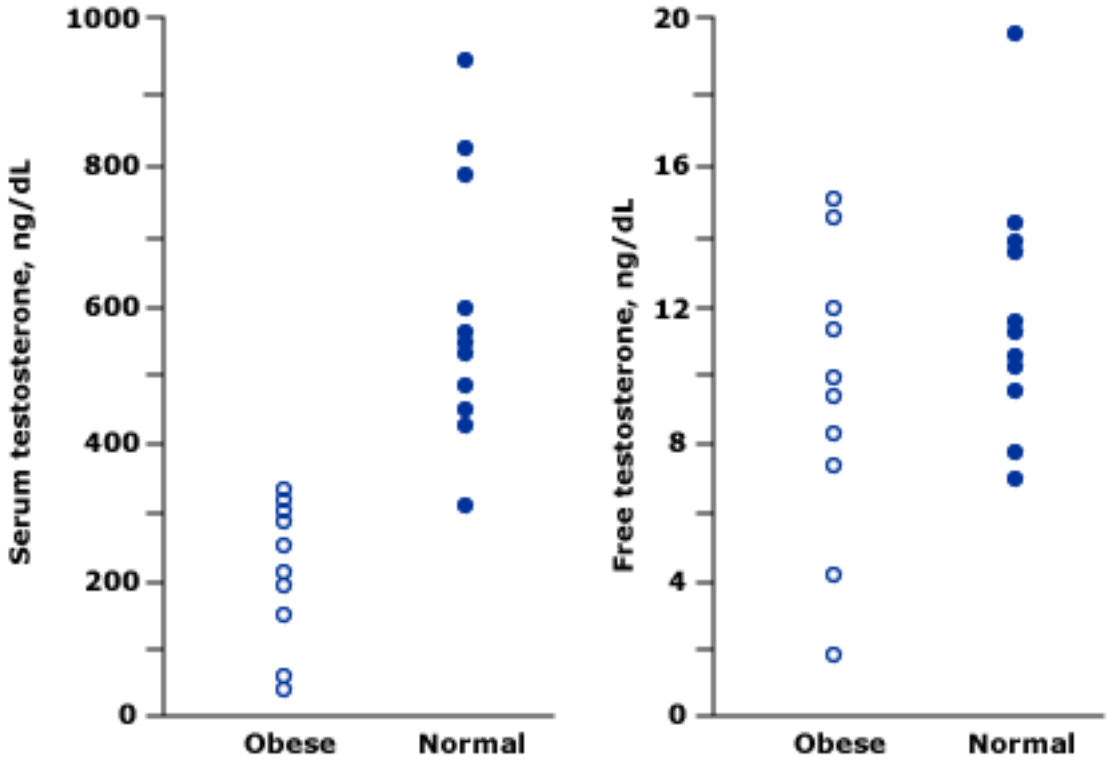
Big pharma creates a new disease: low testosterone

Douglas Kamerow *chief scientist, RTI International, and associate editor, BMJ*

The fifth "A"? Andropause? or the epidemic of testosterone deficiency

- Testosterone in males
  - primarily produced in testes, regulates libido, helps regulate bone mass, fat distribution, muscle mass, strength, erythrocyte and sperm production
  - serum levels decrease with age – and with obesity, diabetes mellitus, pituitary disease or trauma, acute illness, nutritional deficiency, certain drugs (opioids, glucocorticoids, other steroids, GnRH analogs)
  - some studies demonstrate benefit in aging males (sex drive, muscle mass, well-being) but long-term risks unclear
  - high doses may cause erythrocytosis, increased risk testosterone-dependent diseases (prostate cancer, BPH), serum cholesterol and CV risk (mixed reports)
  - FDA approved for hypogonadism, not as anti-aging therapy

Serum testosterone concentrations in obesity



Obesity is characterized by a reduction in serum total testosterone concentration (left panel) but a normal serum free testosterone concentration (right panel) due to diminished protein binding.

