Optimizing Testosterone without using Testosterone in men

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Disclosure

The following potential conflict of interest relationships are germane to my presentation.

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Speakers Bureau: N/A

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Consultant: Tailor Made Compounding

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Status of off label use of devices, drugs or other materials that constitute the subject of this presentation: N/A



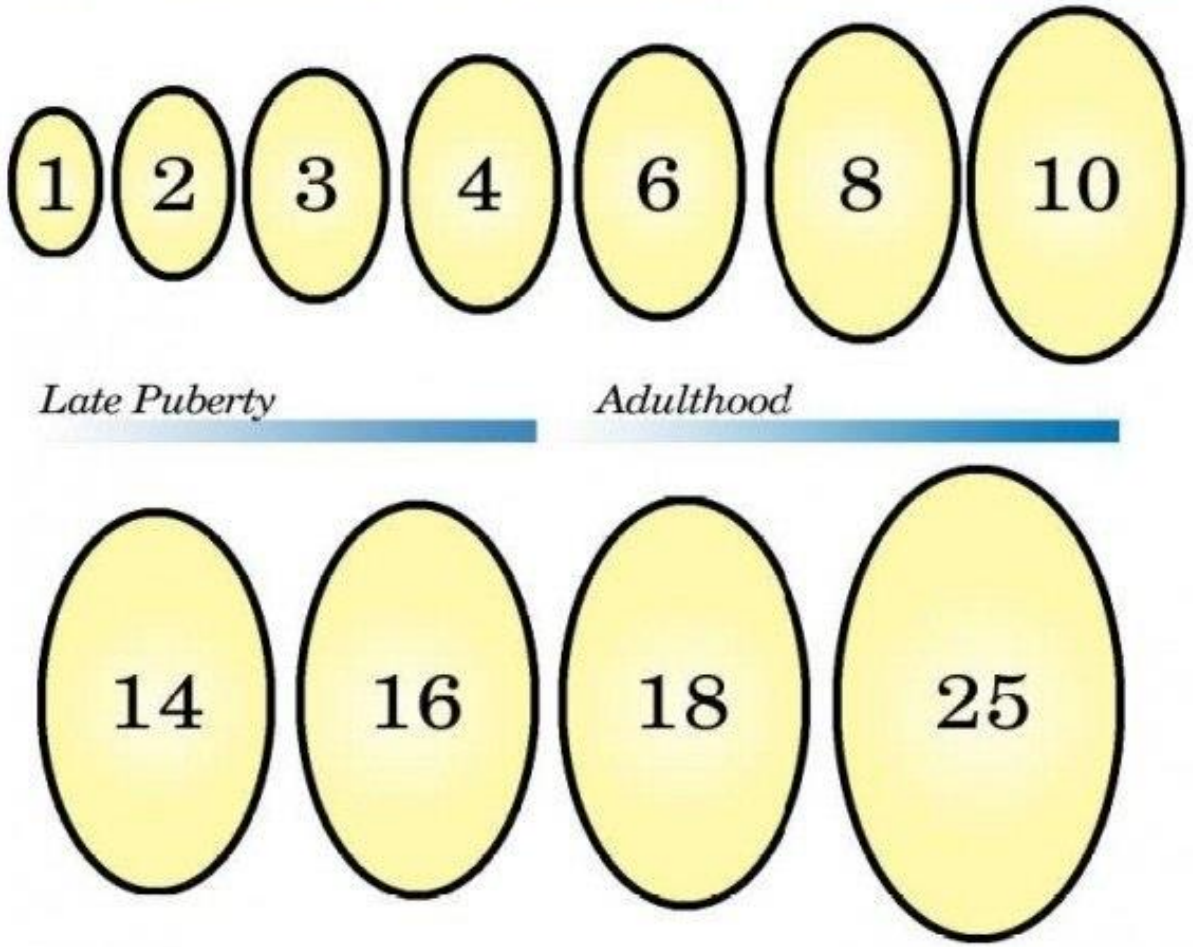

WANTED A GREAT BODY
GOT TESTICULAR SHRINKAGE

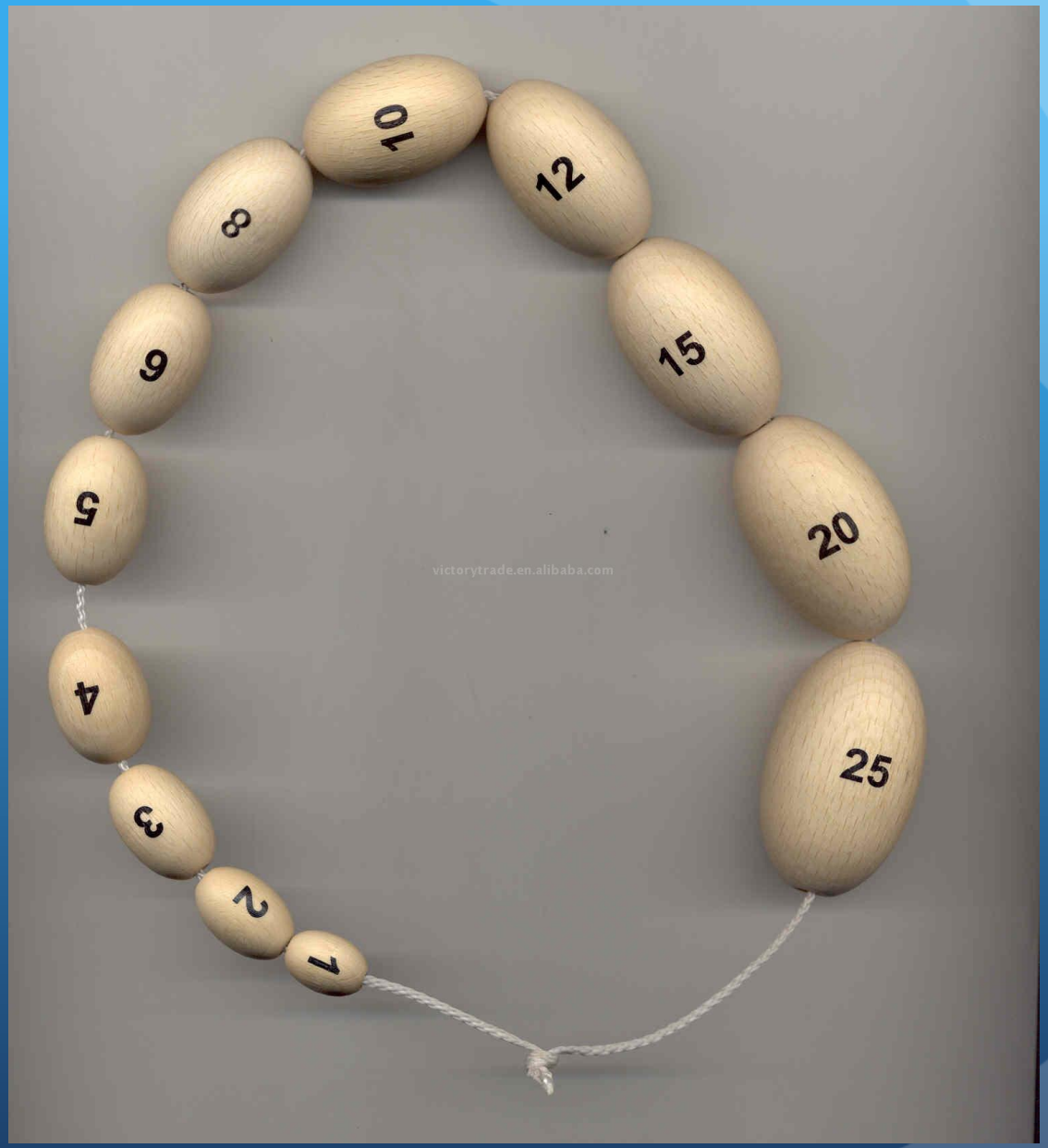



BALLS OF STEEL
KEN SAUNDERS

Orchidometer

Used to measure testicle size and track sexual development in boys.

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victorytrade.en.alibaba.com

Testicular Shrinkage

Palacios A, et al. J Urol. 1981 Jul;126(1):46-8.

- N= 39
- Weekly Testosterone Enanthate 200 mg IM
- 4 months showed 19% reduction of testicular volume and a decrease in sperm count



