Post Finasteride Syndrome

or

A Funny Thing Happened on the Way to a Full Head of Hair

William Clearfield D.O. F.A.A.F.R.M., F.A.A.M.A. , D.A.B.M.A.
9550 S. McCarran Blvd., Suite B
Reno, NV 89523
doctrbil9@gmail.com

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American Osteopathic Society of Rheumatic Diseases
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Objectives

Click Mouse Reveal Next Phase

Discuss Testosterone Metabolism

What are 5 Alpha Reductase inhibitors?

Te

What is Post Finasteride Syndrome?
Is It Real or a Symptom of Mass Hysteria?

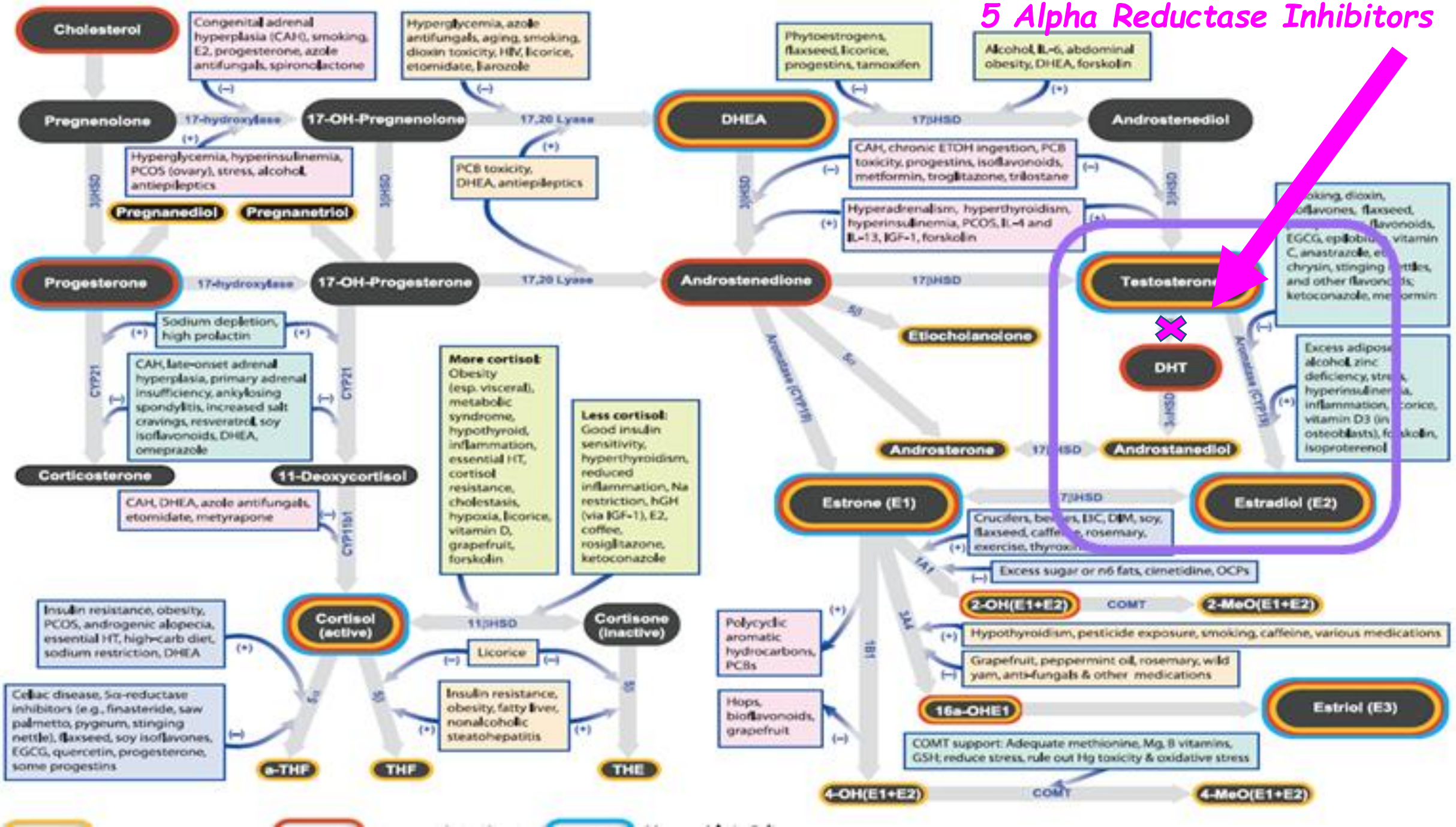
What Are the Symptoms of Post Finasteride Syndrome?

How Do We Diagnose and Treat Post Finasteride Syndrome?

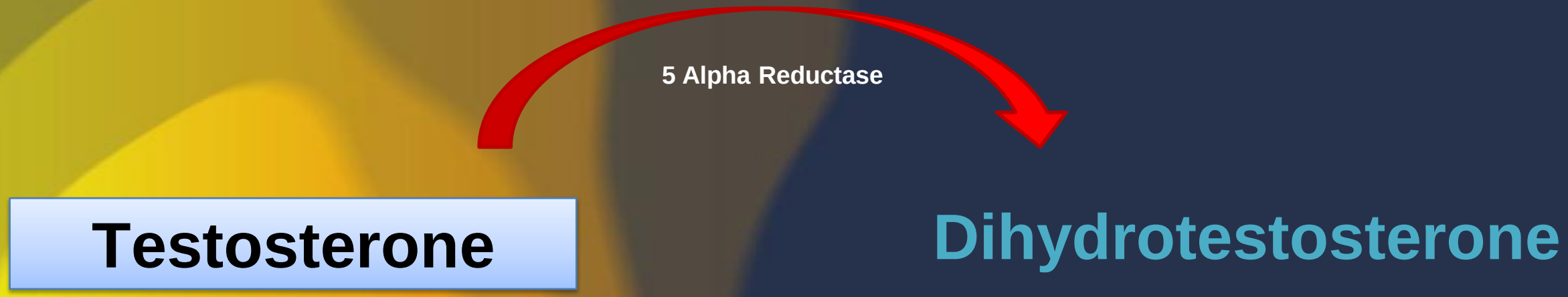
Your Conclusions: I Come Neither to Praise Nor Bury 5ARI
A Primer on a Rational Approach to Non-Surgical Hair Restoration

Financial Disclosures-None

Steroidogenic Pathways



Male Characteristics Are Stimulated by the Conversion via 5 Alpha Reductase of Testosterone to Dihydrotestosterone



Facial Hair, Deep Voice, Muscle Growth, Prostate Enlargement

Discovering 5 Alpha Reductase Inhibition

James B. Hamilton

1947 Yale University Study

Conclusion: DHT is Main Culprit for Acne, Hair Loss, BPH

Julianne Imperato-McGinley

1974 Study of Caribbean Children w Genetic 5 Alpha Reductase Deficiency

At maturity:

No Male Pattern Baldness

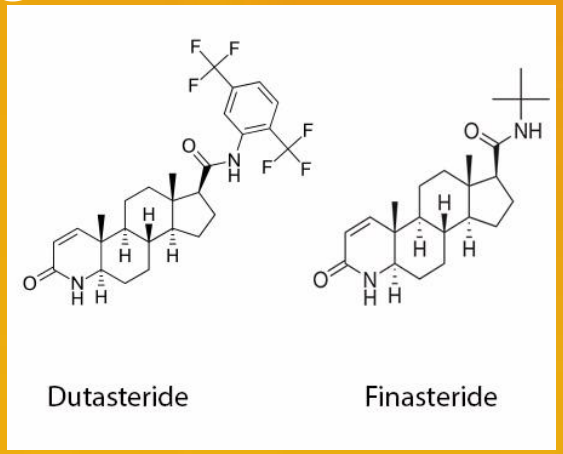
No Prostate Issues

High rates of Anxiety and Panic Disorder

1. Hamilton J (1942). "Male hormone stimulation is prerequisite and an incitant in common baldness." American Journal of Anatomy. 71 (3): 451–480. doi:10.1002/Aja.1000710306.
2. "The extraordinary case of the Guevedoces." BBC News. September 20, 2015. Retrieved September 3, 2018.

MK-906 Approved by FDA in 1992

- **MOA:**
  - Synthetic Transition State Inhibitor
  - Competitively inhibits type II and type III-reductase
- **Effects:**
  - Reduces:
    - Prostatic DHT by 90%
    - Serum DHT by 70%. [7]
- **Dutasteride**
  - Blocks all three 5a-reductase Inhibitors. ⬇ DHT by 98%



Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia. Eur Urol. 2000 Apr;37(4):367-80. doi: 10.1159/000020181. PMID: 10765065.

Finasteride Package Insert

- Indications
  - Benign Prostatic Hypertrophy
  - Androgenic alopecia
- Dosing
  a. Benign Prostatic Hypertrophy-5 mg/d
  b. Androgenetic alopecia (male pattern hair loss)-1 mg/d.
  c. Off Label Female Hair Loss: 2.5-5 mg
    i. Use with oral contraceptives (O.C.s).
    ii. Add if inadequate response to O.C.s after six months.
    iii. Use as initial therapy in females who cannot conceive
    iv. Cellulite reduction-Finasteride 2.5 mg + 1 % Testosterone gel

Finasteride Package Insert

- Contraindications
  1. Females, pregnancy
  2. Children and infants
  3. Hepatic Disease
  4. Prostate Cancer, urinary obstruction
     a. Reduces PSA by 50%
     b. 26 % decreased risk of a prostate cancer diagnosis while on finasteride versus placebo in patients with prostate cancer.
  5. Blood donors
  6. Geriatric
  7. Infertility

Finasteride Package Insert

- **Side Effects:**
  - **Infertility**
    a. 34% decreased sperm count, and 14.5% reduced sperm volume after 26 weeks of use.
    b. Normalization of seminal quality returns after discontinuation of finasteride
  - **Sexual Dysfunction** (Overall rate of sexual dysfunction 3.7%)
    a. Impotence 5-8% incidence
    b. Decreased libido-2.6-6.4 %
    c. Decreased ejaculatory volume-1.5-3.7%
    d. Ejaculation Disorders-0.2-0.8%
    e. Breast tissue dysfunction-0.9-2.5%

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020180s037lbl.pdf, accessed January 25, 2021

Finasteride Package Insert

- **Side Effects:**
  - **Common Cold Like S/S**
  - **Less Common S/S**

    Bloating , Swelling, Breast enlargement and tenderness, Hives, Rapid weight gain, Tingling of the hands or feet
  - **Reported, But of Less Known Incidence**
    - **Breast tissue dysfunction (Why?)**
      - **Discharge from the nipple**
      - **Inverted nipple**
      - **Persistent crusting or scaling of the nipple**
      - **Dimpling of the breast skin**
      - **Lump in the breast or under the arm**
      - **Redness or swelling of the breast**
      - **Sore on the skin of the breast that does not heal**

Finasteride Package Insert

- **Drug Interactions**
  - ***Saw Palmetto***
    - **MOA: 5 Alpha Reductase Inhibitor**
      - » **Cumulative Effect between Finasteride and Saw Palmetto**
  - ***Soy***
    - **MOA: 5 alpha reductase inhibitor**
  - ***Terazosin***
    - **Effect: Increased finasteride concentration by 16%**

Post Finasteride Syndrome-The Skeptics

"Side Effects are Relatively Rare"

2018 # of Rx. Written:

- **Finasteride 8,876,331 (87th Most Commonly Prescribed Medication)**
- **Dutasteride 1,337,420 (288th Most Commonly Prescribed Medication)**

Sexual Dysfunction (Overall rate of sexual dysfunction 3.7%) = *337,908 Patients/94,477 (If each Rx was for 90 Days)*

a. **Impotence 5-8% incidence (510-817K)/(127-204K)**
b. **Decreased libido-2.6-6.4 %**
c. **Decreased ejaculatory volume-1.5-3.7%**
d. **Ejaculation Disorders-0.2-0.8%**
e. **Breast tissue dysfunction-0.9-2.5%**

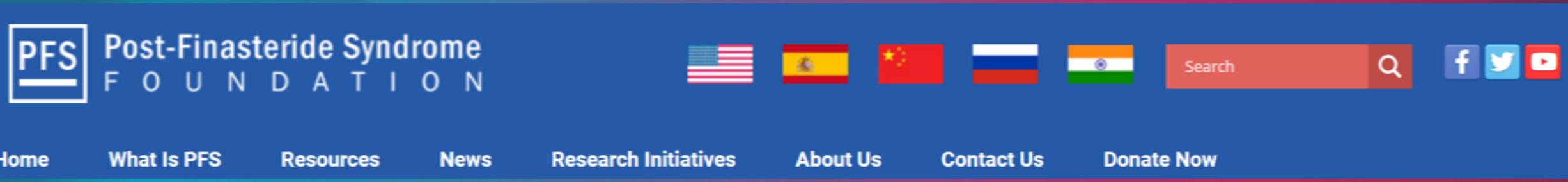
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020180s037lbl.pdf, accessed January 25, 2021

Post Finasteride Syndrome
a Prime-Time Example of
The Law of Unintended Consequences

- **A Funny Thing Happened on the Way to A Full Head of Hair**
  - Patients Complained of a Constellation of Symptoms
  - Many S/S Persisted Long After Discontinuation of the Drug
  - Some claim PERMANENT Side Effects
- **Peculiarities**
  - More common on lower dose 1 mg. hair loss dose
  - More common in younger men (Age 18-43, on average)
- **? Is this Real or as Some Claim:**
  - "An Induced Delusional Disorder with the Potential for Mass Psychogenic Illness"

Post Finasteride Syndrome has its Own Website

"Is it Real or a Delusion?"

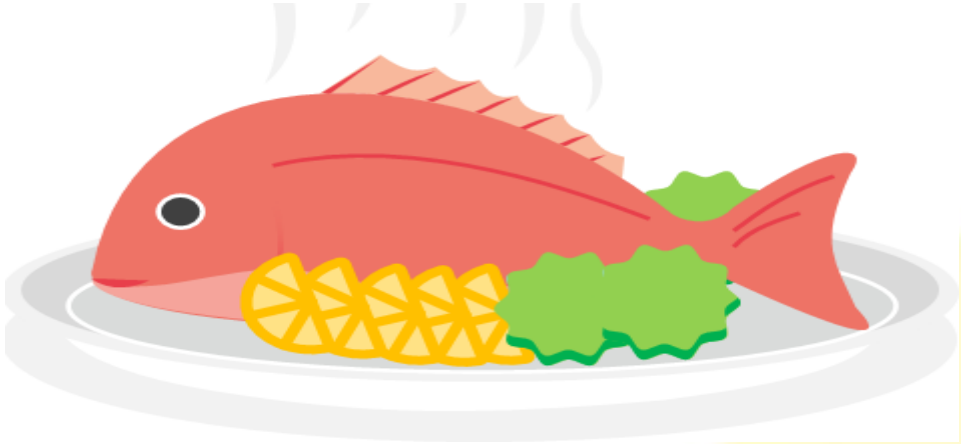


"The Post-Finasteride Syndrome Foundation's primary mission is to facilitate research on the characterization, underlying biologic mechanisms and treatments of post-finasteride syndrome (PFS). "

"Other goals include generating public awareness of PFS and providing support for patients suffering from the condition."

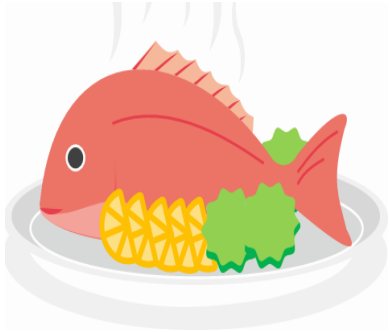
Post Finasteride Syndrome-The Skeptics

- **“An Induced Delusional Disorder with the Potential for Mass Psychogenic Illness”**
  - Trüeb R, M, Régnier A, Dutra Rezende H, Gavazzoni Dias M, F, R: Post-Finasteride Syndrome: An Induced Delusional Disorder with the Potential of a Mass Psychogenic Illness? Skin Appendage Disord 2019;5:320-326. doi: 10.1159/000497362



- **Southern Illinois University Chair of Urology found it “Fishy”**
  - **“There is no drug in the history of medicine where the risk decreases as the dose increases.**
  - **Young men are being hypnotized on the internet by the power of suggestion.”**
    - Marshall, L., The Medical Mystery Behind America's Best-Selling Hair-loss Drug. Vice.com. Mover 21, 2016. https://www.vice.com/en/article/gqywem/the-medical-mystery-behind-americas-best-selling-hair-loss-drug

Drugs with Risks at Lower Doses than Higher Ones



i. **HMG-CoA reductase inhibitors**
ii. **Plasminogen activator-1 (PAI-1)**
iii. **TGF-β1**
iv. **Endostatin**
v. **PPARγ ligand: *Rosiglitazone***
vi. **Low Dose versus high dose Naltrexone**

- Urbich C, Dernbach E, Zeiher AM, Dimmeler S. Double-edged role of statins in angiogenesis signaling. Circ Res. 2002;90:737–44
- Devy L, Blacher S, Grignet-Debrus C, Bajou K, Masson V, Gerard RD, Gils A, Carmeliet G, Carmeliet P, Declerck PJ, Noel A, Foidart JM. The pro- or antiangiogenic effect of plasminogen activator inhibitor 1 is dose-dependent. FASEB J. 2002;16:147–54
- Celik I, Surucu O, Dietz C, Heymach JV, Force J, Hoschele I, Becker CM, Folkman J, Kisker O. Therapeutic efficacy of endostatin exhibits a biphasic dose-response curve. Cancer Res. 2005;65:11044–50.
- Panigrahy D, Singer S, Shen LQ, Butterfield, CE, Freedman DA, Chen EJ, Moses MA, Kilroy S, Duensing S, Fletcher C, Fletcher JA, Hlatky L, Hahnfeldt P, Folkman J, Kaipainen A. PPAR gamma ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. J Clin Invest. 2002 Oct;110(7):923-32. doi: 10.1172/JCI15634. PMID: 12370270; PMCID: PMC151148.