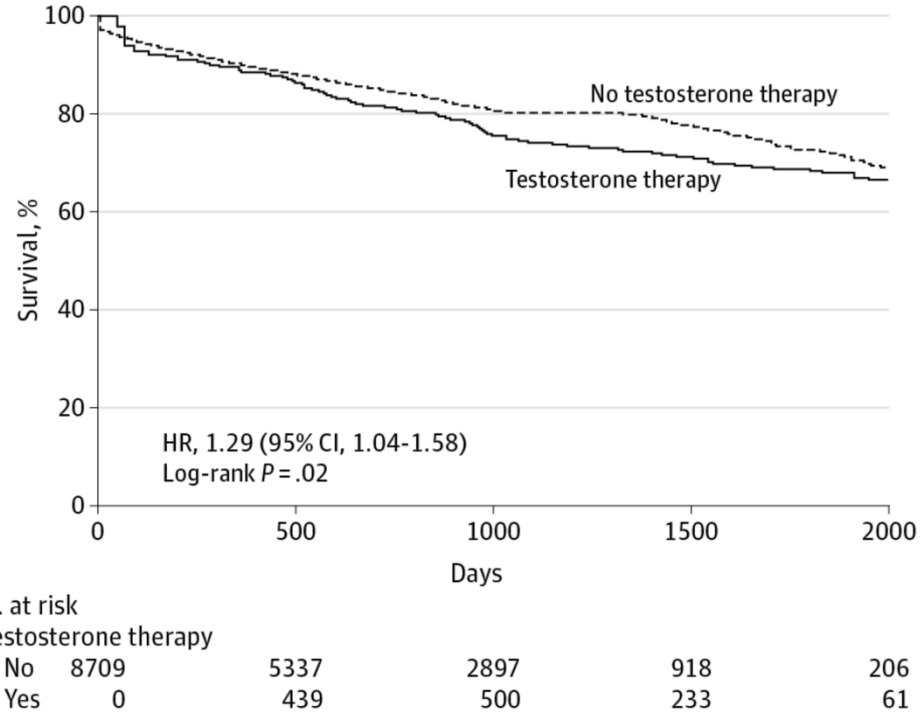
Data from Glass, AR, Swerdloff, RS, Bray, GA, et al, J Clin Endocrinol Metab 1977; 45:1211.

UpToDate®

Testosterone therapy: increased CV events, all-cause mortality risk

Observational retrospective veterans cohort

- 8709 males, mean 63 yrs, T <300ng/dL, 27.5 months follow-up, 748 deaths, 443 MI, 519 strokes
- Co-morbidities - DM 50%, CAD 80%, prior MI 20%, obese 50%
- 1223 Rx T: patch (63%), injectable (36%), gel (1%); initial T 175 increased to 332 mg/dL
- T use associated with increased risk all-cause mortality, MI, & ischemic stroke (HR,1.29; 95%CI,1.05-1.58; P = .02)
- Unchanged after adjusting for CAD (HR,1.29; 95% CI, 1.04-1.58)