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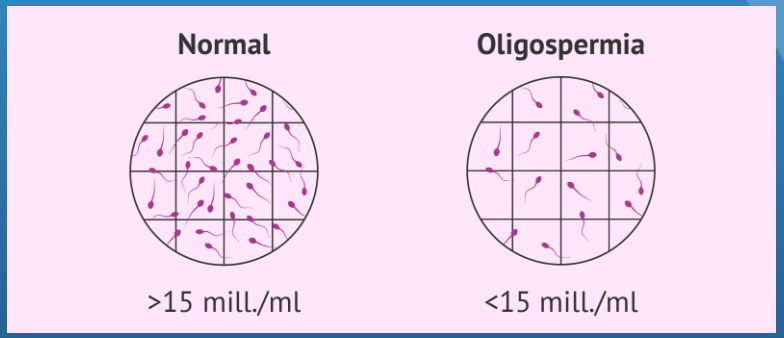
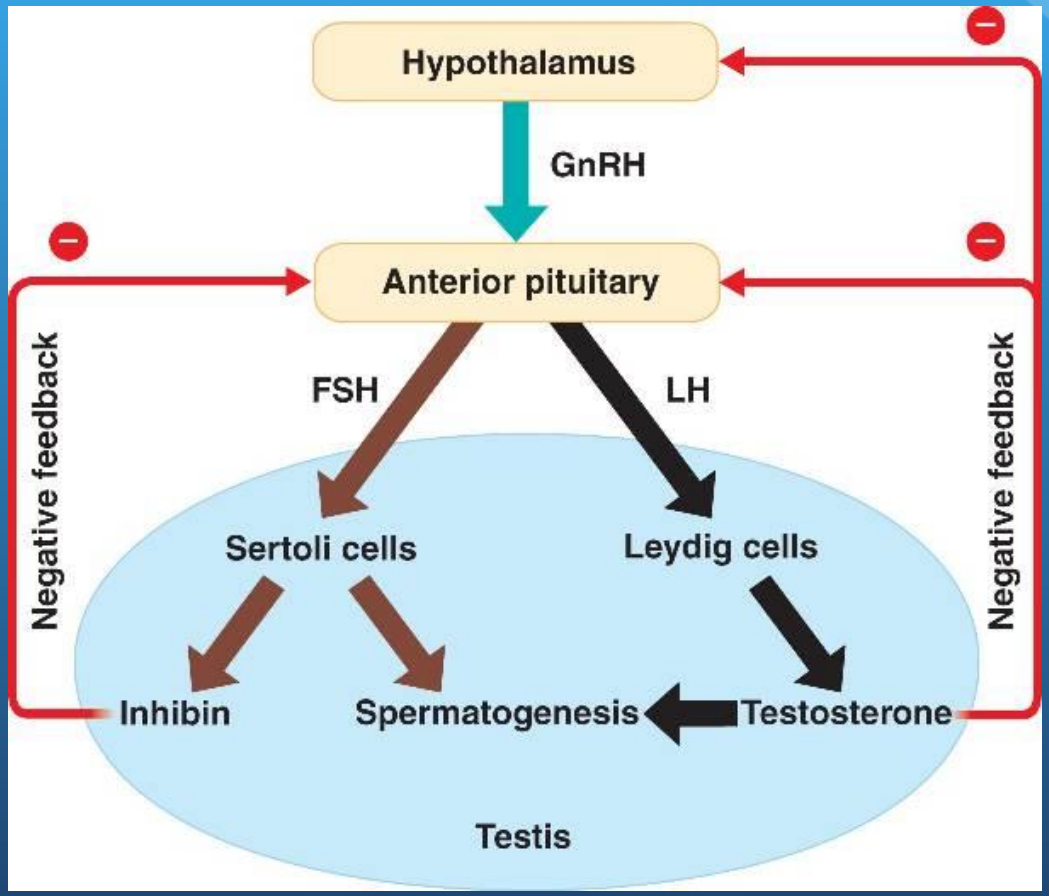
Oligospermia

- 271 men received 200 mg of Testosterone weekly
- 157 (65%) Oligospermia at 6 months with Testosterone therapy
- Only 46% return to baseline at average of 6 months