Permanent Side Effects? Pish Posh

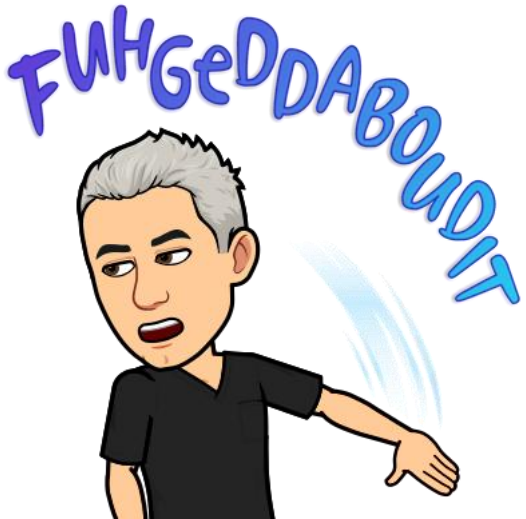
New Study Links Finasteride to Long-Term Sexual Dysfunction

Finasteride users may experience severe sexual side effects for months or years after they discontinue use of the medication.

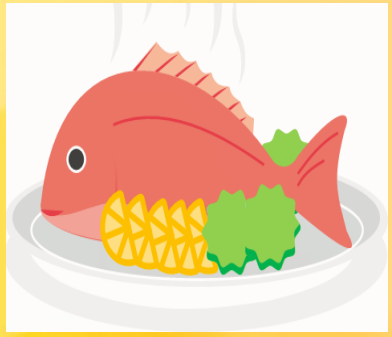
Kiguradze T, Temps WH, Yarnold PR, Cashy J, Brannigan RE, Nardone B, Micali G, West DP, Belknap SM. Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors, finasteride, or dutasteride. PeerJ. 2017 Mar 9;5:e3020. doi: 10.7717/peerj.3020. PMID: 28289563; PMCID: PMC5346286.

"No Drug has Ever Been Documented to Cause Permanent Side Effects"

Trüeb R, M, Régnier A, Dutra Rezende H, Gavazzoni Dias M, F, R: Post-Finasteride Syndrome: An Induced Delusional Disorder with the Potential of a Mass Psychogenic Illness? Skin Appendage Disord 2019;5:320-326. doi: 10.1159/000497362



True or False



Permanent Side Effects?

Is This Even Possible?

Permanent Side Effects?
It's Never Happened. Right?
Is This Even Possible?

1. *Neuroleptic Agents*
   a. Tardive Dyskinesia-Antipsychotic (phenothiazines) meds/GI meds (metoclopramide) reduce intracranial hormones
      i. Sometimes permanent condition of involuntary movements of the tongue, lips, face, trunk, and extremities
2. *Alcohol*
   a. Korsakoff's Syndrome, motor control loss, gait dysfunction, visual Disturbances, cardiomyopathy, cirrhosis
3. *Cocaine*
   a. Hypertension, nasal passage necrosis, acute MI, cognitive deficits, premature ASVD, premature loss of brain volume
4. Ketamine
   a. Visual disturbance, bladder dysfunction, ulcerative cystitis, hydronephrosis
5. *Anabolic Steroids*
   a. Premature ASVD, cardiomyopathy, testicular function suppression, prostate CA.,
   b. Major mood disorders, AAS dependence
   c. Neuropsych. deficits

Post Finasteride Syndrome

Adverse Reactions Persisting for at least Three Months After Discontinuation of Use

Sexual
Side Effects

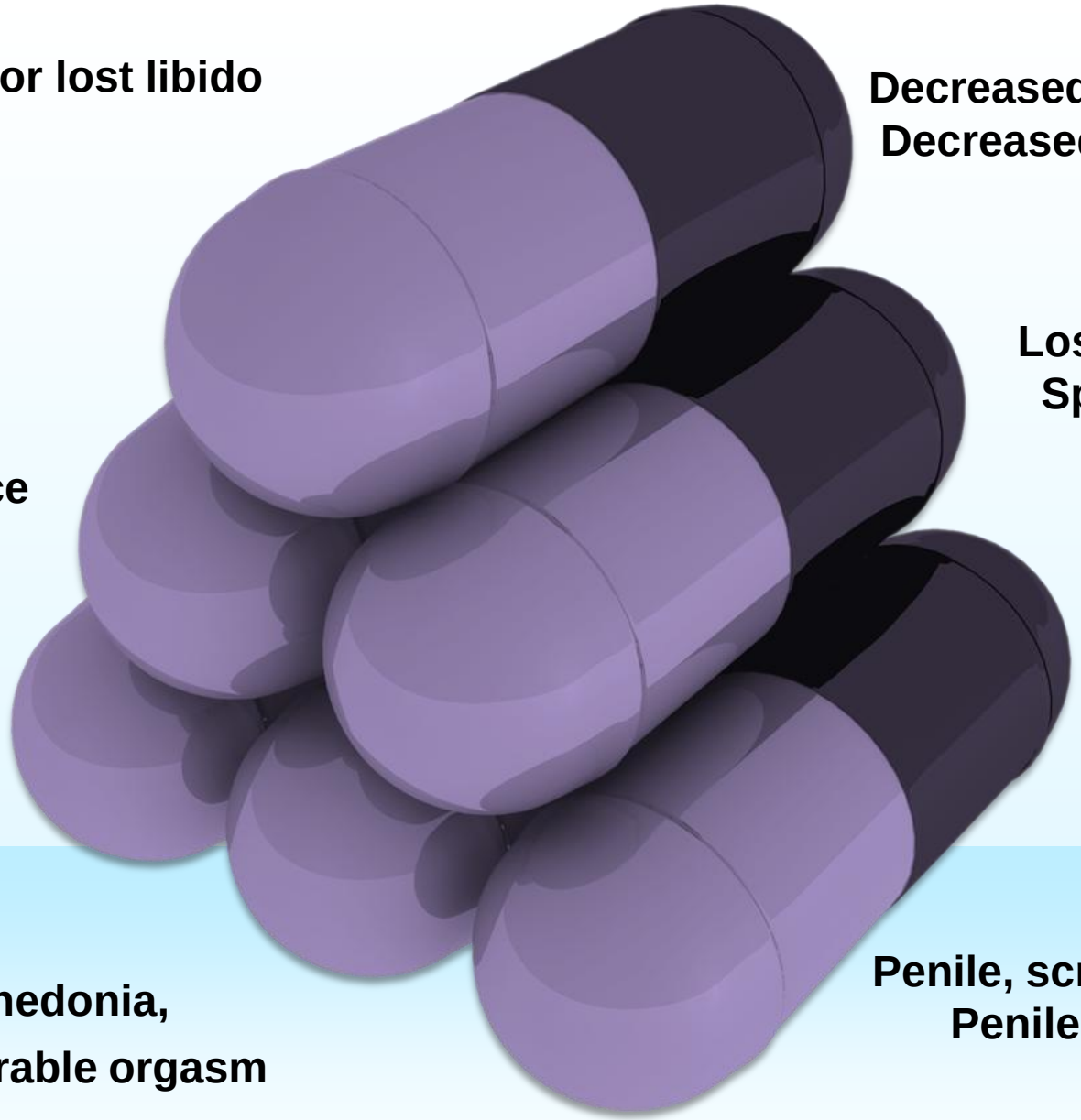
"General"
Side Effects

Mental/Neurological
Side Effects

Post Finasteride Syndrome-Sexual Side Effects

Decreased or lost libido

Decreased semen volume
Decreased semen force



Loss of AM and Spontaneous Erections

ED, Impotence

Peyronie's Disease (Scar Tissue)

Sexual anhedonia,

Loss of pleasurable orgasm

Penile, scrotal shrinkage
Penile numbness

Post Finasteride Syndrome-"General" Symptoms

Chronic Fatigue, Apathy

Gynecomastia

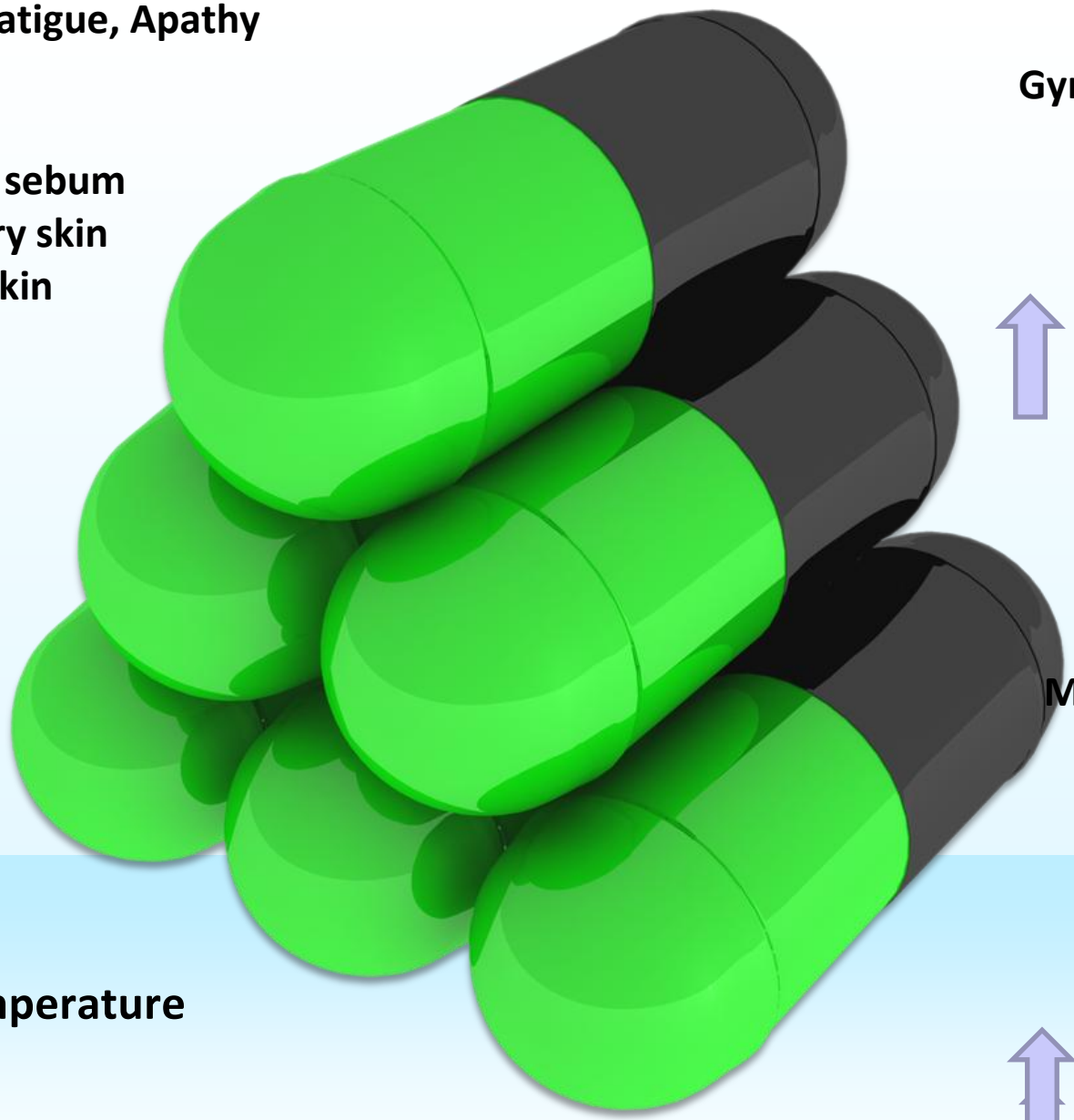
Decreased oil, sebum
Chronically dry skin
Thinning Skin

Fat deposition,
Obesity
BMI

Melasma

Muscle atrophy
Muscle weakness

Tinnitus



Body Temperature

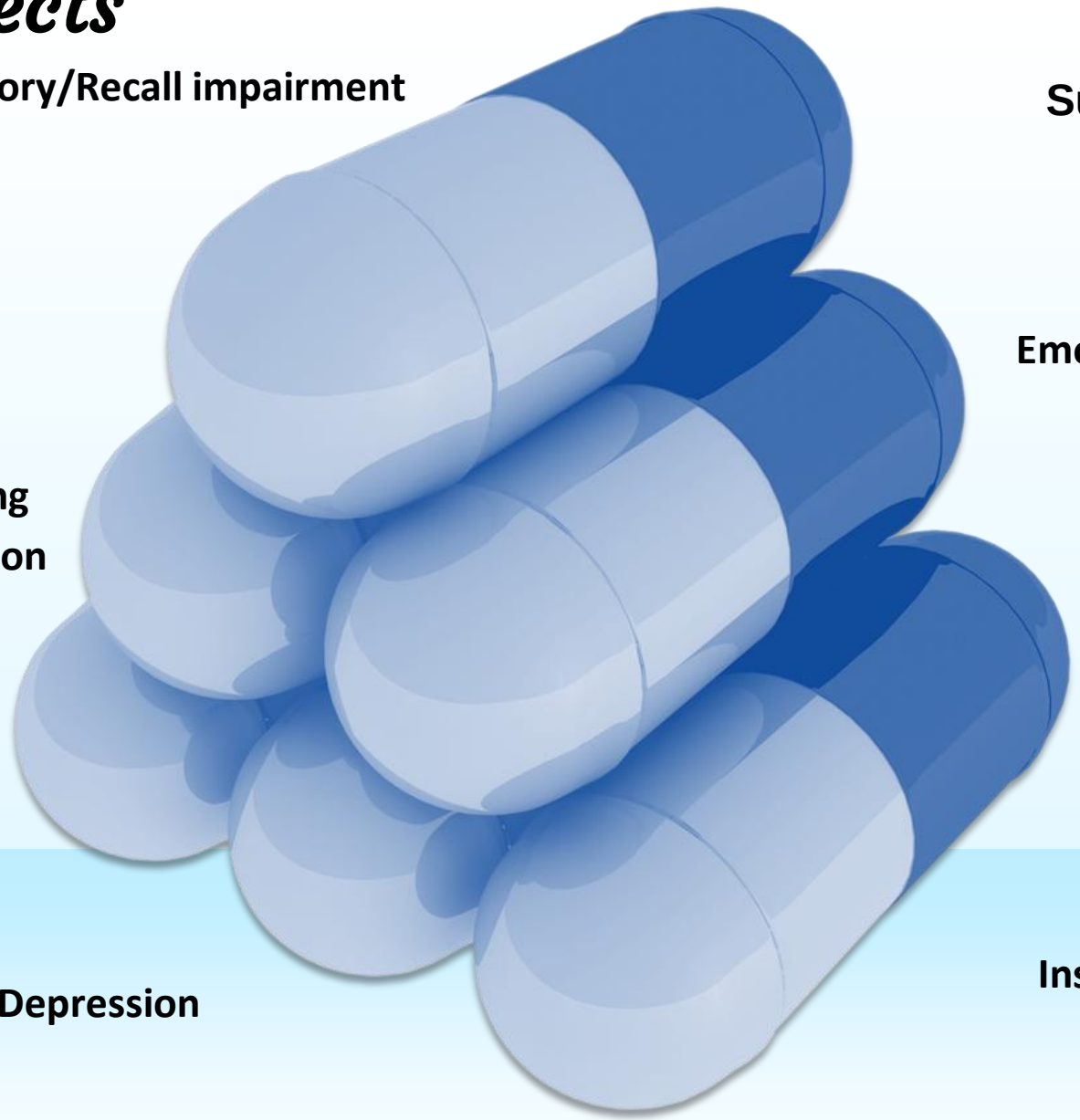
HDL

Glucose
Triglycerides

Post Finasteride Syndrome-Mental Neurological Side Effects

Severe memory/Recall impairment

Suicide Ideation



Emotional flatness

Anhedonia

Impaired problem solving

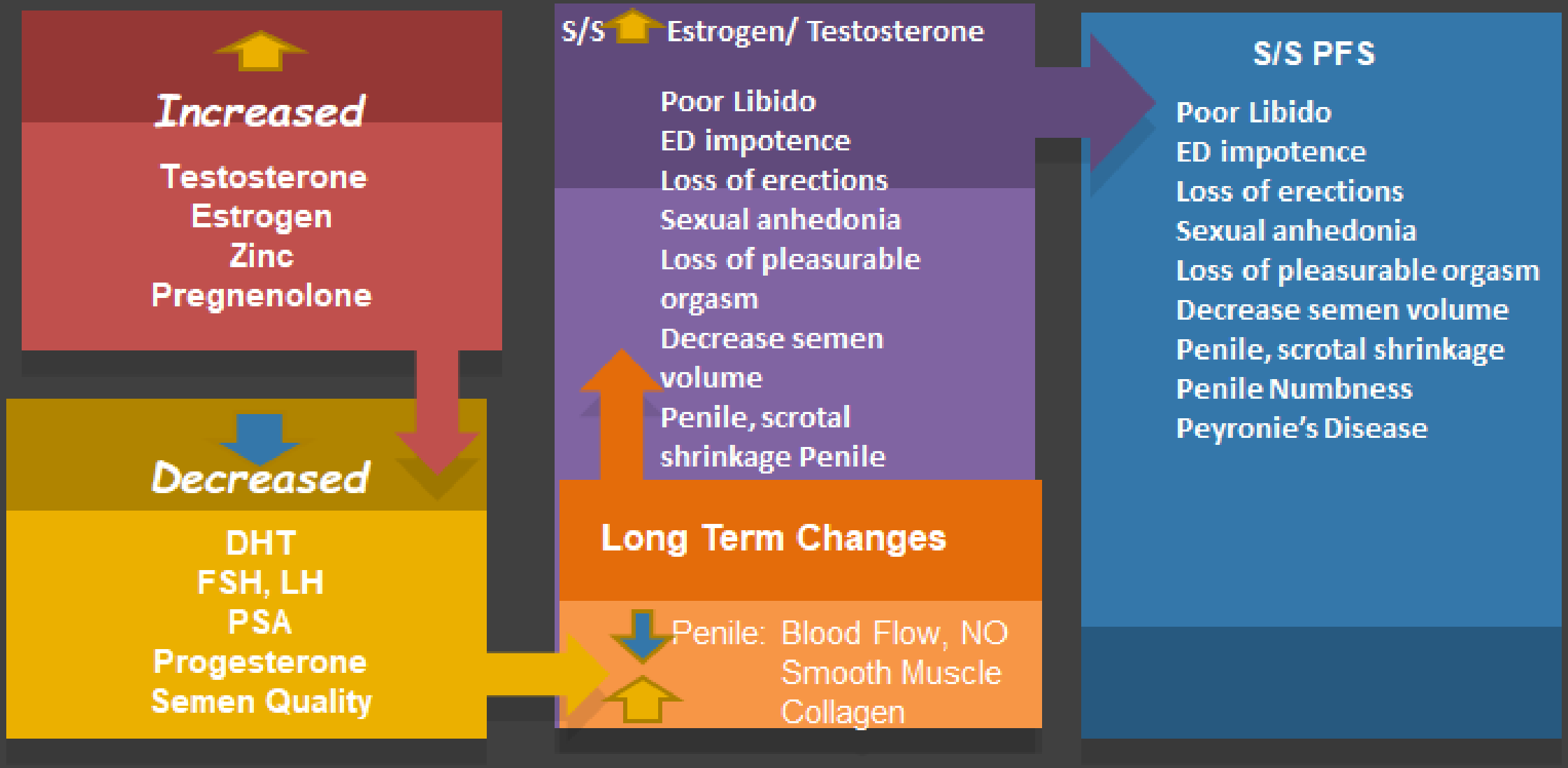
Decreased comprehension

Anxiety

Depression

Insomnia

5 Alpha Reductase Inhibition-Sexual Side Effects



Sexual Side Effects -The Evidence

Vascular Insufficiency **-68% of patients w > 3 mo. 5ARI exhibit significant decreases in penile arterial blood flow**

Khera, Mohit et al. "Penile vascular abnormalities in young men with persistent side effects after finasteride use for the treatment of androgenic alopecia." Translational andrology and urology vol. 9,3 (2020): 1201-1209. doi:10.21037/tau.2020.03.21

Erectile Dysfunction- **50% mean decrease in intracavernosal pressures. Decrease in nitric oxide synthase**

Gur S, Kadowitz PJ, Hellstrom WJ. Effects of 5-alpha reductase inhibitors on erectile function, sexual desire, and ejaculation. Expert Opin Drug Saf. 2013 Jan;12(1):81-90. doi: 10.1517/14740338.2013.742885. Epub 2012 November 22. PMID: 23173718.

