ANABOLIC STEROID ABUSE & PSYCHIATRIC COMPLICATIONS

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Disclosures

No financial or personal disclosures
Objectives

• To be able to identify common types of AAS abused
• To be able to identify psychiatric complications of exogenous anabolic androgen use
• To be able to understand the neurobiology of AAS use and its effects on brain neurotransmitters
• To be identify possible treatments for psychiatric disorders caused by AAS abuse
• To understand potential for AAS dependence
Case Report

• HPI: 22yo CM with history of cannabis use, reported anxiety/depression prescribed Zoloft 50mg, Wellbutrin 150mg by PMD, presents to the hospital by his parents after he had jumped out of secondary story window due to paranoia that his father was trying to kill him

• CPEP: “distressed, psychomotorically agitated…describes his father as “Gaslighting me”…more paranoid and persecutory…disorganized…demanding his Zoloft”

• Utox positive for cannabis
Case Report

- “3 day bender”-abusing DXM
- Symptoms included poor sleep
- On initial exam: guarded, paranoid, internally preoccupied
- Endorsed AH and paranoia regarding his father
- Significant thought blocking and thought latency, struggled to state simple sentences or phrases
- Affect labile-irritable and then tearful during interview
- Sexually preoccupied

- DDX: Psychotic disorder NEC; rule out substance induced psychotic disorder
- Started Risperdal 1mg qhs
- CIWA protocol due to HTN and tachycardia—suspicion for withdrawal
Case Report

• Patient admitted that he had been using Testosterone 500mg IM q weekly and Masterone 100mg IM q few days for the past 9-12 months

• Reportedly bought online to treat perceived sexual dysfunction

• Endocrine was consulted → labs ordered

• Continued to be HTN despite resolution of HR
  • Medicine consult: started on Antihypertensive
    - EKG: wnl
    - Echo: wnl except LV thickness upper range of normal
# Lab Values

<table>
<thead>
<tr>
<th></th>
<th>12/3/19</th>
<th>12/6/19</th>
<th>12/12/19</th>
<th>12/26/19</th>
<th>1/3/20</th>
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<tbody>
<tr>
<td>AST</td>
<td>55 (h)</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>43 (h)</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FSH</td>
<td></td>
<td>&lt;0.1 (L)</td>
<td>&lt;0.1 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td></td>
<td>&lt;0.1 (L)</td>
<td>&lt;0.1 (L)</td>
<td></td>
<td></td>
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<tr>
<td>Prolactin</td>
<td>42.8 (H)</td>
<td>34.5 (H)</td>
<td>2.9</td>
<td></td>
<td></td>
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<tr>
<td>Total testosterone</td>
<td>712</td>
<td>266 (L)</td>
<td>160 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>38.95 (H)</td>
<td>12.4</td>
<td>7.26</td>
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<td></td>
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<tr>
<td>% Free T</td>
<td>5.47 (H)</td>
<td>4.66 (H)</td>
<td>4.54 (H)</td>
<td></td>
<td></td>
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<tr>
<td>SHBG</td>
<td>15.1 (L)</td>
<td>11 (L)</td>
<td>12.3 (L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case Report

• Hospital Course:
  • Risperdal was increased to 3mg with minimal benefit
  • Started on ativan taper—as he appeared to improve on CIWA protocol
    - Discontinuation of taper—appeared more symptomatic
  • Risperdal switched to Abilify due to family’s concerns
    - Abilify increased and titrated to 15mg
    - Began to show some improvement though symptoms were persistent
  • Family adamant about patient returning home
ANABOLIC ANDROGENIC STEROIDS (AAS)
What are Anabolic Androgenic Steroids (AAS)?