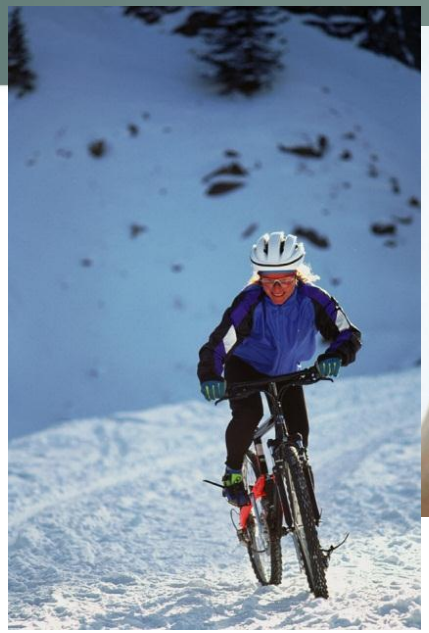


Vigen et al, JAMA 2013

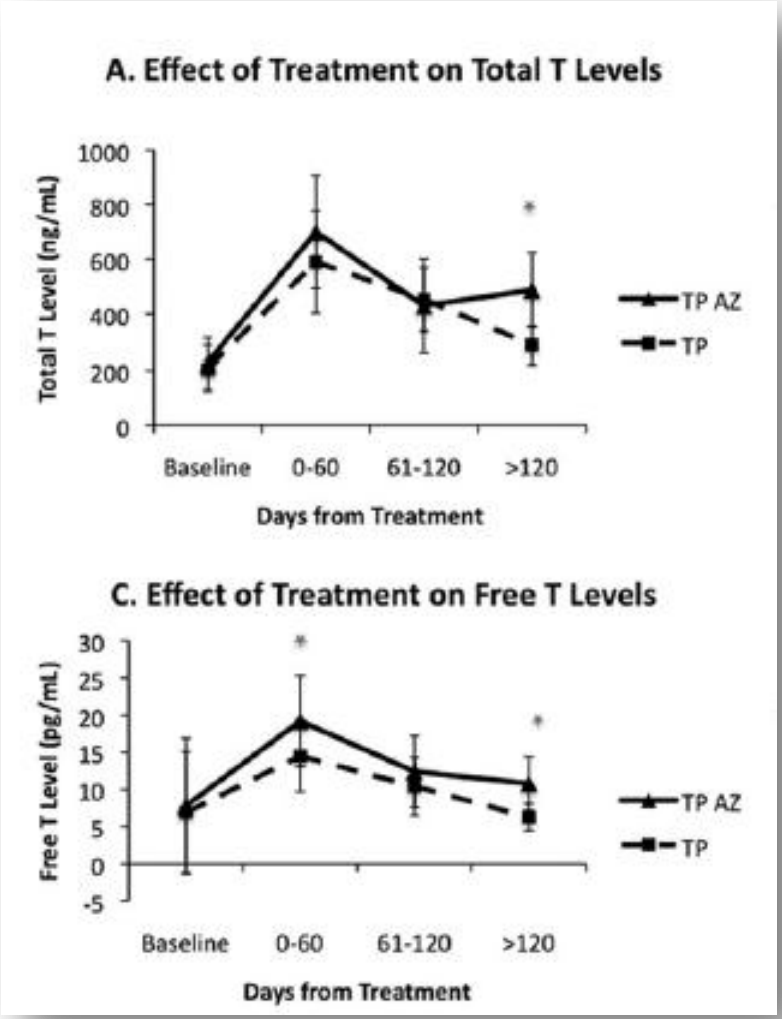
Androgen precursors:

- Androstenedione, "andro"
  - bodybuilders, promoted as nutritional supplement until classified as Rx in 2004
  - may or may not increase testosterone levels and no evidence that it increases muscle strength
- Dehydroepiandrosterone (DHEA)
  - dietary supplement (not FDA regulated), promoted to increase muscle strength
  - although converted to testosterone, studies show DHEA but not testosterone levels increased
  - mixed results, small study - no differences in lean body mass comparing "andro", DHEA, placebo; another study - increased strength in males with DHEA
- Adverse effects:
  - potential for liver damage, estrogen and testosterone dependent cancers, cardiovascular disease

Other enhancers



Aromatase inhibitors increase testosterone levels in males



Anastrozole (AZ): aromatase inhibitor, off-label use for male hypogonadism, increases T levels by lowering serum estradiol (E2), increasing gonadotropin (GTP) levels

38 males, 65 treatments, mean age 60, BMI 32, hypogonadism, tx testosterone pellets (TP), with or without AZ, baseline hormone levels similar

After 120 days tx, total T, free T and average change in T levels higher (E2 lower and GTP higher) in TP AZ group vs. TP alone

Men on TP AZ maintained therapeutic T levels longer than men on TP alone

Mechlin et al, J Sex Med 2014

Cosmetic mesotherapy

The American Board of Aesthetic Mesotherapy was developed to protect the public and advance the science and practice of Mesoplasty (Aesthetic/Cosmetic Mesotherapy). The Board was developed due to recent exploitation of Mesoplasty by unqualified practitioners.