Loss of Libido- **Abnormal somatosensory evoked potentials of the pudendal nerve.**

Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, Diviccaro S, Giatti S, Carrà G, Caruso D, Simoni M, Cavaletti G. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017 July;171:229-235. doi: 10.1016/j.jsbmb.2017.04.003. Epub 2017 Apr 10. PMID: 28408350

Sexual Side Effects -The Evidence

Anhedonia- ↓ nitric oxide synthase. ↓ allopregnanolone ↓ GABA

Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, Diviccaro S, Giatti S, Carrà G, Caruso D, Simoni M, Cavaletti G. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017 July;171:229-235. doi: 10.1016/j.jsbmb.2017.04.003. Epub 2017 Apr 10. PMID: 28408350

Kim, Yoo Sung, and Bo-Eun Yoon. "Altered GABAergic Signaling in Brain Disease at Various Stages of Life." Experimental neurobiology vol. 26,3 (2017): 122-131. doi:10.5607/en.2017.26.3.122

Sperm Function- ↓ sperm count, volume, concentration, motility

Samplaski MK, Lo K, Grober E, Jarvi K. Finasteride use in the male infertility population: effects on semen and hormone parameters. Fertil Steril. 2013 Dec;100(6):1542-6. doi: 10.1016/j.fertnstert.2013.07.2000. Epub 2013 September 4. PMID: 24012200.

Penile and Testicular Shrinkage; Peyronie's Disease

↑ corpus cavernosa collagen density. Atrophy of prostatic and penile epithelial tissue. Decrease in smooth muscle tissue

1. Kilic S, Kolukcu E, Erdemir F, Benli I, Arici A. The Effects of Oral 5-alpha Reductase Inhibitors on Penile Intracavernosal Pressures and Penile Morphology in Rat Model. Urol J. 2019 May 5;16(2):205-211. doi: 10.22037/uj.v0i0.4164. PMID: 30058066.
2. Da Silva, Marcello H A, et al. "The corpus cavernosum after treatment with dutasteride or finasteride: A histomorphometric study in a benign prostatic hyperplasia rodent model." Asian Journal of andrology vol. 20,5 (2018): 505-510. doi:10.4103/aja.aja_28_18

Sexual Side Effects - The Evidence

Pelvic Neuropathy

Abnormal somatosensory evoked potential of the pudendal nerve

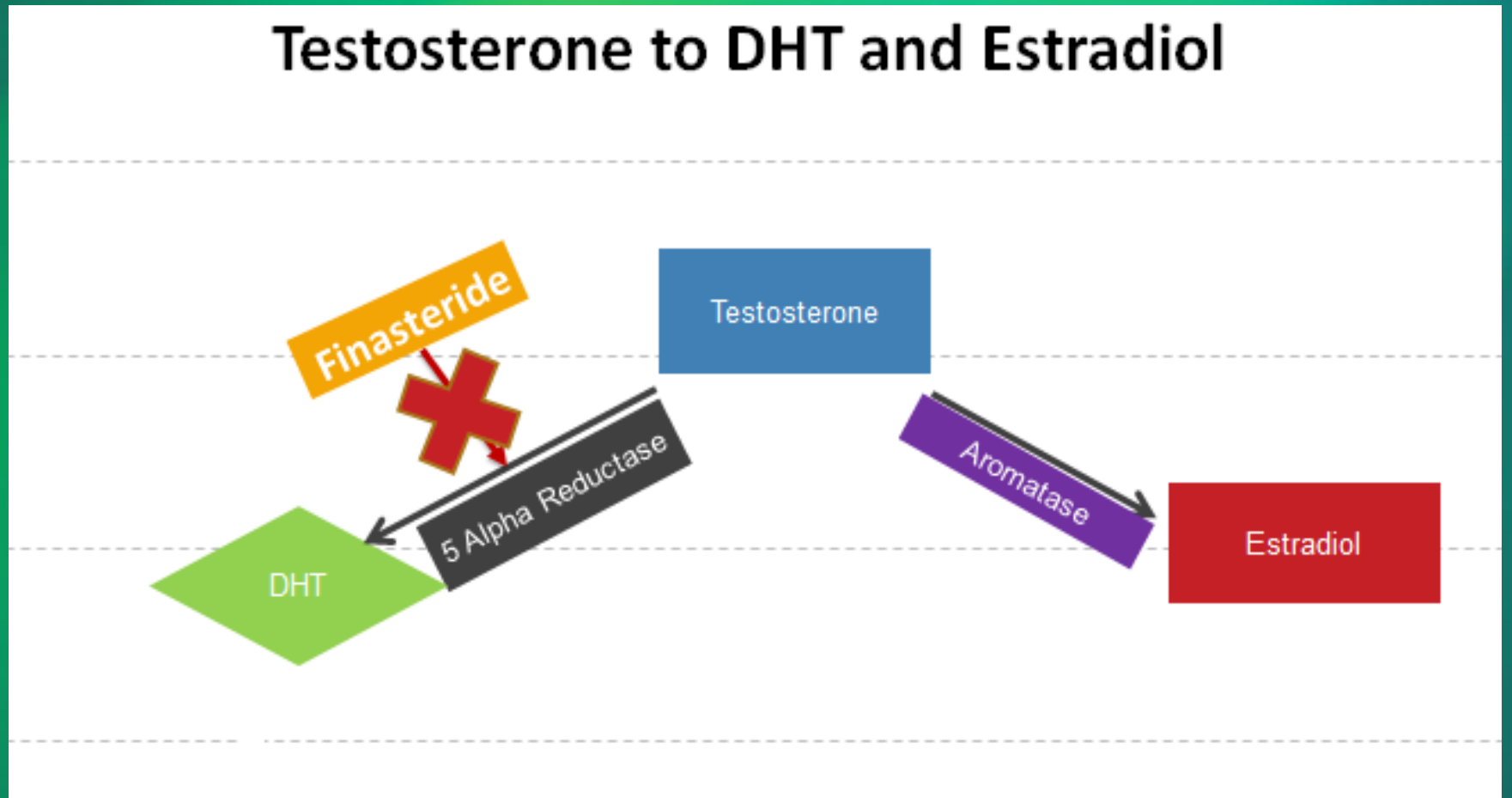
Decrease in androgen receptor density

Di Loreto, Carla et al. "Immunohistochemical evaluation of androgen receptor and nerve structure density in human prepuce from patients with persistent sexual side effects after finasteride use for androgenetic alopecia." PloS one vol. 9,6 e100237. June 24. 2014, doi:10.1371/journal.pone.0100237

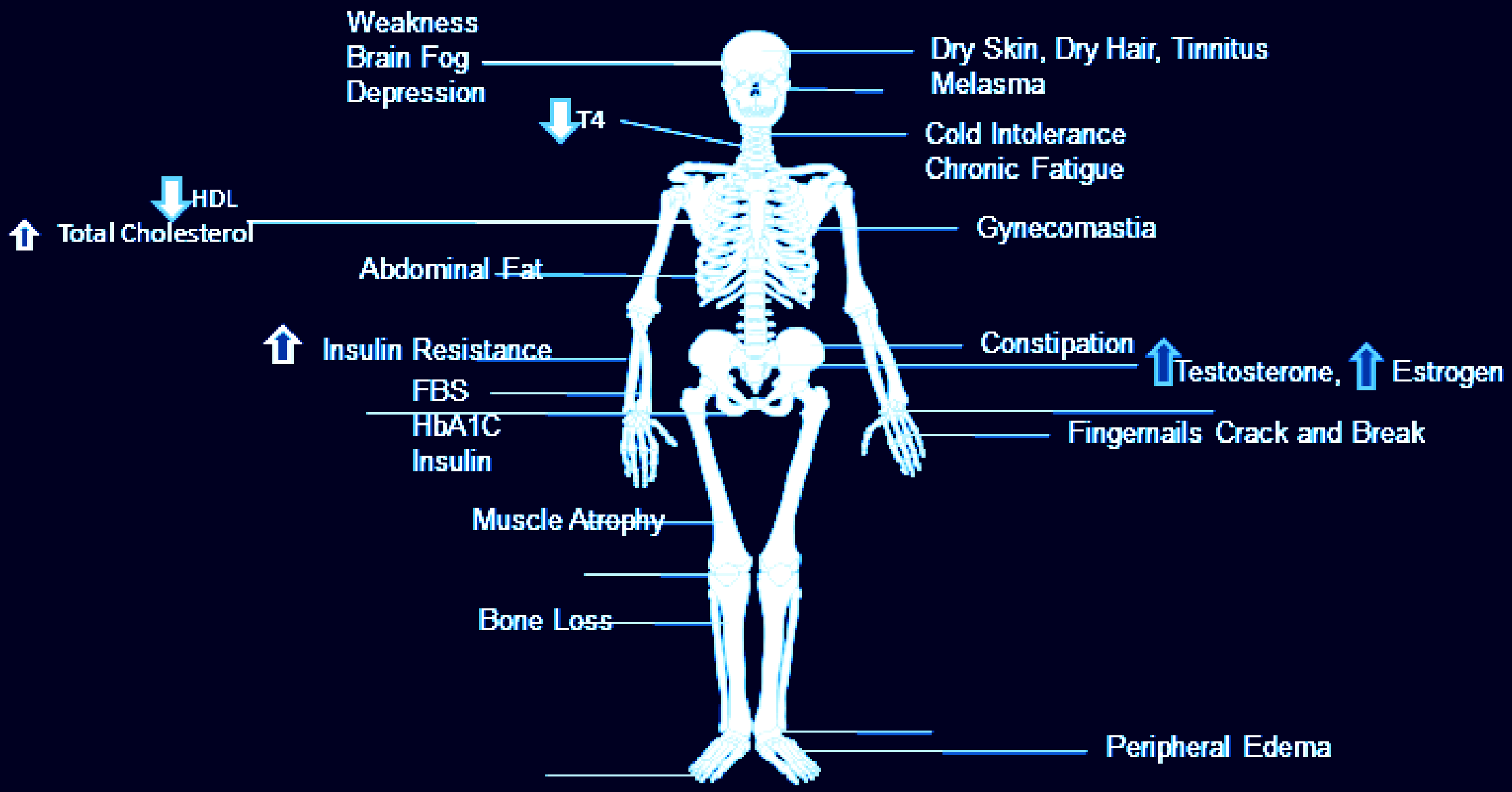
Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, Diviccaro S, Giatti S, Carrà G, Caruso D, Simoni M, Cavaletti G. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017 Jul;171:229-235. doi: 10.1016/j.jsbmb.2017.04.003. Epub 2017 Apr 10. PMID: 28408350

"General" Side Effects-The Evidence

- **Blocked Testosterone has to go somewhere**
- **DHT Metabolizes to Estradiol**



"General" Side Effects



Oral Cavity Anomalies

Erythema

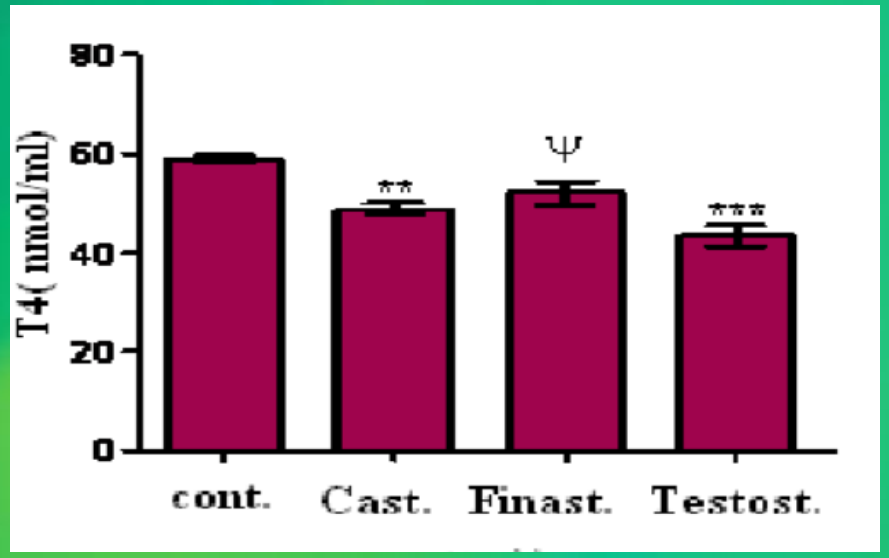
Purpura

Gingival hypertrophy

Paunica, Stana; Giurgiu, Marina; Vasilache, Andrei; Paunica, Ioana; Motofei, Ion; Vasilache, Adriana; Dumitriu, Horia Traian; and Dumitriu, Anca Silvia (2016) "Finasteride adverse effects and post-finasteride syndrome; implications for dentists," Journal of Mind and Medical Sciences: Vol. 3 : Iss. 1 , Article 9. Available at: http://scholar.valpo.edu/jmms/vol3/iss1/9

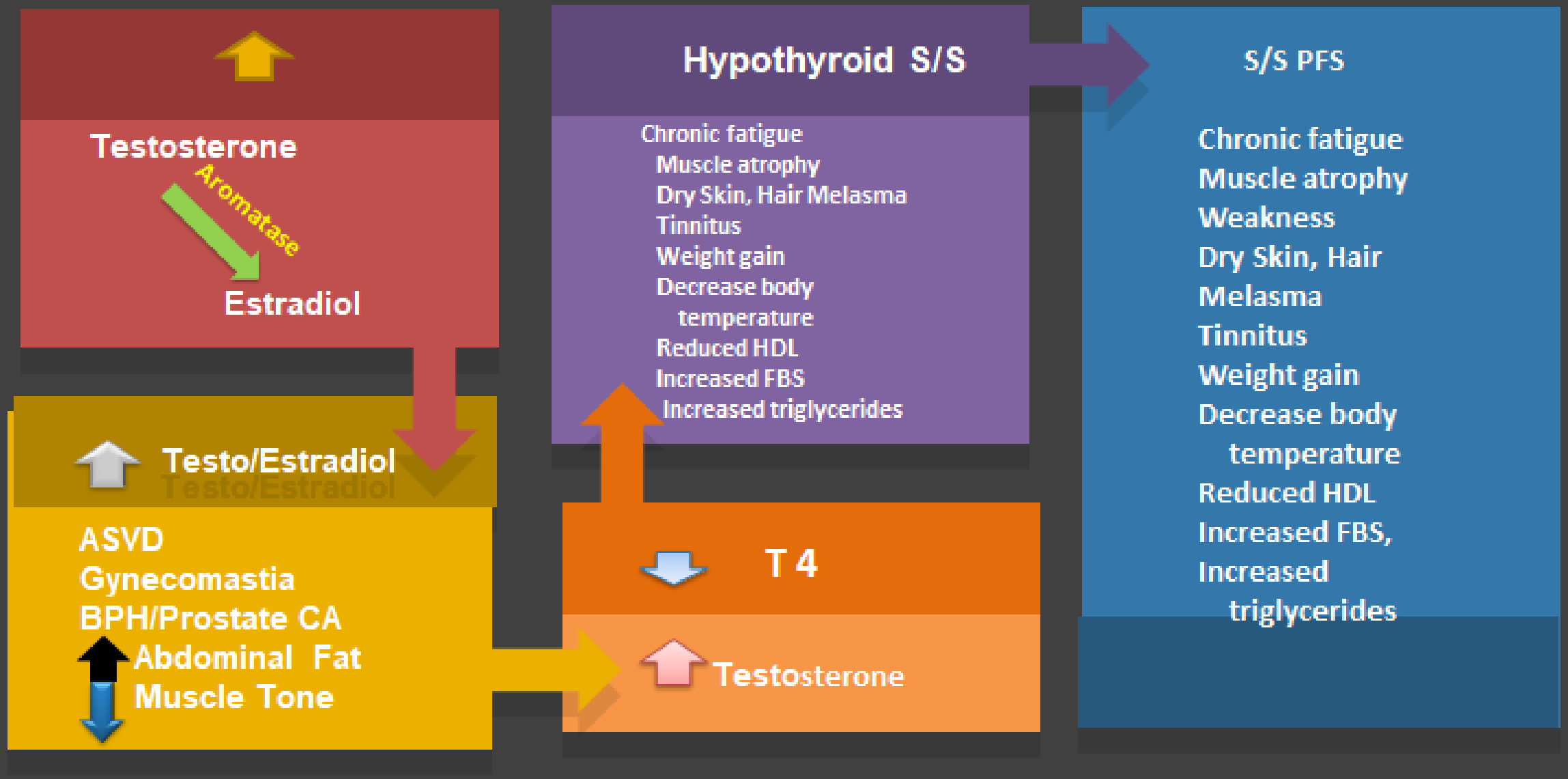
"General" Side Effects-The Evidence

Testosterone Levels are Inversel Related to Thyroid Function



- https://www.nhs.uk/conditions/underactive-thyroid-hypothyroidism/symptoms/
- Famenini S, Gharavi NM, Beynet DP. Finasteride associated melasma in a Caucasian male. J Drugs Dermatol. 2014 Apr;13(4):484-6. PMID: 24719069.
- Zarei, Fatemeh & Yousofvand, Namdar & Khazaei, Mozafar & Ghanbari, Ali. (2013). Effect of Exogenous Testosterone, Finasteride, and Castration on Serum Level of Thyroxine. Iranian Biomedical Journal. 17. 221-4. 10.6091/ibj.1234.2013.
- Chen, Dawei et al. "The association between subclinical hypothyroidism and erectile dysfunction." *Pakistan journal of medical sciences* vol. 34,3 (2018): 621-625. doi:10.12669/pjms.343.14330