• Synthetic androgens that have greater anabolic (growth promoting) activity relative to androgenic (masculinizing) activity

• Indicated in treatment of:
  • Aplastic anemia
  • Hereditary angioedema
  • Hypogonadism in males
  • Breast cancer

• Most commonly misused APED

# Commonly Misused AAS

<table>
<thead>
<tr>
<th>Administered orally</th>
<th>Administered intramuscularly</th>
<th>Administered transdermally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxymesterone (Halotestin, Android-F, Ultradren)</td>
<td>Boldenone undecylenate (Equipose&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>Testosterone (Androderm, AndroGel, Testim, Testoderm)</td>
</tr>
<tr>
<td>Mesterolone (Mestonum, Proviron)</td>
<td>Methenolone enanthate (Primobolan depot)</td>
<td></td>
</tr>
<tr>
<td>Methandienone, methandrostenolone (Dianabol)</td>
<td>Nandrolone decanoate (Deca-Durabolin)</td>
<td></td>
</tr>
<tr>
<td>Methylandrosterone (Android, Testred, Virilon)</td>
<td>Nandrolone phenpropionate (Durabolin)</td>
<td></td>
</tr>
<tr>
<td>Mibolerone (Cheque Drops&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>Nandrolone undecanoate (Dynabolan)</td>
<td></td>
</tr>
<tr>
<td>Oxandrolone (Anavar, Oxandrin)</td>
<td>Stanozolol (Winstrol-V&lt;sup&gt;5&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Oxymetholone (Anadrol-50, Hemogenin)</td>
<td>Testosterone cypionate (Depo-Testosterone, Virilon IM)</td>
<td></td>
</tr>
<tr>
<td>Stanozolol (Winstrol)</td>
<td>Testosterone enanthate (Delatestryl)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testosterone esters blends (Sustanon, Sten)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testosterone propionate (Testoviron, Androlan)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testosterone undecanoate (Andriol, Restandol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trenbolone acetate (Finajet, Finaplix&lt;sup&gt;5&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trenbolone hexahydrobenzylcarbonate (Parabolan)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>5</sup>Some foreign brand names are listed but are included because of the widespread illicit use of foreign steroid preparations in the United States.

<sup>5</sup>Veterinary compound.

1935 - First synthesized in Germany

1940s - Widespread use of testosterone and other AAS to treat "male climacteric" and various medical conditions

1962 - Mr. Olympia bodybuilding contest premiers

1970s - Widespread dissemination of AAS throughout elite sports


1982 - "Canon the Barbarian" and "Ronnie" released by Hollywood

1987 - In revised position stand, American College of Sports Medicine concedes that AAS are effective for muscle gains

1989 - Monitoring the Future Study adds AAS to its annual high school questionnaire

1990 - DEA enforcement largely eliminates domestic illicit AAS production, but has little effect on supply of AAS from overseas

1996 - "Mr. Joe Estes" action toy, with the equivalent of a 26-inch biceps and a 55-inch chest, released

2000 - Present - Increasingly frequent cases of elite athletes exposed for using performance-enhancing drugs

2003 - The World Anti-Doping Code first adopted

2004 - Anabolic Steroid Control Act of 2004 signed into law - expands list of prohibited AAS and imposes increased penalties

2005 - Congressional hearings on use of AAS

2006 - Operation Raw Deal: DEA seizes 11.6 million dosage units of AAS in largest seizure ever

2008-present - News stories regarding use of AAS by military and by private security contractors in Iraq and Afghanistan

2008-present - News stories regarding use of AAS by law enforcement officers in many U.S. cities

2012 - Lance Armstrong retroactively stripped of his titles

1954 Olympics-Russian weightlifters

1996: GI Joe Extreme
Prevalence of Use

• Estimated >1 million current or former steroid users in the US

• Majority: male (2-3x), non-athlete weightlifters in 20s or 30s

• Sixty to 70% of AAS abusers actively participate in organized sports

• Some people who misuse steroids have experienced physical or sexual abuse.

Prevalence of Use

• Steroid misuse is associated with muscle dysmorphia

• DSM5 Body Dysmorphic Disorder
  • Specifier- “The individual is preoccupied with the idea that his or her body build is too small or insufficiency muscular. This specifier is used even if the individual is preoccupied with other body areas, which is often the case”

Past Year Anabolic Steroid Use Among Middle and High School Students, 2007-2017
Data are from the 2017 Monitoring the Future survey, funded by the National Institute on Drug Abuse and conducted annually by the University of Michigan’s Institute for Social Research.
### Monitoring the Future Study: Trends in Prevalence of Various Drugs for 8th Graders, 10th Graders, and 12th Graders; 2016 - 2019 (in percent)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time Period</th>
<th>8th Graders</th>
<th>10th Graders</th>
<th>12th Graders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Lifetime</td>
<td>0.90</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Past Year</td>
<td>0.50</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Past Month</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Why are AAS abused?