- Injection of substances locally into subcutaneous tissue;
  - "microscopic quantities of homeopathic medications, traditional pharmaceuticals, vitamins, minerals, amino acids into the skin to treat a variety of conditions"
    - local fat reduction, skin rejuvenation, hair restoration, (back pain)
- Two forms of mesotherapy for local fat reduction:
  - Lipolytic: activation of lipolysis in fat cells - aminophylline, isoproterenol, yohimbine (additive)
  - Ablative: fat cell destruction using a detergent - phosphatidylcholine, deoxycholate
- Complications, case reports:
  - infection (most frequent, atypical mycobacterium), skin reactions, acute psychosis, ischemic colitis, thyrotoxicosis, nephropathy
    - *Jayasinghe , Bissoon et al, Obes Rev. 2013*

Human growth hormone (HGH) (somatropin): athletics, anti-aging, appearance

- Decline in serum GH with age is observed yet clinical consequences are unknown, "replacement" is not recommended, and off-label use in USA is not approved
- Potential benefits:
  - increase in lean body mass (more muscle) decrease in fat mass
  - sprint capacity increased, no effect on strength, power or endurance
- Adverse effects
  - glucose intolerance, diabetes, edema, hypertension, arthralgias, myopathy
  - possible association with substance misuse, other PEDs (AAS), opioids, cocaine
- $$$$
- US Brand Names: *Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Serostim, Tev-Tropin, Zorbtive*

Creatine: athletics

- Popular nutritional supplement:
  - increase strength, improve high-intensity performance, such as weight lifting (heavy resistance training)
  - not banned BUT supplements containing creatine may be contaminated with banned drugs
- Sources:
  - endogenous production liver, kidney, pancreas; also dietary meat and fish
- Open, 21-month study in college football players, average 5 grams/day, no detectable adverse effects *(Kreider et al, Mol Cell Biochem 2003)*
- Adverse effects:
  - edema, weight gain, muscle cramps, acute interstitial nephritis (?later chronic renal disease) *(Persky & Brazeau, Pharmacol Rev 2001)*

Erythropoietin (EPO) and other methods: athletics

- Enhance oxygen-carrying capacity of blood, increase aerobic exercise tolerance
- Blood doping (autologous transfusion), recombinant human erythropoietin (EPO), darbepoetin, hemoglobin-based solutions, perfluorocarbon-based emulsions (blood substitutes), others
- Increased erythropoiesis
  - polycythemia, hypertension, myocardial infarction, stroke, thromboembolic disease

Dietary supplements: proceed with caution

FDA NEWS RELEASE

For Immediate Release: Dec. 23, 2013
FDA warns consumers not to use muscle growth product

Product marketed as a dietary supplement contains potentially harmful synthetic steroids

The U.S. Food and Drug Administration is advising consumers to immediately stop using a product called Mass Destruction, marketed as a dietary supplement for muscle growth. The product is labeled to contain at least one synthetic anabolic steroid and has been linked to at least one reported serious illness.

The FDA was alerted by the North Carolina Department of Health and Human Services of a serious injury associated with use of Mass Destruction. The report described a previously healthy 28-year-old male with liver failure requiring transplant after several weeks of product use. Liver injury is generally known to be a possible outcome of using products that contain anabolic steroids and steroid-like substances. The product's ingredients are undergoing further analysis by the FDA.