5 Alpha Reductase Inhibition-"General Side Effects"



Mental/Psychological Effects-The Evidence

- **How Could These Symptoms Possibly Relate to 5ARI's?**
  - **Memory Loss**
  - **Slowed Thoughts**
  - **Mood Changes**
  - **Parkinson's Like Symptoms**
  - **Decreased Comprehension**
  - **Anxiety/Depression**
  - **Suicidal Ideation**
  - **Insomnia**
  - **Emotional Flatness**

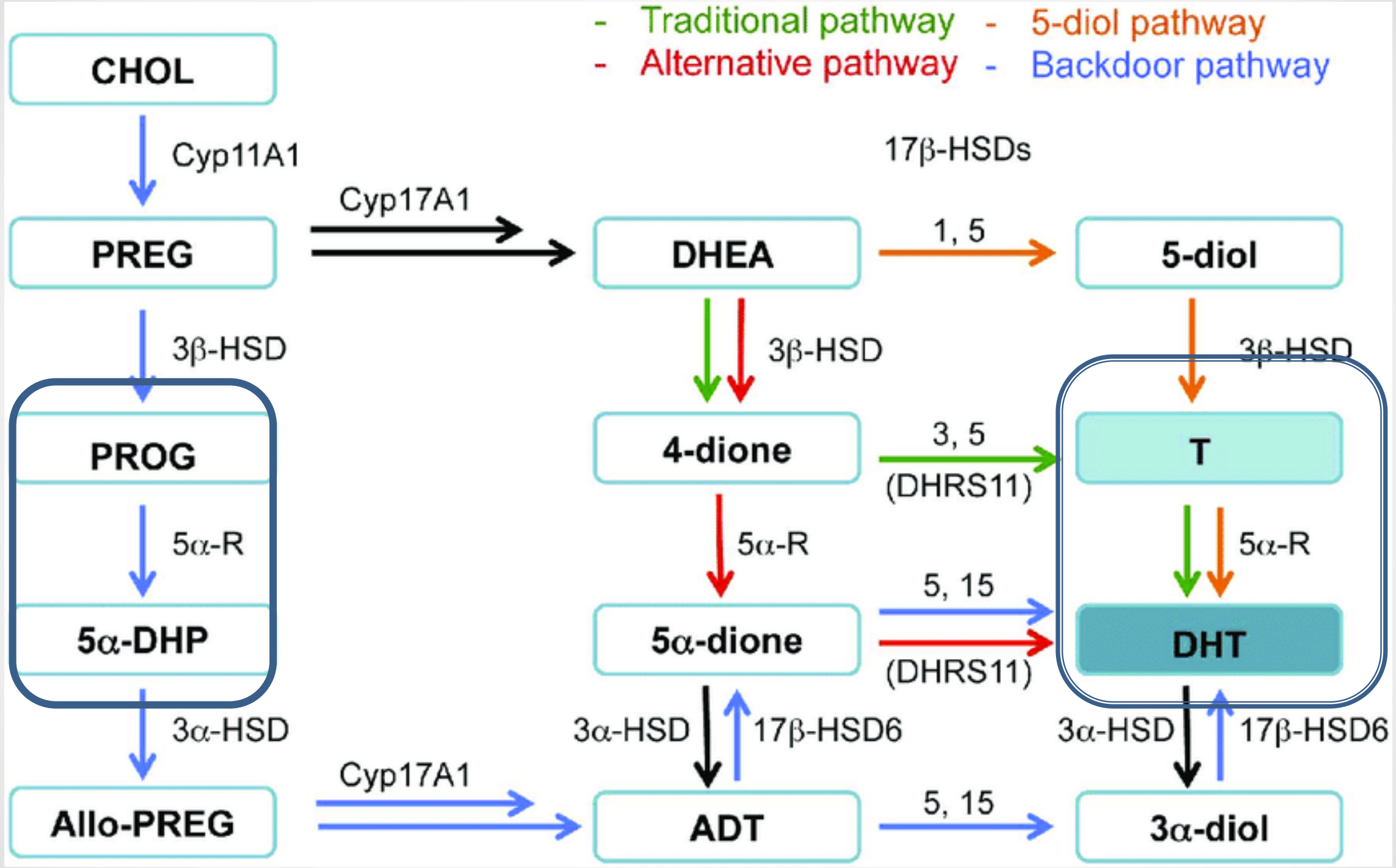
Mental/Physical Effects

- Memory Loss
- Anxiety
- Depression
- Slowed Thoughts
- Suicide Ideation
- Mood Changes t
- Insomnia
- Decreased Comprehension
- PTSD
- Apathy

Your Logo

Mental/Psychological Effects-The Evidence

- **Neurosteroids**
  - Hormones manufactured regionally in the brain
  - Follow the same Steroidogenic Pathway as peripherally generated "neuroactive" steroids.
  - Regulate the excitatory/inhibitory balance of the neurotransmitters glutamate and GABA.
  - Act as "micro-hormones," fine-tuning the peripheral "macro-hormones."
  - Sufficient GABA levels relieve anxiety, reduces stress, improves sleep, and are neuroprotective.

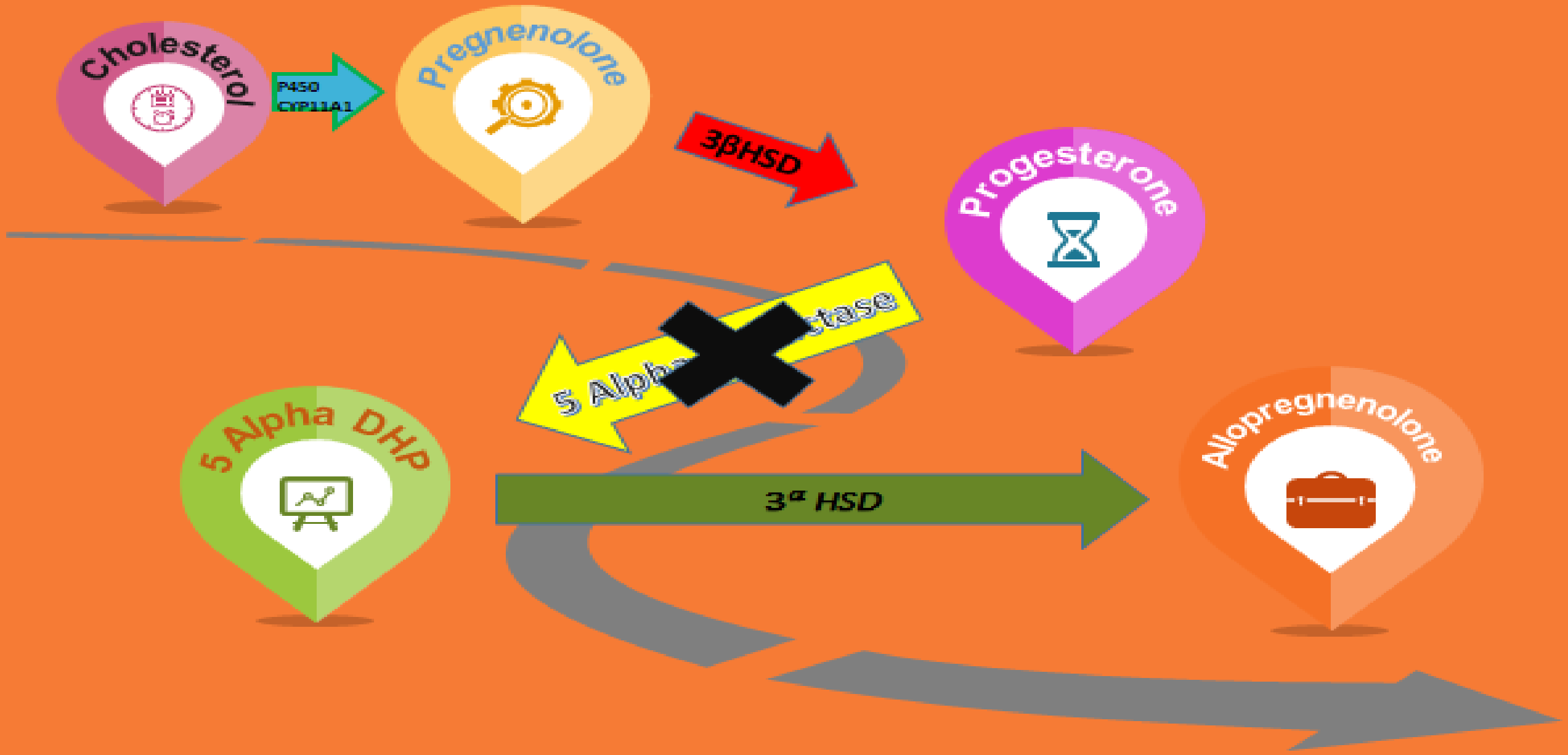

- Traditional pathway
- Alternative pathway
- 5-diol pathway
- Backdoor pathway
CHOL
Cyp11A1
PREG
Cyp17A1
17β-HSDs
DHEA
1, 5
5-diol
3β-HSD
3β-HSD
3β-HSD
PROG
4-dione
3, 5
(DHRS11)
T
5α-R
5α-R
5α-R
5α-DHP
5α-dione
5, 15
(DHRS11)
DHT
3α-HSD
3α-HSD
17β-HSD6
3α-HSD
17β-HSD6
Cyp17A1
Allo-PREG
ADT
5, 15
3α-diol

Mental/Psychological Effects-The Evidence

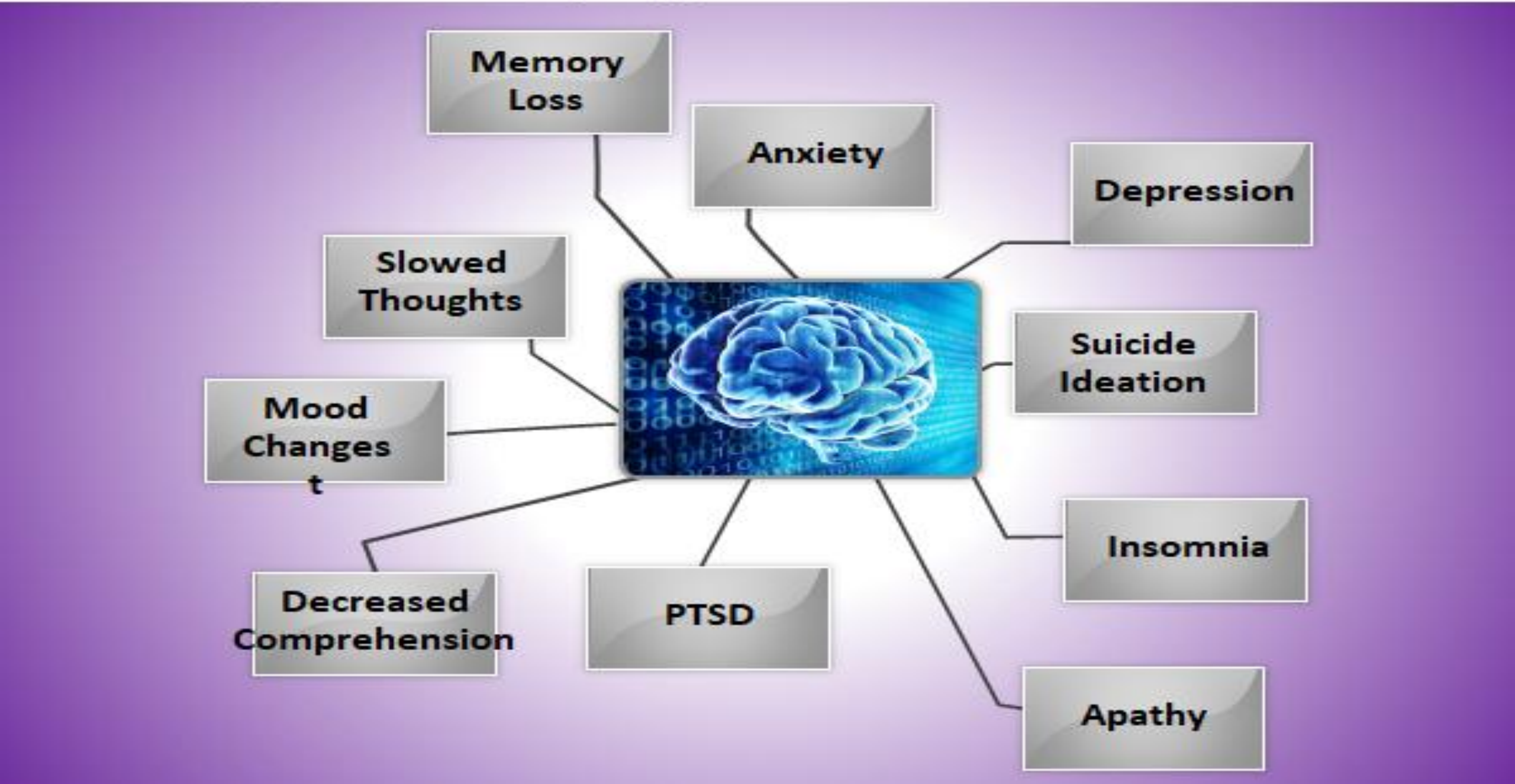
- Neurosteroids are generated from cholesterol by a series of steps that include the trafficking of cholesterol to a cell's outer mitochondrial membrane using the steroidogenic acute regulatory protein (StAR). The StAR protein shuttles cholesterol to the cell's inner mitochondrial membrane via translocator protein 18 kDa (TSPO).
-
- These maneuvers set in motion cholesterol's conversion to allopregnanolone by way of [73]

1. Pregnenolone via the P450 side-chain cleavage enzyme, CYP11A1 then:
2. Progesterone by the sequential actions of the 3β-hydroxysteroid dehydrogenase/isomerase enzyme. Then:
3. Progesterone converts to 5-α-dihydroprogesterone (3α-DHP) via:
   a. Wait for it, sports fans! It's so exciting. I can't hold back anymore…….
   b. …. *5α-reductase!*
   c. Yes, sports fans, the same enzyme that reduces prostate enlargement and regrows
      - hair, converts cholesterol (via the 3β-hydroxysteroid dehydrogenase/isomerase enzyme. [74]

The Hidden Pathway: Progesterone to Allopregnenolone



S/S ↓ Allopregnanolone ↓ GABA



5ARI = ↓ Allopregnanolone = ↓ GABA. [75]

Decreased GABA S/S

- Memory Loss
- Slowed Thought Process
- Mood Changes
- Impulsive Aggression
- Decreased Comprehension
- Anxiety/Depression
- Suicide Ideation
- Insomnia
- Emotional Flatness

PFS Mental/Psych S/S

- Memory Loss
- Slowed Thoughts
- Mood Changes
- Parkinson's Like Symptoms
- Decreased Comprehension
- Anxiety/Depression
- Suicidal Ideation
- Insomnia
- Emotional Flatness

More S/S ↓ Allopregnanolone = ↓ GABA. (75)

- Premenstrual dysphoric disorder
- PTSD
- Negative symptoms of schizophrenia
- Anorexia or obesity
- Severe recall impairment
- Impaired problem solving,
- Panic attacks
- Phobias
- Psychosis
- Suicide ideation and impulsive aggression. (76-78)