• Increase lean body mass and strength
• Reduce recovery time between workouts
• Increase endurance
• Competitive advantage?
Pattern of use

- “Cycling”: taking multiple doses of steroids over a specific period of time, stopping for a period, and starting again
  - 2-3 per year
  - Cycle lasts 6-18 weeks
  - *Most common*

- “Stacking”: multiple AAS to produce synergistic effect by exploiting different androgen receptors

- “Pyramiding”- taper gradually instead of abruptly

- “Plateauing”: staggering, overlapping, or substituting with another type of steroid to avoid developing tolerance

Steroid Abuse Side Effects

- Depression
- Hypertension
- Headaches
- Dermatological problems
- Growth of facial hair
- Growth of underarm hair
- Development of secondary female characteristics in men
- Gynecomastia (enlargement of breast tissue in men)
- Reduced volume of testicles
- Altered libido
- Aggression
- Mood swings (including fear)
- Hormonal imbalance
- Sleep disturbances
- Acne
- Hyperproduction of sebum (skin oil)
- Development of secondary male characteristics (in women)
- Deepening of voice
- Cardiovascular complications
- Liver damage
- Fluid retention
Adverse Effects AAS

- Affects HPG axis by activating negative feedback loop → decreased levels LH & FSH

- Severity:
  - Age
  - Duration use
  - Dose
  - “Stacking”
  - Parallel use other drugs

- To minimize AE:
  - Aromatase inhibitors, tamoxifen-gynecomastia
  - hCG-restore HPA, HPG axis

Neurobiology

- In blood: 98% testosterone is bound; 1-2% unbound
  - Controlled levels of hSHBG

- Lipid soluble substance-crosses cell membranes including BBB

- Androgen receptor—intracellular receptor ligand activated transcription factor

- Induces rapid increase in intracellular calcium

- Expressed in skeletal muscle, reproductive organs, adrenal gland, liver, CNS

- CNS—expressed amygdala, hippocampus and hypothalamus

Genomic

androgen steroid

Non-Genomic

PI3K

mAR

Ras/Raf/ERK/MAPK

Src

nucleus

Actin polymerization

Ca²⁺ release

activation of other NRs and TFs

cytoplasm
Animal Studies

• AAS affects dopamine system → reward pathway
  - Long term administration of nandrolone in rats increases dopamine transporter density in caudate putamen

• Increase gene expression for opioid peptide precursors

• Serotonergic Pathways

• Glutaminergic Pathways—important in neuronal plasticity
Psychiatric Complications

- Depression
- Insomnia
- Mood instability
- Mania
- Psychosis
- Delirium
- Aggression
- Suicidal and Homicidal Ideation

Literature Review

• Su, Tung-Ping, et.al: *Neuropsychiatric Effects of Anabolic Steroids in Male Normal Volunteers*

• Design: 2 week, double blind, fixed order, placebo controlled cross over trial of methyltestosterone

• Subjects: 20 male volunteers without medical or psychiatric illness

• Intervention: 3 days each of 1) placebo (baseline); 2) low dose (40mg) methyltestosterone; 3) high dose (240mg) methyltestosterone; 4) placebo withdrawal

• Results: Significant (p<0.05) increases in symptom scores during 240mg administration compared with baseline in:
  • positive mood (euphoria, energy and sexual arousal);
  • negative mood (irritability, mood swings, violent feelings and hostility)
  • cognitive impairment (distractibility, forgetfulness, confusion)
  • Manic episode observed in 1/20 subjects representing 5% incidence
  • Another subject hypomanic
Literature Review

• Pope, Kouri, et. Al. *Effects of Supraphysiologic Doses of Testosterone on Mood and Aggression in Normal Men: A Randomized Controlled Trial*

• Design: randomized, placebo-controlled crossover trial
• Subjects: 56 men, ages 20-50yo
• Method: Administered Testosterone cypionate for 6 weeks in doses ranging to 600 mg/week, followed by 6 weeks of no treatment and then placebo for 6 weeks
• Results: testosterone significantly increased mania, elevating scores on multiple instruments; that the drug was liked and sought after; and that aggression increased.
• The investigators noted that the response to the drug, however, was highly variable.
• 84% of the subjects exhibited minimal to no psychiatric effects,
• 12% became mildly hypomanic, and 4% became markedly hypomanic.