Mass Destruction is manufactured for Blunt Force Nutrition in Sims, N.C. and sold in retail stores, fitness gyms, and on the Internet. An investigation is underway to identify the product's manufacturer. Consumers who suspect they are experiencing problems associated with Mass

FDA NEWS RELEASE

Update: Nov. 19, 2013: Recall expanded to include Raspberry Lemonade OxyELITE Pro Super Thermo Powder

For Immediate Release: Nov. 10, 2013
Media Inquiries: Theresa Eisenman, 301-796-2805 (office) or 240-328-3137 (cell), theresa.eisenman@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

USPlabs LLC recalls OxyElite Pro dietary supplements; products linked to liver illnesses

The U.S. Food and Drug Administration announced today that USPlabs LLC, of Dallas, Texas, is recalling certain OxyElite Pro dietary supplement products that the company markets. The company took this action after receiving a letter from the FDA stating that the products have been linked to liver illnesses and that there is a reasonable probability that the products are adulterated.

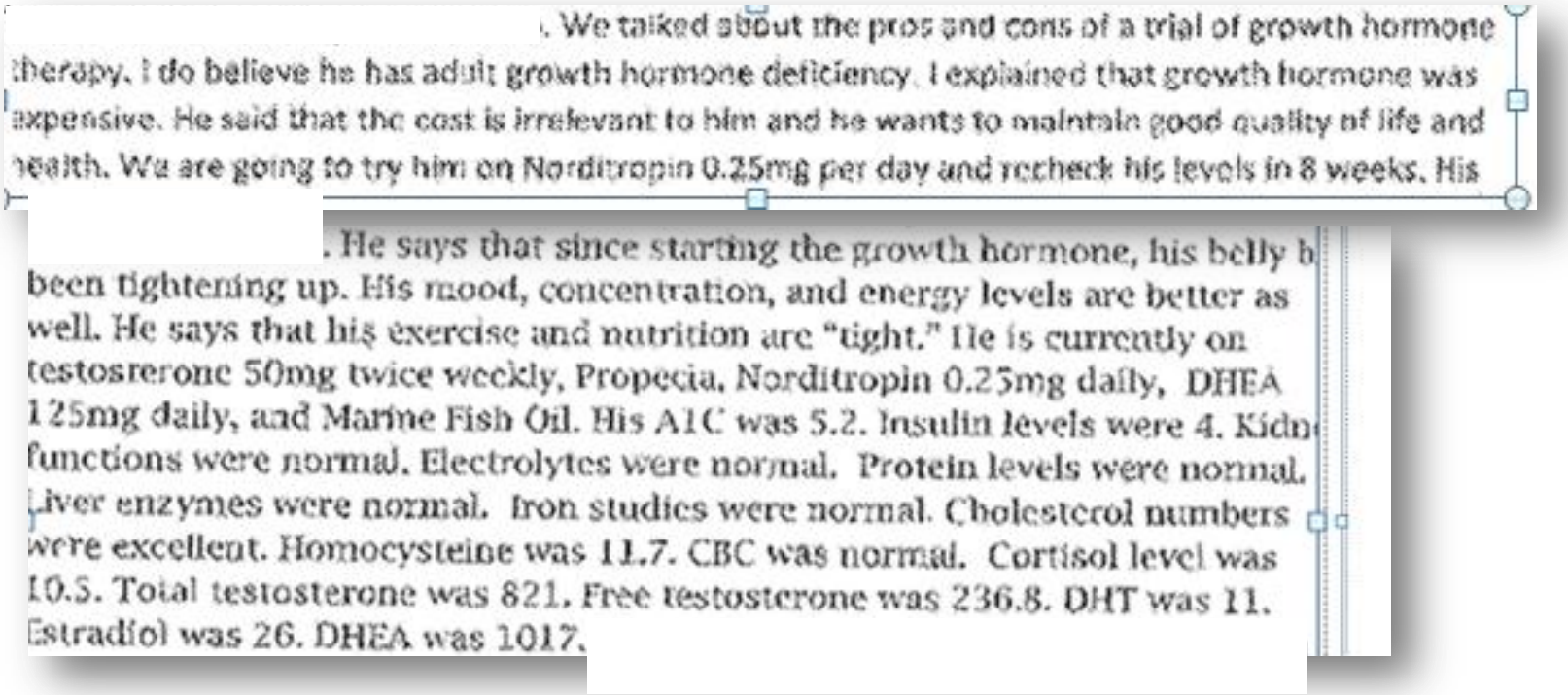
The letter also notified USPlabs that if the company did not initiate a voluntary recall, the FDA could by law order the company to immediately stop distributing the dietary supplements and immediately notify other parties to stop distributing the dietary supplements. The action marks the second time the FDA has exercised its recall authority under the FDA Food Safety Modernization Act (FSMA) by sending such a letter.