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2. Schüle, Cornelius & Nothdurfter, Caroline & Rupprecht, Rainer. (2013). The role of Allopregnanolone in Depression and Anxiety. Progress in neurobiology. 113. 10.1016/j.pneurobio.2013.09.003
3. J. Strömberg, D. Haage, M. Taube, T. Bäckström, P. Lundgren, Neurosteroid modulation of allopregnanolone and GABA effect on the GABA-A receptor, Neuroscience,Volume 143, Issue 1, 2006,Pages 73-81,ISSN 0306-4522, https://doi.org/10.1016/j.neuroscience.2006.07.031.
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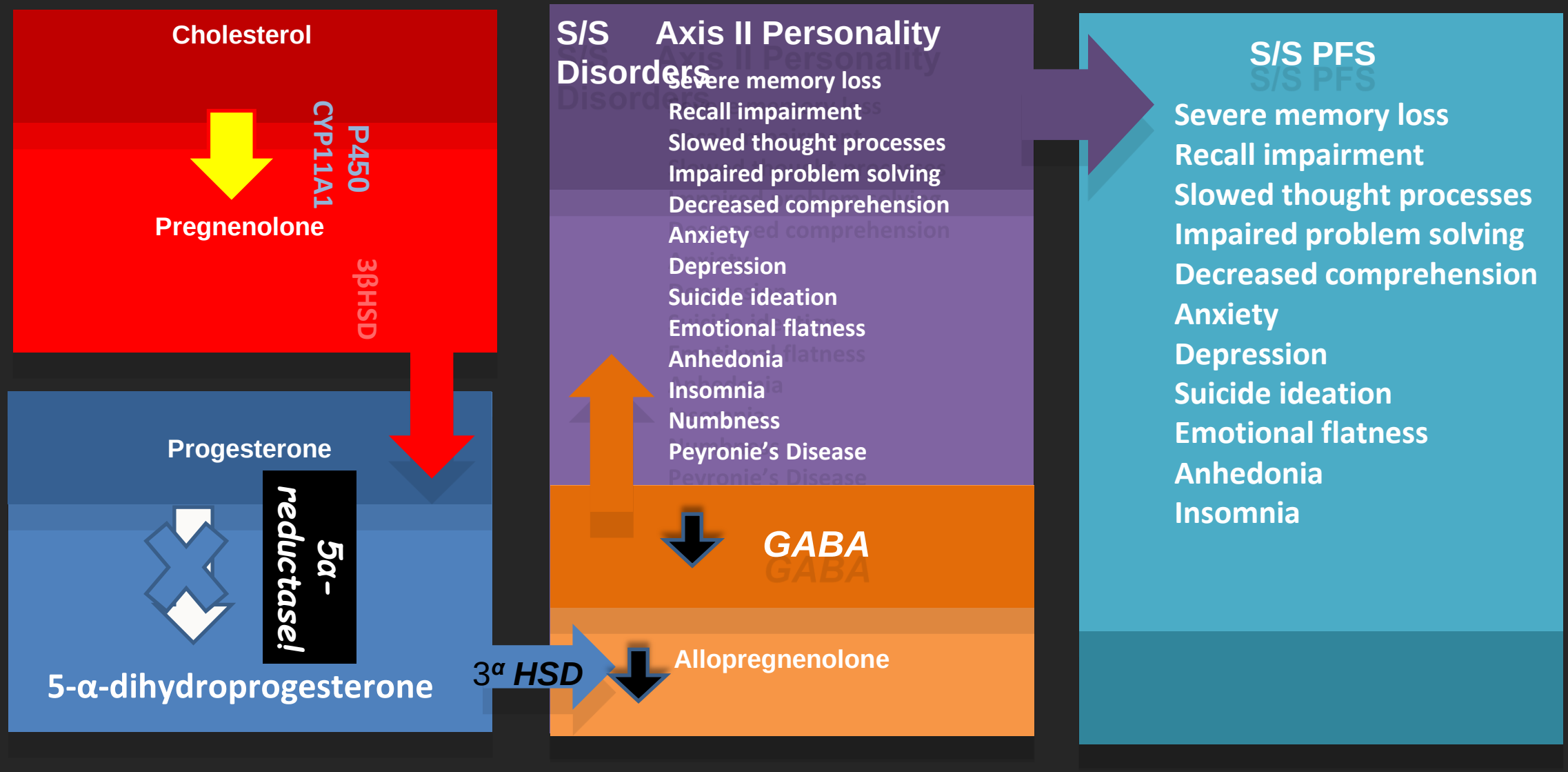
5 Alpha Reductase Inhibition-Mental/Neurological



A Word on Suicide and Finasteride

Men ages 18-45 years (Years 1998 and 2013)-1 mg Finasteride x 6 months

2015 Retrospective Pharmacovigilance Disproportionality Analysis:

4910 adverse effects associated with low dose (1 mg/day) finasteride use.

- **Suicide ideation incidence 0.7%**
- **87% of these men suffered from concomitant depression and insomnia.**
- **11.8 % suffered from persistent sexual dysfunction**
- **7.9% harbored suicidal thoughts**
- **15 % with suicidal thoughts completed suicide.**

1. Nguyen D, Marchese M, Cone EB, et al. Investigation of Suicidality and Psychological Adverse Events in Patients Treated With Finasteride. *JAMA Dermatol.* 2021;157(1):35–42. doi:10.1001/JAMA Dermatol.2020.3385
2. Ali AK, Heran BS, Etminan M. Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study. Pharmacotherapy. 2015 Jul;35(7):687-95. doi: 10.1002/phar.1612. Epub 2015 July 1. PMID: 26133534
3. Ali AK, Heran BS, Etminan M. Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study. Pharmacotherapy. 2015 Jul;35(7):687-95. doi: 10.1002/phar.1612. Epub 2015 July 1. PMID: 26133534.

Suicide and Finasteride

- **January 2021 Court Record Release**
  - **2011-Present**
    - **700 Reports of Suicide Ideation (4x expected rate for non treated population)**
    - **356 Deaths (63% increased incidence vs. non treated population)**
  - **1997-2010**
    - **34 Reports of Suicide Ideation**
    - **10 Reports of Suicide completion**
    - **4x incidence of depression and anxiety vs. non treated population**
  - **Suicide more common with lower dose 1 mg finasteride and in younger population (age 18-45)**
  - **Manufacturer Stance:**
    - **"Premature hair loss itself is associated with low self-esteem, poor body image, and depression."**

•Levine, D., Terhune, C., Exclusive: Merck anti-baldness drug Propecia has long trail of suicide reports, records show. *Reuters.com,* FEBRUARY 3, 2021. https://www.reuters.com/article/us-merck-propecia-suicide-exclusive-idUKKBN2A32XU

MOA-Post Finasteride Syndrome-Sexual Side Effects

Laboratory Changes

Increased vs. Control

- Testosterone 15%
- Estradiol 15%
- Pregnenolone
- Vitamin D3
- Zinc
- Insulin, Insulin Resistance
- FBS, HbA1c

Decreased vs. Control

- Progesterone 90%
- DHT 60-98%
- PSA 50 %
- FSH 24 %/LH 16%
  - Insulin Sensitivity
  - Chromium
  - Allopregnanolone
  - GABA
- Semen Analysis
  - Total Sperm Count
  - Semen volume, concentration, motility

Sexual Side Effects-Remedies

Vascular Insufficiency-

PDE-5 Inhibitors
Extracorporeal Shockwave,
Venous Ligation Surgery

Erectile Dysfunction-

PDE 5 Inhibitors, Pentoxifylline
Trimix,
Cannabis
Aromatase Inhibitors
PT-141

Loss of Libido-

Keto/Mediterranean Diet
Exercise
Mucuna pruriens
PT-141
Tribulus Terrestris
Tongkat ali
Horny Goat Weed
Maca
Fenugreek

Sexual Side Effects-Remedies

Anhedonia-

- Mediterranean Diet
- Oxytocin
- Ashwagandha
- Cannabis
- Exercise

Sperm Function

- Mucuna pruriens
- Pentoxifylline
- Shilajit
- Ashwagandha

Penile and Testicular Shrinkage; Peyronie's Disease-

- Pentoxifylline, PDE 5I
- Mucuna pruriens
- Trimix
- PRP, Exosomes

Numbness

- PT-141

"General" Side Effects Remedies

Aromatase Inhibitors

1. Anastrozole
2. Exemestane
3. Letrozole

Off Label Aromatase Inhibitors

1. Spironolactone
2. Metformin

"General" Side Effects Remedies

- **OTC Aromatase Inhibitors**
  - Resveratrol
  - Chasteberry
  - Spearmint Tea
  - Deglycerinated Licorice (DGL)
  - Omega 3 Fatty Acids
  - N-acetyl cysteine

- **Thyroid Stabilization**

  Medications

  T4 Only, T3 Only, T3/T4 combo (synthetic/5

- *Diet*

  Gluten free

  Food Sensitivity

  4 R's

- *Autoimmune Protocol*

  Gluten Free

  Plant Sterolins

  Low Dose Naltrexone

- *Supplements*
  - *Iodine (150-225 mcg/d)/Selenium)200 mcg/d)*

"General" Side Effects Remedies

- **Fatigue**
  - Pregnenolone
  - N-acetyl cysteine
  - Vitamin D3
  - Shilajit
- **Penile Muscle Atrophy**
  - Testosterone/DHEA Optimized
  - Trimix
  - PDE 5 Inhibitors
  - Vitamin D3
  - Ashwagandha
- **Dry Skin/Dry Hair**
  - Testosterone/Thyroid Optimized
  - Resveratrol
  - DGL
  - 1% Melatonin + 1 % Naltrexone Compounded Cream
- **Tinnitus**
  - Meclizine
  - Vasopressin
  - Battlefield Acupuncture

Mental/Psychological Effect Remedies

Enhances Allopregnenolone

- Progesterone
- Pregnenolone
- Fenofibrate
- Pioglitazone
- Brexanalone

Enhanced GABA

- Pharma Gaba
- Chinese Skullcap (Scutellaria baicalensis)
- Fenofibrate
- Phenylethylamine (PEA)
- Ashwagandha
- L-Theanine

Memory Loss

- Progesterone
- Pregnenolone
- Green Tea Extract
- Spironolactone/Metformin
- Ashwagandha
- Mucuna pruriens
- L-Theanine

Slowed Thoughts

- Progesterone
- Pregnenolone
- Saw Palmetto

Mental/Psychological Effect Remedies

Mood
- Fenofibrate
- Vitamin D3
- Green Tea Extract

Comprehension
- Fenofibrate
- Progesterone

Anxiety
- Spearmint Tea
- Resveratrol
- Progesterone/Pregnenolone
- Vitamin D3
- L-Theanine
- DGL
- Ashwagandha
- Chinese Skullcap (Scutellaria baicalensis)

Depression
- Progesterone
- Pioglitazone
- Brexanalone
- GABA
- PEA
- Vitamin D3
- Saw Palmetto

Suicide Ideation
- Counseling
- Testosterone Sufficiency
- Growth Hormone Sufficiency
- Progesterone
- Fenofibrate
- GABA/L-Theanine

Mental/Psychological Effects Remedies

Insomnia

- Progesterone
- GABA
- Inositol
- Ashwagandha
- Omega 3 FA
- Vitamin D3

Emotional Flatness

- Progesterone

Natural 5 Alpha Reductase Inhibitors

5ARI

- Green Tea Extract
- Coconut Oil
- Quercetin
- Turmeric (Curcumin)
- Pumpkin Seeds
- Edamame
- Saw Palmetto
- Red Reishi

Erectile Dysfunction-Pentoxifylline

- *MOA:* Anti-inflammatory, Antifibrogenic activity.
- *Effects:* Increased:
  - Peak systolic velocity
  - International Index of Erectile Function [IIEF] score versus placebo (42% versus 11%)
  - 37% of w improved penile curvature and plaque volume vs. 5% of patients w placebo
  - Decreased:
    - (Peyronie's) plaque volume, penile curvature, and pain
- Contraindications
  - End-diastolic velocity
  - Bleeding disorders
- Dose
  - 400 mg 2-3x/d

Supplements-Male Enhancement Supplements

Lepidium Meyenii (Maca): Testosterone mimic, supports sexual function, alleviates SSRI-induced sexual dysfunction

Epimedium Sagittatum (Horny Goat Weed): Promotes testosterone production. It also increases sexual response

Tongkat ali (Eurycoma longifolia): Stimulates the Leydig cells of testes, boosting testosterone production. Maintains normal testosterone levels that supports sexual desire and fertility, (sperm concentration/motility), mood and energy.

References:

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*SahooHB, NandyS, SenapatiAK, SarangiSP, SahooSK. Aphrodisiac activity of polyherbal formulation in experimental models on male rats. PharmacognosyRes. 2014 Apr;6(2):120-6.

*BucciLR. "Selected herbals and human exercise performance." Am J ClinNutr2000;72(2 Suppl):624S-636S

*AdimoeljaA. "Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions" [abstract]. IntJ Androl. 2000;23:82-84.

Supplements-Male and Female Enhancement Supplements

Tribulus Terrestris: Increases sexual desire in by releasing nitrogen from endothelium and nitrergic nerve endings

TrigonellaFoenum-Graecum(Fenugreek): Increases sexual cognition, sexual arousal, sexual experience, and orgasm/ sexual drive

References:

*PuriD, PrabhuKM, Dev G, Agarwal S, Murthy PS. Mechanism of Antidiabetic Action of Compound GII Purified from Fenugreek (Trigonellafoenumgraecum) Seeds. Indian J ClinBiochem. 2011 Oct;26(4):335-46.

*SreejaS, AnjuVS, SreejaS. In vitro estrogenic activities of fenugreek Trigonellafoenumgraecumseeds. Indian J Med Res. 2010 Jun;131:814-9.

*Brooks NA, Wilcox G, Walker KZ, et al. Beneficial effects of Lepidiummeyenii(Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. Menopause. 2008 15(6):1157-62

*Shin BC, Lee MS, Yang EJ, Lim HS, Ernst E. Maca(L. meyenii) for improving sexual function: a systematic review. BMC Complement AlternMed. 2010 Aug 6;10:44. doi: 10.1186/1472-6882-10-44. Review.

Erectile Dysfunction-Trimix

- Alprostadil 15 mcg/Papaverine 30 mg/Phentolamine 1.5mg/ml. (92% effective.) Add Prostaglandin E1 20-25mcg, or atropine 0.02-0.08 mg/ml if ineffective.
  - Alprostadil
    - » Stimulates production of cAMP (Cyclic adenosine monophosphate) in penile smooth muscle and blood vessels
  - Papaverine
    - » Vasodilator-Relaxes smooth muscle in arterial walls
  - Phentolamine

    Alpha blocker-Smooth muscle relaxer due to vascular constriction blockade

Injection Site

Dose: Inject 0.05-0.2 cc mixture into corpus callosum laterally with 29-31 G, 0.3-1 cc syringe

Caution: Risk of priapism

- Rx: Phenylephrine 1 mg/ml

Erectile Dysfunction-PT-141 (Bremelanotide)

Melanocyte-stimulating hormone (MSH)

Activates hypothalamic neurons to increase sexual desire.

Enhances sexual arousal, libido and penile erections.

Indications:

HSDD (hypoactive sexual desire disorder) in premenopausal women. (FDA)

Low libido (male & female)

Increases energy

ED (erectile dysfunction)

Enhances sexual satisfaction

Can create a sunless tan

Dose: 1.75 mg/0.3 cc prefilled syringe daily

Contraindications: none

Side Effects:

Nausea, stretching and yawning.

Erectile Dysfunction-*Mucuna pruriens*

MOA: Lowers prolactin/enhances dopamine

Indications:

- Improved Sperm Quality/Infertility
- Increase in adrenaline/noradrenaline
- Decrease in cortisol/prolactin
- Increase in testosterone
- Increased libido
- Improves insulin resistance/diabetic cataracts
- Symptoms
- Improves memory
- Neuroprotective
- Protease inhibitor

Contraindications:

- Children
- Pregnancy
- Schizophrenia
- Psychosis
- Dopamine agonists
  - Rotigotine
  - Pramipexole
  - Ropinirole

Side Effects

- Sweating
- Nausea
- HBP
- Heart Palpitations

Dose

- 250-1000 mg/d

Anhedonia-Oxytocin

Attenuates the activity of the amygdala

Mediates trust, cooperation, and social interactions

Increases 5-alpha-reductase activity of prostatic epithelial cells

Oxytocin significantly increases isoenzyme type II activity in prostate epithelial cells

Reduces social anxiety improves sexual function, libido, erection, and orgasm.

Improves:

Social Ability, Repetitive Motion, Cognition

Dose: Stand alone: 10-50 IU sublingual or intranasal

Combos:

Oxytocin 50-125 IU/Tadalafil 5 mg can use daily or prn 2-6 hours before the deed

Oxytocin 50-125 IU/Sildenafil 25-100 mg or daily.

Oxytocin 50 I.U./Tadalafil 5 mg /PT-141/1.75 mg

Sperm Function-Shilajit

- MOA:
  - Active Ingredient: Fulvic Acid
  - Anti-inflammatory
  - Antioxidant
  - Increases iron levels
- Indications :
  - Low Testosterone (1)
  - Oligospermia (2)
  - Dementia
  - Improves Cognitive Function (3)
  - Blocks Tau aggregation in Alzheimer's Disease (4)
  - Chronic Fatigue Syndrome
  - Infertility
  - Hair Loss
- Effects:
  - Increase Testosterone 23.5%
  - Increased DHEA
  - Increase Spermia 37.6%, Total Sperm count 61.4%, Motility 12-17.4%,
  - Sperm Count 18.9%
  - Increase FSH 9.4%

Sperm Function-Shilajit

- Side Effects:
- Rash
- Dizziness
- Contraindications:
- Gout
- Hemochromatosis
- Dose:
- 300-600 mg/d
-

1. Pandit S, Biswas S, Jana U, De RK, Mukhopadhyay SC, Biswas TK. Clinical evaluation of purified Shilajit on testosterone levels in healthy volunteers. Andrologia. 2016 Jun;48(5):570-5. doi: 10.1111/and.12482. Epub 2015 Sep 22. PMID: 26395129.
2. Biswas TK, Pandit S, Mondal S, Biswas SK, Jana U, Ghosh T, Tripathi PC, Debnath PK, Auddy RG, Auddy B. Clinical evaluation of spermatogenic activity of processed Shilajit in oligospermia. Andrologia. 2010 Feb;42(1):48-56. doi: 10.1111/j.1439-0272.2009.00956.x. PMID: 20078516.
3. Cornejo A, Jiménez JM, Caballero L, Melo F, Maccioni RB. Fulvic acid inhibits aggregation and promotes disassembly of tau fibrils associated with Alzheimer's disease. *Journal of Alzheimer's Disease*. 2011;27(1):143–153.