Pope HG, Kouri EM, Hudson JI. Effects of Supraphysiologic Doses of Testosterone on Mood and Aggression in Normal Men: A Randomized Controlled Trial. *Arch Gen Psychiatry.* 2000;57(2):133–140. doi:10.1001/archpsyc.57.2.133
## Literature Review

Table 2. Psychiatric Measures at Baseline and End Point With Placebo and Testosterone Treatment in 53 Evaluable Participants*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo Treatment</th>
<th>Testosterone Treatment</th>
<th>Effect of Testosterone Treatment†</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End Point</td>
<td>Baseline</td>
<td>End Point</td>
<td>Baseline</td>
</tr>
<tr>
<td>YMRS score</td>
<td>0.3 ± 0.8</td>
<td>1.1 ± 2.5</td>
<td>0.5 ± 1.0</td>
<td>3.9 ± 4.9</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>PSAP score‡</td>
<td>206 ± 235</td>
<td>222 ± 241</td>
<td>208 ± 235</td>
<td>362 ± 301</td>
<td>167 ± 75</td>
</tr>
<tr>
<td>Daily diaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manic score</td>
<td>7.9 ± 3.8</td>
<td>7.4 ± 4.4</td>
<td>7.5 ± 4.2</td>
<td>9.2 ± 4.9</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Liking score</td>
<td>50 ± 2.8</td>
<td>50 ± 4.9</td>
<td>51 ± 2.9</td>
<td>55 ± 12.0</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Significant other diaries, manic score§</td>
<td>9.6 ± 4.4</td>
<td>9.7 ± 5.2</td>
<td>9.9 ± 5.1</td>
<td>11.4 ± 7.4</td>
<td>0.8 ± 1.4</td>
</tr>
<tr>
<td>Aggression Questionnaire total score</td>
<td>56.4 ± 15.0</td>
<td>56.9 ± 16.0</td>
<td>55.7 ± 13.5</td>
<td>56.2 ± 15.8</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>SCL-90-R global severity index</td>
<td>0.10 ± 0.16</td>
<td>0.07 ± 0.10</td>
<td>0.07 ± 0.13</td>
<td>0.08 ± 1.6</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale score</td>
<td>1.0 ± 1.6</td>
<td>0.8 ± 1.2</td>
<td>0.9 ± 1.6</td>
<td>0.8 ± 1.4</td>
<td>−0.06 ± 0.37</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD at the beginning and end of each treatment period as defined in the text. YMRS indicates Young Mania Rating Scale; PSAP, Point Subtraction Aggression Paradigm; and SCL-90-R, Symptom Checklist-90-R.

† The effect of testosterone treatment represents the estimate of the mean ± SE value of change during the testosterone period minus the change during the placebo period.

‡ \( N = 27 \).

§ \( N = 51 \).
Literature Review

• Studies using Pope and Katz’s categories of steroid use:
  • Medium steroid use (between 300 and 1000 mg/week of any AAS)
  • High use (more than 1000 mg/week of any AAS)

• 23% of subjects using these doses of steroids met the DSM criteria for a major mood syndrome (mania, hypomania, and major depression)

• 3.4%–12% developed psychotic symptoms.

Treatment

- No evidence based guidelines on treatment
- Case Reports:
  - Valproic Acid for mania
  - Haldol IM agitation
  - fluoxetine depression (especially withdrawal depression)
  - Atypicals for psychosis
AAS Dependence

• AAS Dependence among steroid users → 32.5%

• Strong association with opioid dependence
AAS Dependence
Thank you!