"We took this step to ensure that adulterated and harmful products do not reach the American public," said Deputy Commissioner for Foods and Veterinary Medicine Michael R. Taylor. "We will continue to work with our state, industry and regulatory partners to prevent such products from reaching the public."

Performance enhancement: underwriting considerations

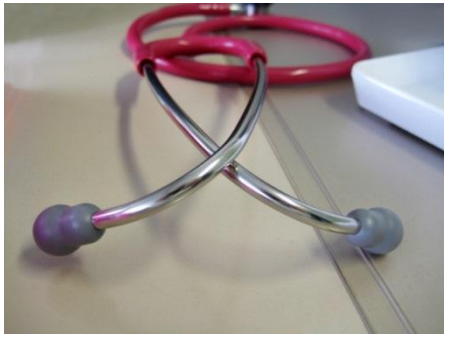
58 year old male, successful entrepreneur, life insurance applicant

- testosterone cyprionate injection – previous 50 mg 2x/weekly, increased to 140 mg weekly (200 mg/ml inject 0.35 ml twice weekly)
- growth hormone (Norditropin) 0.25 mg/d, increased to 0.3mg/d


. We talked about the pros and cons of a trial of growth hormone therapy. I do believe he has adult growth hormone deficiency. I explained that growth hormone was expensive. He said that the cost is irrelevant to him and he wants to maintain good quality of life and health. We are going to try him on Norditropin 0.25mg per day and recheck his levels in 8 weeks. His

. He says that since starting the growth hormone, his belly b been tightening up. His mood, concentration, and energy levels are better as well. He says that his exercise and nutrition are "tight." He is currently on testosrerone 50mg twice weekly, Propecia, Norditropin 0.25mg daily, DHEA 125mg daily, and Marine Fish Oil. His A1C was 5.2. Insulin levels were 4. Kidn functions were normal. Electrolytes were normal. Protein levels were normal. Liver enzymes were normal. Iron studies were normal. Cholesterol numbers were excellent. Homocysteine was 11.7. CBC was normal. Cortisol level was 10.5. Total testosterone was 821. Free testosterone was 236.8. DHT was 11. Estradiol was 26. DHEA was 1017.

Enhancers: underwriting considerations



Likely favorable	Less favorable
• full disclosure on application • single Rx, FDA approved for a condition, regular dosage • legitimate prescription and manufacture • regular monitoring by a physician • no co-existing medical conditions • no or well controlled cardiovascular risk factors • no psychiatric impairments • no alcohol or substance misuse	• inadequate information • multiple Rx, high dosage, and/or dietary supplements • no prescription and questionable source of medication • no monitoring, physician unaware • co-existing medical conditions • presence of cardiovascular risk factors • psychiatric history • alcohol or substance misuse

Additional factors: age, enhancer properties, reason for use, therapeutic substitute, sport-related risk

Enhancers: underwriting information

- underwriting source of drug information, i.e. admitted or from third party
- indication(s) for drug use
- current drug(s) and/or dietary supplements, dosage, duration of use
- prescriber details
- drug source details
- any complications resulting from current or previous PED use
- liver and renal function test results
- any co-existing medical or psychiatric conditions
- any current or history of alcohol or substance misuse or use disorder
- drug questionnaire

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