Sperm Function-Ashwagandha

- MOA:
  - Improves insulin sensitivity (1)
  - Promotes the formation of reactive oxygen species (ROS) inside cancer cells (2)
  - Reduces cortisol
  - Anti-anxiety (69% reduction in anxiety and insomnia,) (3)
  - Antidepressant
  - Increased Sperm count and motility
  - Increased Testosterone
  - Increased muscle mass and strength (4)
  - Anti-inflammatory
  - Anti-lipid properties
  - improved general memory, task performance, and attention (5)
  - Increases RBC concentration
  - Anti Seizure-stimulates GABA-A Receptors (6)
- Effects:
  - Neuroprotective (7)
  - Improves Thyroid Function (8)
    - Increases (T3) 41.5%; (T4) 19.6%
    - Decreases thyroid-stimulating hormone (TSH) levels decreased by 17.5%

Sperm Function-Ashwagandha

Side Effects:

- Nausea
- Headache
- Drowsiness
- Stomach irritation
- Diarrhea

Dose: 300 mg 2x/d

1. Gorelick J, Rosenberg R, Smotrich A, Hanuš L, Bernstein N. Hypoglycemic activity of withanolides and elicited Withania somnifera. Phytochemistry. 2015 Aug;116:283-289. doi: 10.1016/j.phytochem.2015.02.029. Epub 2015 Mar 18. PMID: 25796090.
2. Nishikawa Y, Okuzaki D, Fukushima K, Mukai S, Ohno S, Ozaki Y, Yabuta N, Nojima H. Withaferin A Induces Cell Death Selectively in Androgen-Independent Prostate Cancer Cells but Not in Normal Fibroblast Cells. PLoS One. 2015 Jul 31;10(7):e0134137. doi: 10.1371/journal.pone.0134137. PMID: 26230090; PMCID: PMC4521694.
3. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized, double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012 Jul;34(3):255-62. doi: 10.4103/0253-7176.106022. PMID: 23439798; PMCID: PMC3573577.
4. Wankhede S, Langade D, Joshi K, Sinha SR, Bhattacharyya S. Examining the effect of Withania somnifera supplementation on muscle strength and recovery: a randomized controlled trial. J Int Soc Sports Nutr. 2015 Nov 25;12:43. doi: 10.1186/s12970-015-0104-9. PMID: 26609282; PMCID: PMC4658772.
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8. Sharma AK, Basu I, Singh S. Efficacy and Safety of Ashwagandha Root Extract in Subclinical Hypothyroid Patients: A Double-Blind, Randomized Placebo-Controlled Trial. J Altern Complement Med. 2018 Mar;24(3):243-248. doi: 10.1089/acm.2017.0183. Epub 2017 Aug 22. PMID: 28829155.

General Side Effects-Aromatase Inhibitors

MOA: Binds w heme iron of enzyme (Anastrozole)

Mimics androstenedione (Exemestane)

Decreases mean plasma mean plasma estradiol/testosterone ratio by 77%

Lowers estrogen, LH, FSH, Testosterone

Side effects: Decrease in bone mineral density

Typical Estrogen Deficiency Symptoms

Inflammatory Action: *Aromatase Inhibitors* down-regulate IL-6, TNF-alpha

Dose: Anastrozole; 1 mg/week to 1 mg/day

Exemestane; 25-50 mg/d

Letrozole; 2.5 mg 1/week

1. Raven G, de Jong FH, Kaufman JM, de Ronde W: In men, peripheral estradiol levels directly reflect the action of estrogens at the hypothalamo-pituitary level to inhibit gonadotropin secretion. J Clin Endocrinol Metab. 2006, 91: 3324-3328. 10.1210/jc.2006-0462.
2. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM: Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006, 91: 1995-2010. 10.1210/jc.2005-2847.
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General Side Effects-Resveratrol

MOA: **A polyphenol found in red wine, grape skin, berries, peanuts, and soy, resveratrol exhibits antioxidant, anti-inflammatory, anti-aging phytoestrogen properties. [104]**

1. **Lowers testosterone levels up to 23.1% in controlled trials (1)**
2. **Resveratrol exerted a potent ameliorative effect against testicular injury caused by finasteride. (2)**
3. **Resveratrol improves social impairment, stereotypy, hyperactivity, anxiety, and cognitive function. [3]**

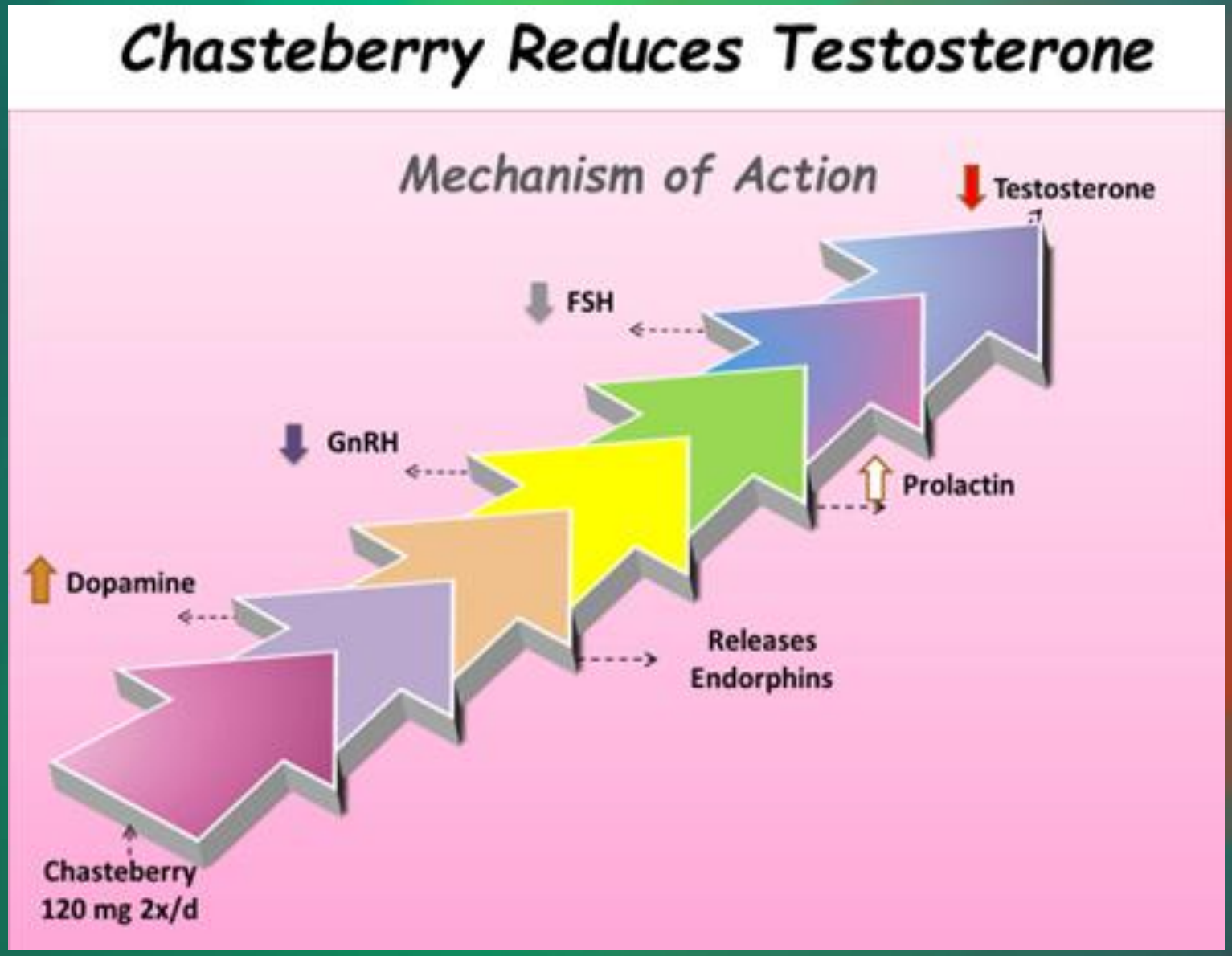
Side effects: **Mild to moderate gastritis. Restlessness. Diarrhea at a high dose.**

Inflammatory Action: ***IL-6:*** **Resveratrol down-regulates IL-6**

Dose**: 250 mg in am, 250 mg in pm.**

1. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997;275(5297):218-220. doi:10.1126/science.275.5297.218
2. Banaszewska, B., Wrotyńska-Barczyńska, J., Spaczynski, R.Z., Pawelczyk, L., "Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial," http://press.endocrine.org/doi/10.1210/jc. 2016-1858
3. Shalaby, A., Alabiad, M., & El Shaer, D. (2020). Resveratrol Ameliorates the Seminiferous Tubules Damages Induced by Finasteride in Adult Male Rats. Microscopy and Microanalysis, 26(6), 1176-1186. doi:10.1017/S1431927620024514

General Side Effects-Chasteberry



General Side Effects-Chasteberry

MOA: **Low dose Chasteberry blocks the activation of D2 receptors in the brain = prolactin 120 mg increases Prolactin 16% = decrease in testosterone**

High dose Chasteberry has the opposite effect.

480-milligram Chasteberry prolactin 10%.

A tween dose of 240 milligrams is neutral as it affects prolactin levels. (110)

Chasteberry binds to estrogen receptors = Rx. For intervention in PMS

Chasteberry influences LH signaling the ovaries = Progesterone. (112)

Dose:

Low dose: !00-120 mg 2x/d

High dose: 480 mg

Side effects**: Nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus, and erythematous rash. (113)**

Cytokine Effect**: IL-6: Chasteberry reduces IL-6 secretion.**

General Side Effects-Spearmint Tea

MOA:

Increases L.H. and FSH
Reduces free testosterone-Leaves total testosterone intact. (115)
Inhibits 5-alpha reductase

Effects:

Relieves nausea, vomiting, abdominal pain, and bloating (116)
Acts as an antioxidant (117)
Enhances memory (118)
Acts as an anti-bacterial and antimicrobial (119)
Improves insulin resistance (120)
Improves sleep
Relieves anxiety via GABA receptor manipulation (121)
Lowers blood pressure (122)
Topically relieves joint pain.

Dose: 70-150 mg per day. (1.5-3 cups of tea/d)
Side effects: May increase pre-existing renal and hepatic disease.
Cytokine Effect: Significantly decreased the production of NO, TNF-α, IL-6, and PGE2. (

General Side Effects-Glycyrrhizinate Licorice

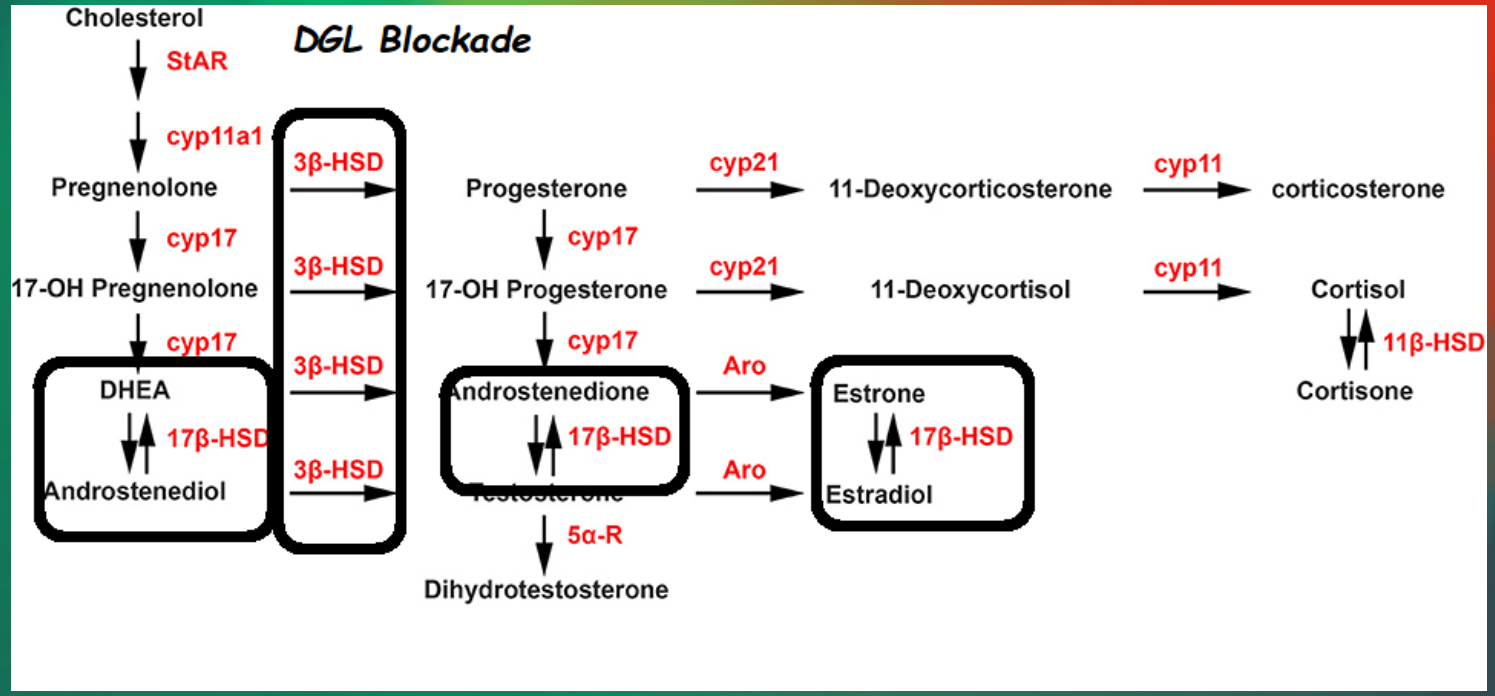
MOA:

Inhibits 17,20-lyase catalyst for 17-hydroxyprogesterone to convert to androstenedione.

Inhibits 17β-hydroxysteroid dehydrogenase responsible for converting androstenedione to testosterone.

Inhibits 11-ß-hydroxysteroid dehydrogenase enzyme type 2

Active component *glycyrrhizic acid* contains phytoestrogens,



General Side Effects-Deglycyrrhizinated Licorice

Effects:

Licorice root is anti-inflammatory, anti-viral, antimicrobial, antioxidative, anticancer, immunomodulatory, hepatic, and cardioprotective. (125)

Peptic ulcers, hepatitis C, sore throats, pulmonary and skin diseases

Anti Androgen Properties:

- Hirsutism
- Agitation
- Anxiety
- Irritability.

Dose: 150 mg reduces testosterone up to 26%

Side effects:

Cortisol like induced mineralocorticoid effect

Elevation of sodium and reduction of potassium levels. (127)

Muscle weakness, hypertension, cardiac arrhythmias, congestive heart failure, renal, and hepatic failure.

***Cytokine Effect*:** Licorice inhibits IL-6 and IL-1β.

General Side Effects-Omega 3 Fatty Acid

MOA:

Anti-inflammatory

Ant-allergy

Effects:

Reduces testosterone without significant SHBG or free androgen index changes. [131]

Reduces lethargy, social withdrawal, and hyperactivity [132]

Dose: 1-4 grams daily

Side effects:

Burping, Bad breath, "Fishy" taste in the mouth

To relieve burping and the "fishy" taste:

Always use pharmaceutical grade omega 3 F.A.

Store fish oil in the freezer

Administer fish oil directly from the freezer

Headache

Heartburn, Stomach upset, Nausea, Diarrhea

Cytokine Effect: Significant reduction in IL-6 within 24 hours of administration

General Side Effects-N-acetylcysteine (NAC)

MOA:

Antioxidant

Oxidative stress reduction

Prevents and reverses alcohol-induced fatty liver cirrhosis, hepatitis, and liver tumors (135)

Chelating agent-Removes mercury, lead, cadmium, and arsenic

Effects:

Neuromodulator, neurotransmitter, neuroprotection [136]

Dementia preservation

Alzheimer's protection

Liver detoxification agent [137]

Cardiac preservation [138]

Acute acetaminophen toxicity [139]

Cataracts, glaucoma [140]

Chronic fatigue syndrome [141]

Cancers of all kinds [142]

Asthma, arthritis [14]

Corrects imbalances in synaptic excitation and inhibition neurotransmitters [143]

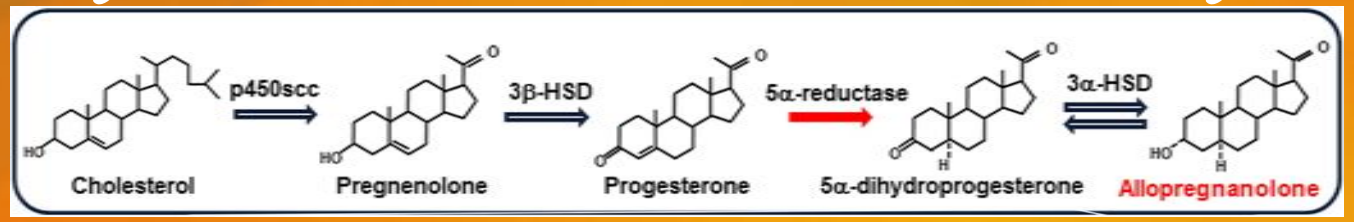
Reduces, and in some cases, eliminates obsessive-compulsive behavior. [144]

Reduces aggression, irritability, hyperactivity, and non-compliance behaviors decrease, and sleep issues. [145]

Dose: **600-900 mg 2-3 x/d**

Neurological/Mental Side Effects-Progesterone

MOA:



Pre-treatment with finasteride blocks the disease-modifying effect of P (147)

Effects

Spermiogenesis, sperm capacitation/acrosome reaction, and testosterone biosynthesis in the Leydig cells. (148)

Improves:

- Memory/recall
- Thought process
- Problem solving, comprehension
- Anxiety, depression

Reduces:

- Suicide Ideation
- Anhedonia
- Emotional Flatness

Neurological/Mental Side Effects-Progesterone

Contraindications

- Gonadal Cancers
- Bleeding Disorders

Side Effects

- Feeling "Drunk" or "Hungover," Drowsiness
- G.I. Bloating
- Increased Cortisol
- Decreased Glucose Tolerance
- Increased Fat Storage
- Increased Appetite/Carb Cravings
- Hot Flashes
- Depression (If P levels are high or low)
- Water Retention

Dose

2-5% (20-50 mg/gm) cream nightly. Apply to inner wrist, leg, or abdomen. Apply to breast tissue if tender or evidence of gynecomastia.

Neurological/Mental-PPAR-γ (Pioglitazone) + PPAR-α (Fenofibrate)

a. MOA:
    i. Pioglitazone
        1. Inhibits NFκB
        2. Reduces pro-inflammatory cytokines TNF-α, IL-1β and IL-6, prostaglandins, nitric oxide (NO), reactive oxygen species (ROS) (149)
        3. COX-2 inhibitor
        4. Neuroprotective-decreases oxidative stress in the brain
        5. Mediates:
            a. Intestinal anti-inflammatory effects
            b. Increases insulin sensitization (150)
    ii. Fenofibrate
        1. Stimulates biosynthesis of allopregnanolone (151)
        2. Anti-inflammatory
        3. Blocks TLR-4
        4. Inhibits NFκB

Neurological/Mental Side Effects-PPAR-γ (Pioglitazone) + PPAR-α (Fenofibrate)

a. Indications
    i. Pioglitazone
        1. Diabetes Mellitus type II
        2. Depression, chronic stress
    ii. Fenofibrate
        1. Hyperlipidemia
        2. Mood disorders
b. Contraindications
    i. Pioglitazone
        1. Known hypersensitivity to pioglitazone its components
        2. Diabetic ketoacidosis or type 1 diabetes
        3. Hypoglycemia
        4. Patients with established New York Heart Association (NYHA) Class III or IV heart failure
        5. Symptomatic heart failure patients
        6. Bladder cancer
    ii. Fenofibrate
        1. Severe renal impairment
        2. Active liver disease
        3. Primary biliary cirrhosis
        4. Pre-existing gallbladder disease
        5. Known hypersensitivity to fenofibrate

Neurological/Mental Side Effects-PPAR-γ (Pioglitazone) + PPAR-α (Fenofibrate)

i. Combination PPAR-γ (Pioglitazone) + PPAR-α (Fenofibrate)
ii. Regulates:
    a. Mitochondrial and proteasomal function
    b. Neuroinflammation,
    c. Oxidative stress
    d. Neurodegeneration
    e. Non-alcoholic steatohepatitis (NASH) (152)

Dose

i. Pioglitazone
    1. 7.5-15 mg./d
ii. Fenofibrate
    1. 48-145 mg/d

Neurological/Mental Side Effects-Brexanalone (Zulesso)

MOA:

- An allosteric modulator (allopregnanolone) of both synaptic and esynaptic GABA-A receptors. (153)
- Restores normal allopregnanolone levels
  - Fine-tunes GABAergic neurotransmission
    - Improves symptom severity with post-partum depression patients

Indications

- Postpartum Depression (FDA Approved)

Side Effects

- Excessive sedation
- Possible loss of consciousness
- Suicidal thoughts
- Dry mouth, flushing of the skin or face

Dose

- Continuous infusion (IV) for 60 hours

Neurological/Mental Side Effects-Brexanalone (Zulesso)

a. Notes:
    i. Must be administered in a company certified designated inpatient center
        1. Results: [154]
            a. Responders
                i. Brexanalone 70%
                ii. SSRI 40-60%
        2. Time to Respond
                i. Brexanalone 2-3 days
                ii. SSRI's 3-6 weeks
        3. Relapse
            a. Brexanalone 6%
            b. SSRI's 20-80%
            c. Oral form SAGE-217 (Zuranalone) in Phase 3 Trials (Side effect profile similar to IV

ALLOPREGNANOLONE ENHANCEMENT-

Scutellaria baicalensis "Chinese Skullcap."

a. MOA: Anti-inflammatory and antioxidant activity.

b. Indications:

i. Calming agent: + influence on GABA receptors [155]

ii. Stimulates hair follicle growth via WNT pathway [156]

iii. Anti-neoplastic [157]

iv. Activates caspase-3, resulting in apoptosis of leukemia-derived T cells

v. High doses inhibited angiogenesis by inducing cell death.

vi. Anti-inflammatory (Rx. Arthritis)

vii. Neuroprotective

viii. Anticonvulsant

ix. Liver Protection

x. DMT2: Improves Insulin Sensitivity, Gut microflora

xi. Reduces Gum inflammation and Plaque

c. Dose : 1-2 gm/d

ALLOPREGNANOLONE ENHANCEMENT-

Phenylethylamine (PEA)

a. MOA:
   i. Activates PPAR-α receptors
   ii. Endocannabinoid
   iii. StAR enzyme and cytochrome P450 enzyme (P450scc) expression
   iv. Reduces oxidative stress due to allopregnanolone synthesis
b. Indications (158).
   i. Pain including neuropathic pain
   ii. Anti-inflammatory
   iii. Mast cell inhibitor
   iv. Endocannabinoid System Agonist Neuroprotective
      1. Seizure control
      2. Neurotoxicity
   v. Anxiolytic
   vi. PTSD
   vii. Major Depression
c. Dose : 400-600 mg/d
   a. May combine w Quercetin, hemp or curcumin

ALLOPREGNANOLONE ENHANCEMENT-

Pregnenolone

a. MOA
   i. Inhibits tonic (NMDA) receptor-mediated neurotransmission provides neuroprotection
   ii. Preferentially metabolizes to allopregnanolone. (159)
   iii. ALLO levels triple two hours post oral administration of 400 mg pregnenolone (160)
   iv. Pregnenolone protects the brain from cannabis intoxication (161)

b. Indications (162)
   i. Memory
   ii. Neuroprotection
   iii. Anti-stress, anti-anxiety, anti-depressive
   iv. Anti-arthritic
   v. Lowers Lipids
   vi. Improves mental alertness
   vii. Improves psychomotor performance
   viii. Anti-fatigue

c. Dose
   i. Maintenance-25-50 mg/25-50 mg/d
   ii. Memory Enhancement-150 mg/d
   iii. Fatigue-150-200 mg 2x/d (High dose for no more than 2-4 months)

ALLOPREGNANOLONE ENHANCEMENT-

Zinc

a. MOA:
   i. Modulates PPAR-γ signaling [165]
   ii. Antioxidant
   iii. Anti Inflammatory
b. Indications
   i. Testosterone enhancement
   ii. Aromatase inhibitor (lowers estrogen)
   iii. Diarrhea
   iv. Slow wound healing
   v. Wilson's Disease
   vi. Short stature in children
c. Dose
   a. 25-30 mg 1-2 x/d

ALLOPREGNANOLONE ENHANCEMENT-

Vitamin D3

a. MOA:
   i. Contributes to hair follicle stimulation [167]
   ii. Creates new hair follicles
   iii. Improves urinary blood flow
   iv. Neuroprotective [168]

b. Indications
   i. Hair loss
   ii. Prevention and amelioration of BPH and prostate cancer
   iii. Prostate enlargement
   iv. Mood, anxiety, depression
   v. Osteoporosis
   vi. Muscle weakness
   vii. High blood pressure
   viii. Fatigue
   ix. Chronic pain
   x. Infertility

c. Dose
   a. Titrate to 50-80 ng/dl

ALLOPREGNANOLONE ENHANCEMENT-

L-Theanine

a. MOA:
    a. Increases in serotonin, dopamine, GABA, glutathione
    b. Stimulates alpha brain wave activity
b. Indications
    a. Memory, learning
    b. Antioxidant
    c. Anxiolytic
        a. Blocks excitatory stimuli at glutamate receptors in the brain
    d. Cognition (Eliminates jitteriness when combined w caffeine)
    e. Stroke Prevention
c. Dose
    a. 200-400 mg/d

Natural 5 Alpha Reductase Inhibitors

1. Green Tea Extract
2. Coconut Oil
3. Quercetin
4. Turmeric
5. Pumpkin Seeds
6. Edamame
7. Saw Palmetto
8. Red Reishi

Remedy Summary-Sexual Side Effects

First Line

Keto or Mediterranean Diet

Exercise aerobic and anaerobic 5x/wk

RX:

1. *Mucuna pruriens*-250-1000 mg/d
2. PDE 5 Inhibitors
   - Daily-*Tadalafil* 5 mg/d
   - As Needed-*Tadalafil* 20 mg/*Sildenafil* 50-100 mg
3. *Tribulus/Tongkat ali/Horny Goat Weed Combos*

Second Line

1. *Pentoxifylline*-400 mg 2x/d
2. *Trimix*-0.05-0.2 cc injected into corpus callosum
3. Oxytocin/Tadalafil-50-125 IU/5 mg daily or as needed

Fertility

1. *Shilajit*-300-600 mg/d
2. *Ashwagandha*-300 mg 2x/d

Remedy Summary-Sexual Side Effects

Nerve Damage/Structural Damage (Peyronie's Disease)

1. *Ashwagandha*-300 mg 2x/d
2. *PT 141-* 1.75 mg/0.3 cc prefilled syringe daily
3. *Platelet Rich Fibrin/Platelet Rich Plasma/Exosomes*

"General" Side Effects Remedies

Aromatase Inhibitors

1. Anastrozole-1 mg 1-7x/week (usual dose 1 mg 2x/wk)
2. Exemestane-25-50 mg/d
3. Letrozole-2.5 mg 1/week

Off Label Aromatase Inhibitors

1. Spironolactone-25-100 mg/d
2. Metformin-500-2000 mg/d

"General" Side Effects Remedy Summary

- **Testosterone Aromatization**
  - Resveratrol-250 mg 2x/d
  - Chasteberry-100-120 mg 2x/d
  - Spearmint Tea-100 mg/d
  - Degly. Licorice (DGL) -150mg/d
  - Omega 3 Fatty Acids-1-4 gm/d
  - N-acetyl cysteine-900 mg 2x/d

- **Thyroid Stabilization**

Medications
  - T4 Only, T3 Only, T3/T4 combo (synthetic/5

- Diet
  - Gluten free
  - Food Sensitivity
  - 4 R's
- Autoimmune Protocol
  - Gluten Free
  - Plant Sterolins
  - Low Dose Naltrexone
- Supplements
  - Iodine (150-225 mcg)
  - Selenium (200 mcg)

"General" Side Effects Remedies

- **OTC Aromatase Inhibitors**
  - Resveratrol
  - Chasteberry
  - Spearmint Tea
  - Deglycerinated Licorice (DGL)
  - Omega 3 Fatty Acids
  - N-acetyl cysteine

- **Thyroid Stabilization**

  Medications

  T4 Only, T3 Only, T3/T4 combo (synthetic/5

- *Diet*

  Gluten free

  Food Sensitivity

  4 R's

- *Autoimmune Protocol*

  Gluten Free

  Plant Sterolins

  Low Dose Naltrexone

- *Supplements*
  - *Iodine (150-225 mcg/d)/Selenium)200 mcg/d)*

"General" Side Effects Remedy Summary

- **Fatigue**
  - Pregnenolone 25-100 mg/d
  - N-acetyl cysteine-900 mg 2x/d
  - Vitamin D3-Titrate to 50-80 ng/dL
  - Shilajit 300-600 mg/d
- **Penile Muscle Atrophy**
  - Testosterone/DHEA Optimized
  - Trimix
  - PDE5 Inhibitors
  - Vitamin D3
  - Ashwagandha
- **Dry Skin/Dry Hair**
  - Testosterone/Thyroid Optimized
  - See Hair Restoration at End
- **Tinnitus**
  - Meclizine-250 mg 3x/d
  - Vasopressin-0.1-0.2 mg/d
  - Battlefield Acupuncture

Mental/Psychological Effect Remedies

First Line

Progesterone- 2-5 % cream @ bedtime
Pregnenolone – 25-100 mg @ 2x/d
Fenofibrate -48-145 mg/d

Second Line

Pharma Gaba- 100-400 mg/d
Chinese Skullcap 1-2 gm/d
Phenylethylamine (PEA)-400-600 mg/d
L-Theanine-250-400 mg/d

Memory Loss (add)

Pregnenolone (30-100 mg/d)
Green Tea Extract-338 mg (9 mg/kg)
Spironolactone/Metformin
Ashwagandha -300 mg 2x/d
Mucuna pruriens 250-1000 mg/d

Slowed Thoughts

Progesterone 2-5 % Cream
Pregnenolone 30-100 mg/d
Saw Palmetto 450-500 mg/d

Mental/Psychological Effect Remedies

Mood
- Fenofibrate
- Vitamin D3
- Green Tea Extract

Comprehension
- Fenofibrate
- Progesterone

Anxiety
- Spearmint Tea (70-150 mg/d)
- Resveratrol
- Progesterone/Pregnenolone
- Vitamin D3
- Saw Palmetto (400-500 mg/d)
- DGL
- Ashwagandha
- Chinese Skullcap (Scutellaria baicalensis)

Depression
- Progesterone/Pregnenolone
- Pioglitazone
- Brexanalone
- GABA
- PEA
- Vitamin D3
- Saw Palmetto

Suicide Ideation
- Counseling
- Testosterone/GH

Sufficiency
- Progesterone
- Fenofibrate
- GABA
- Esketamine Nasal Spray

Mental/Psychological Effect Remedies

Insomnia

Progesterone
GABA (100-400 mg/night)

Combos

Inositol Combo

B-6 (as Pyridoxal-5-Phosphate 10 mg
Inositol
500 mg
L-Theanine
200 mg
5 HTP
100 mg
Melatonin
3-9 mg

Vitamin D3 Combo (2 hours before bedtime)

Vitamin D3
1K-5K IU

Single Insomnia Remedies

Myo Inositol-12-18 gms/d
Ashwagandha
Omega 3 FA
L-serine 2 gm
@ bedtime

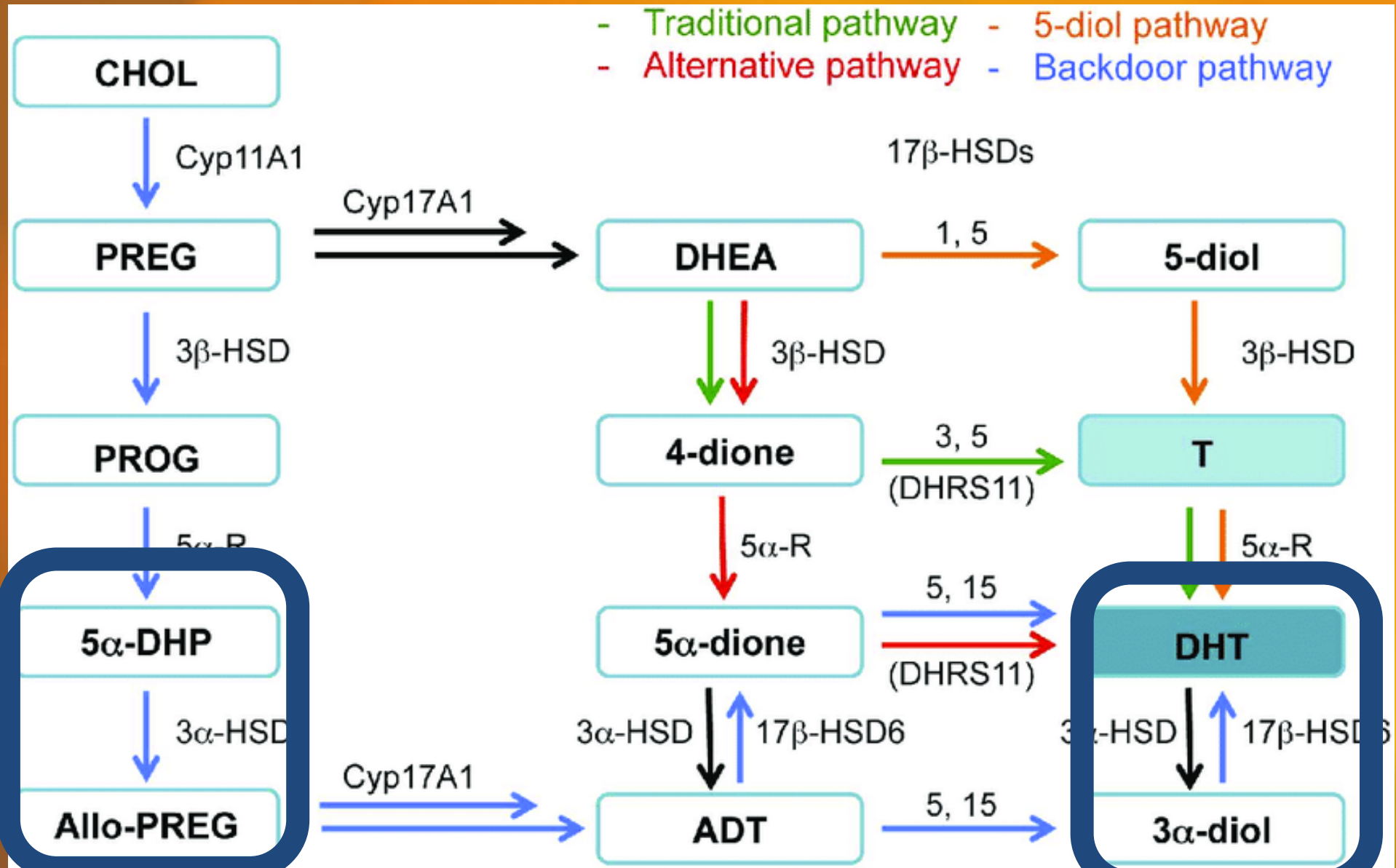
Emotional Flatness

Progesterone

Increase 3 H alpha SD

Sulforaphane
Activates Nrf2

Mental/Psychological Effect Remedies-
3 α-Hydroxysteroid dehydrogenase



Mental/Psychological Effect Remedies-
3 α-Hydroxysteroid dehydrogenase

1 . Converts 5α-dihydroprogesterone conversion into allopregnanolone.
2. Converts DHT to 3 alpha androstanediol

Isoenzymes AKR1C3 and AKR1C2

AKR1C2 converts DHT to 3 alpha androstanediol and androstanediol to DHT

AkR1C3 is a one way ticket DHT to 3 alpha androstanediol

Sulforaphane (dose 0.1-0.5 mg/kg)

Increases *3 α-Hydroxysteroid dehydrogenase Activity =*

Increases 5α-dihydroprogesterone conversion into allopregnanolone.

Increases DHT to 3 alpha androstanediol

Results : Increase cognition, reduce neuroinflammation

5 Alpha Reductase Inhibitors

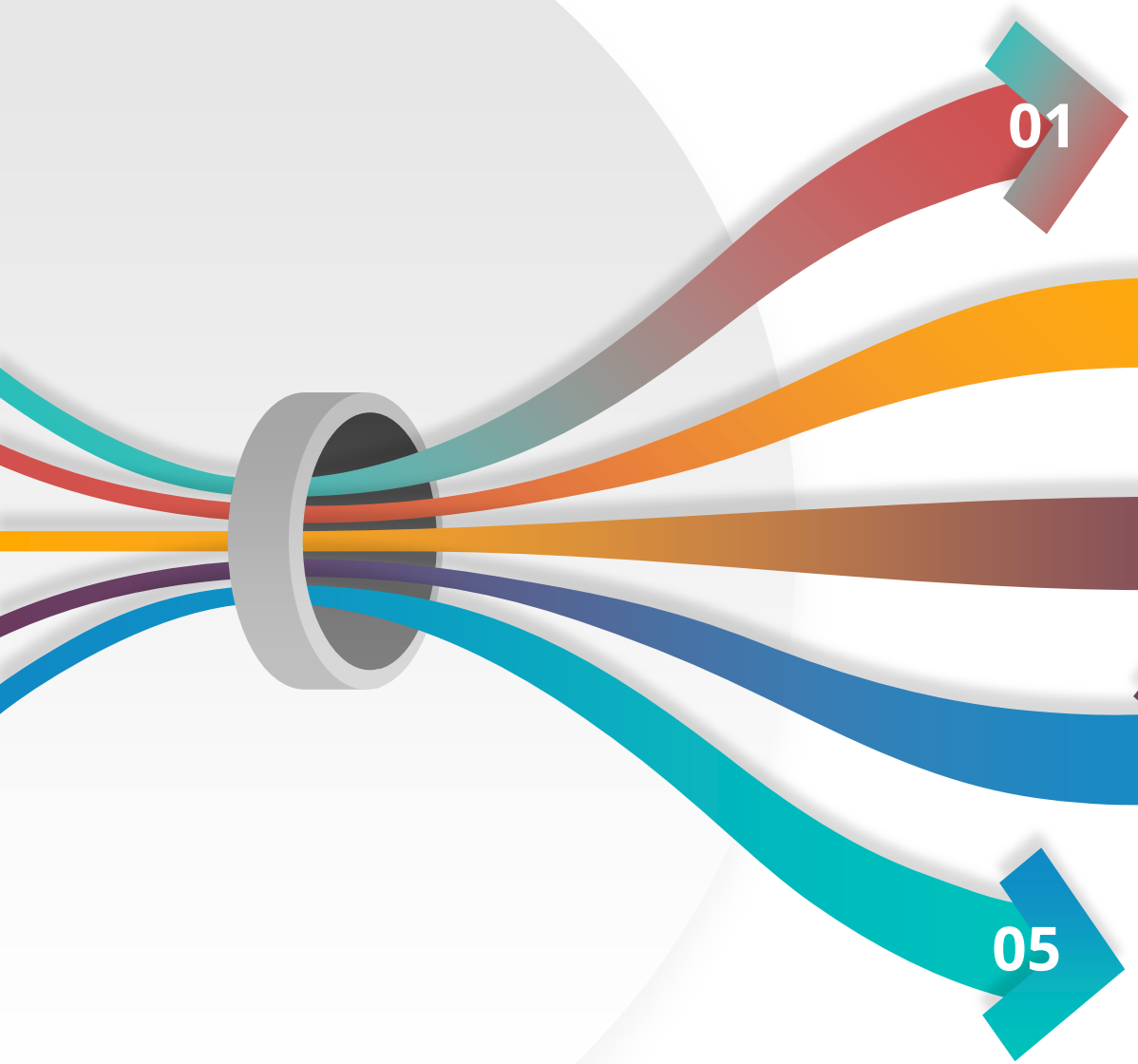
A Rational Approach to Hair Loss

No Drug Techniques

1. **Microneedling-** ↑ hair count over 6 months by 15%
2. **Target Scalp Massage-** 15 minutes 2x/d ↑ blood flow 75%
3. **Low Level Laser-** ↑ 39% thickening of hair after 16 wks.
4. **PRP/Exosomes-**30 % ↑ hair growth

1. Dhurat, Rachita et al. “A randomized evaluator blinded study of effect of microneedling in androgenetic alopecia: a pilot study.” International journal of trichology vol. 5,1 (2013): 6-11. doi:10.4103/0974-7753.114700
2. English, R.S., Barazesh, J.M. Self-Assessments of Standardized Scalp Massages for Androgenic Alopecia: Survey Results. *Dermatol Ther (Heidelb)* 9, 167–178 (2019). https://doi.org/10.1007/s13555-019-0281-6
3. Khatu, Swapna S et al. “Platelet-rich plasma in androgenic alopecia: myth or an effective tool.” Journal of cutaneous and aesthetic surgery vol. 7,2 (2014): 107-10. doi:10.4103/0974-2077.138352
4. Lanzafame RJ, Blanche RR, Bodian AB, Chiacchierini RP, Fernandez-Obregon A, Kazmirek ER. The growth of human scalp hair mediated by visible red light laser and LED sources in males. Lasers Surg Med. 2013 Oct;45(8):487-95. doi: 10.1002/lsm.22173. Erratum in: Lasers Surg Med. 2014 Apr;46(4):373. PMID: 24078483.

Decrease Free Testosterone=Increase SHBG



Spironolactone

Sufficient T3

S-Equol (Estrogen B agonist 10 mg 2x/d)
Danazol
Tamoxifen

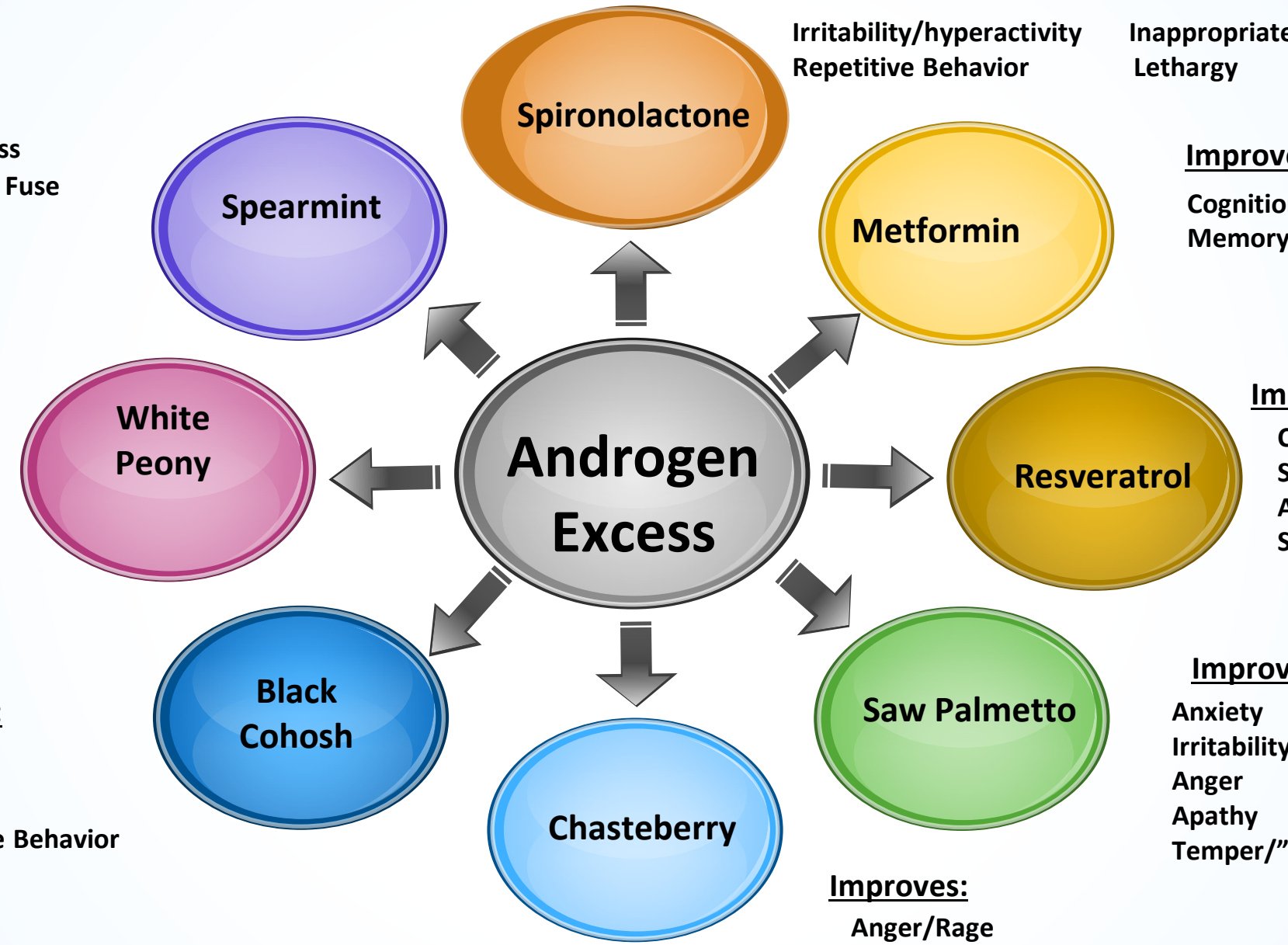
Adequate T3

ECG
Flaxseed 1-2 tsp/d

H-2 Antagonists-Cimetidine

Soy Isoflavones
Coffee

Decrease Androgen Excess Remedies



Improves:

Irritability/hyperactivity
Repetitive Behavior
Inappropriate Speech
Lethargy

Improves:

Cognition
Socialization
Memory
Hyperactivity

Improves

Cognition
Stereotypy
Anxiety
Socialization

Improves:

Anxiety
Irritability
Anger
Apathy
Temper/"Short Fuse"

Improves:

Anger/Rage

Improves:

Mood
Anxiety
Repetitive Behavior

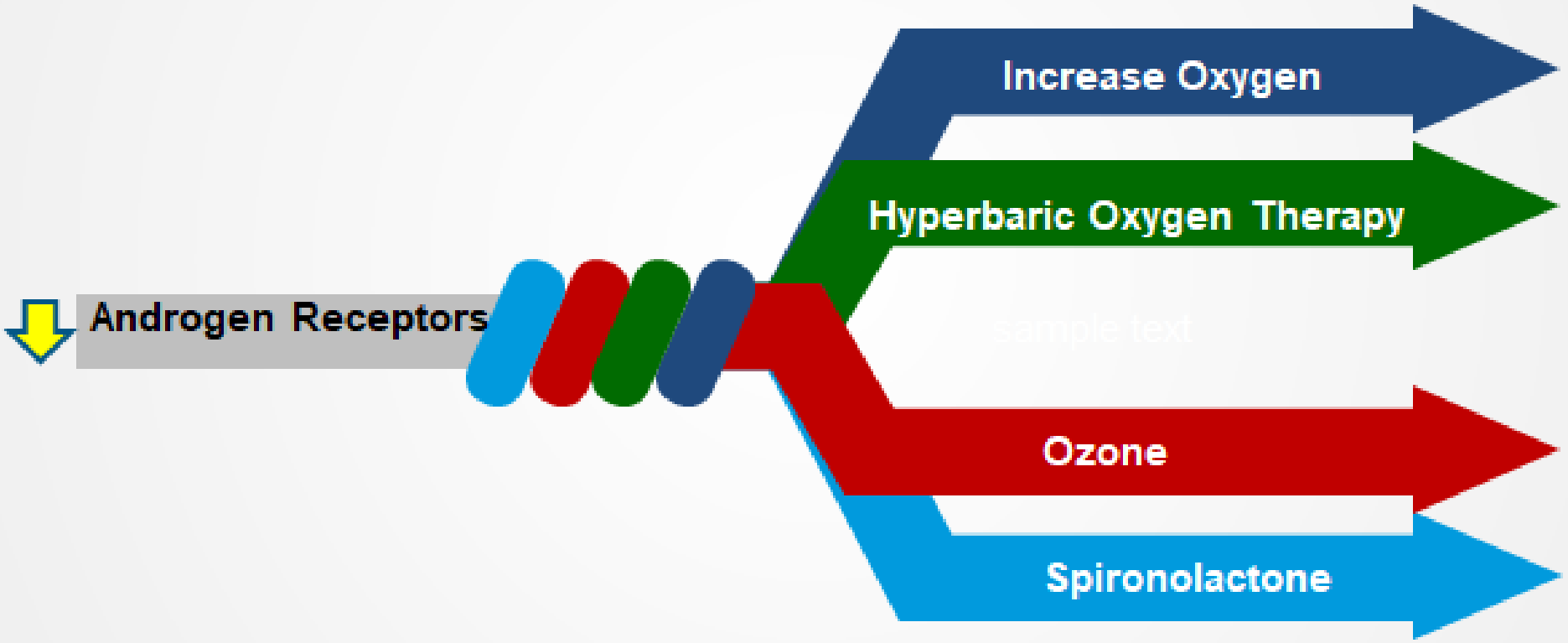
Improves:

Executive Function
Cognition
Speech

Improves:

Anxiety
Obsessiveness
Anger/Short Fuse
Memory
Apathy

Reduction in Androgen Receptors

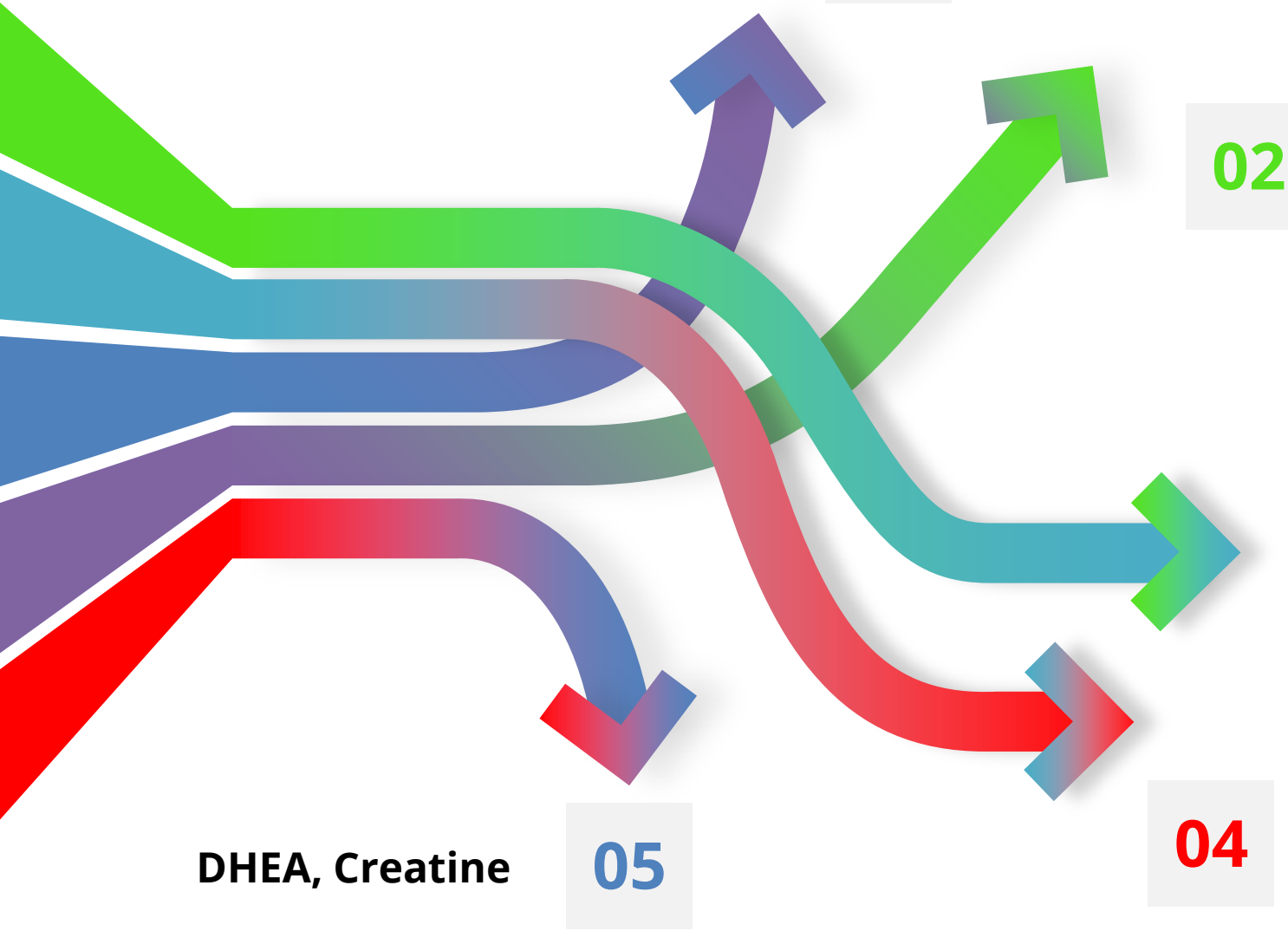


DHT Metabolism

Sulforaphane

01

Broccoli derivative increases the metabolism DHT via inc. 3 alpha HSD
Also: ***3 alpha HSD converts DHP to Allopregnenolone!***



Flutamide

02

Antiandrogen w Neuroprotective Properties
Increases Hair Growth In Nanoparticle Cream

Tongkat ali (Eurycoma longifolia):

Stimulates the Leydig cells of testes, boosting testosterone production. Maintains normal testosterone levels that supports sexual desire and fertility, (sperm concentration/motility), mood and energy

Tribulus Terrestris

04

Increases sexual desire in by releasing nitrogen from endothelium and nitrergic nerve endings

DHEA, Creatine

05

Thank You !
Questions?

William Clearfield DO
doctrbil9@gmail.com