- WHO Task Force, *Lancet*, 336:955-959, 1990

Hypothalamus Pituitary Testicular Axis



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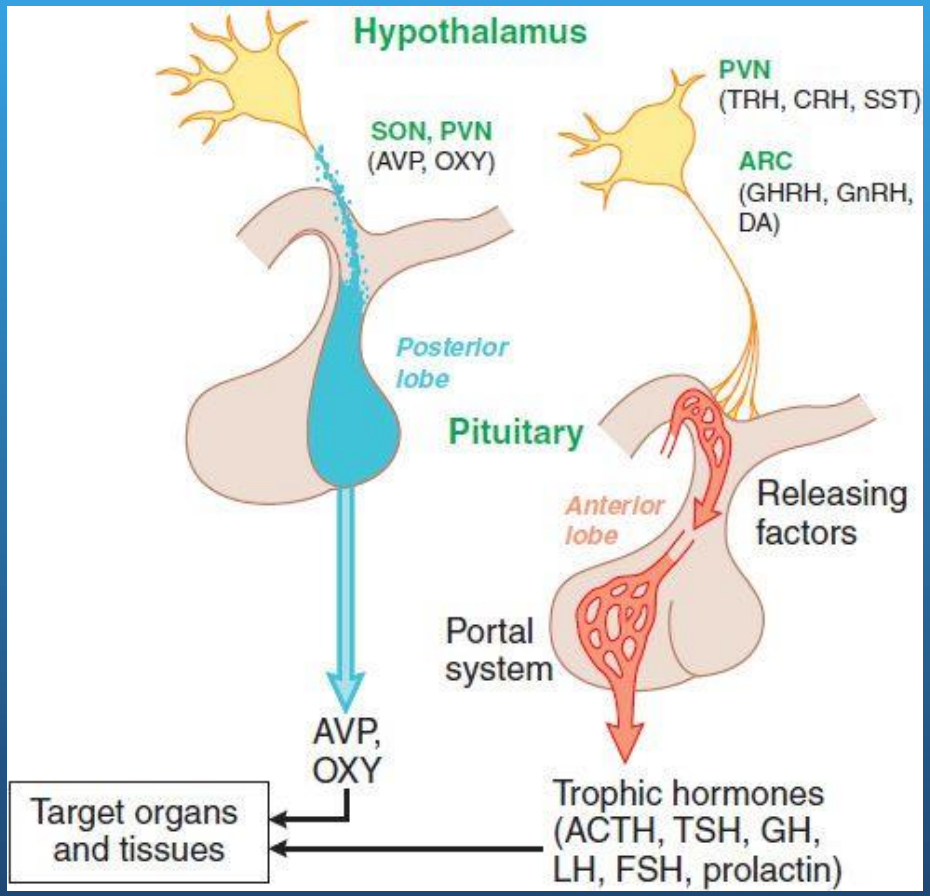
Different Neurons in the Hypothalamus

SON – Supraoptic Neuron, PVN – Paraventricular Neuron, ARC – Arcuate nucleus



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First Step in treating hypogonadism



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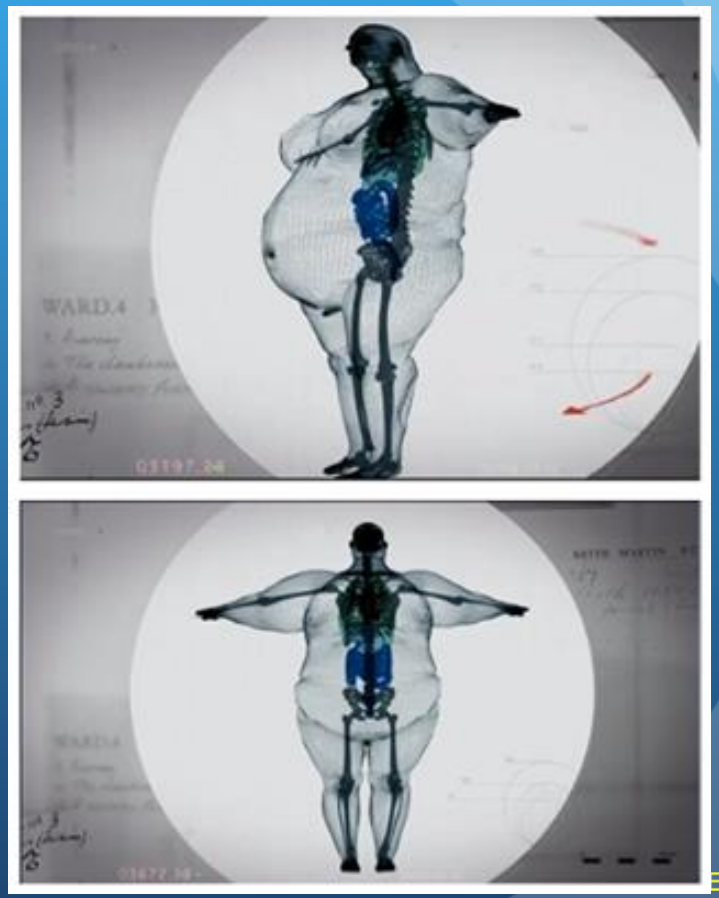
Weight Loss increases Testosterone levels

Dr Hayes, The Endocrine Society's 94th Annual Meeting in Houston in 2012.

- Average age of 54 years old
- Exercising for 150 minutes a week and eating less fat and fewer calories
- Average weight loss of 17 pounds in 1 year



Weight Loss increases Testosterone levels

- With lifestyle modification, the prevalence of low testosterone levels decreased from about 20% to 11% after one year

- Dr Hayes presented at The Endocrine Society's 94th Annual Meeting in Houston in 2012.



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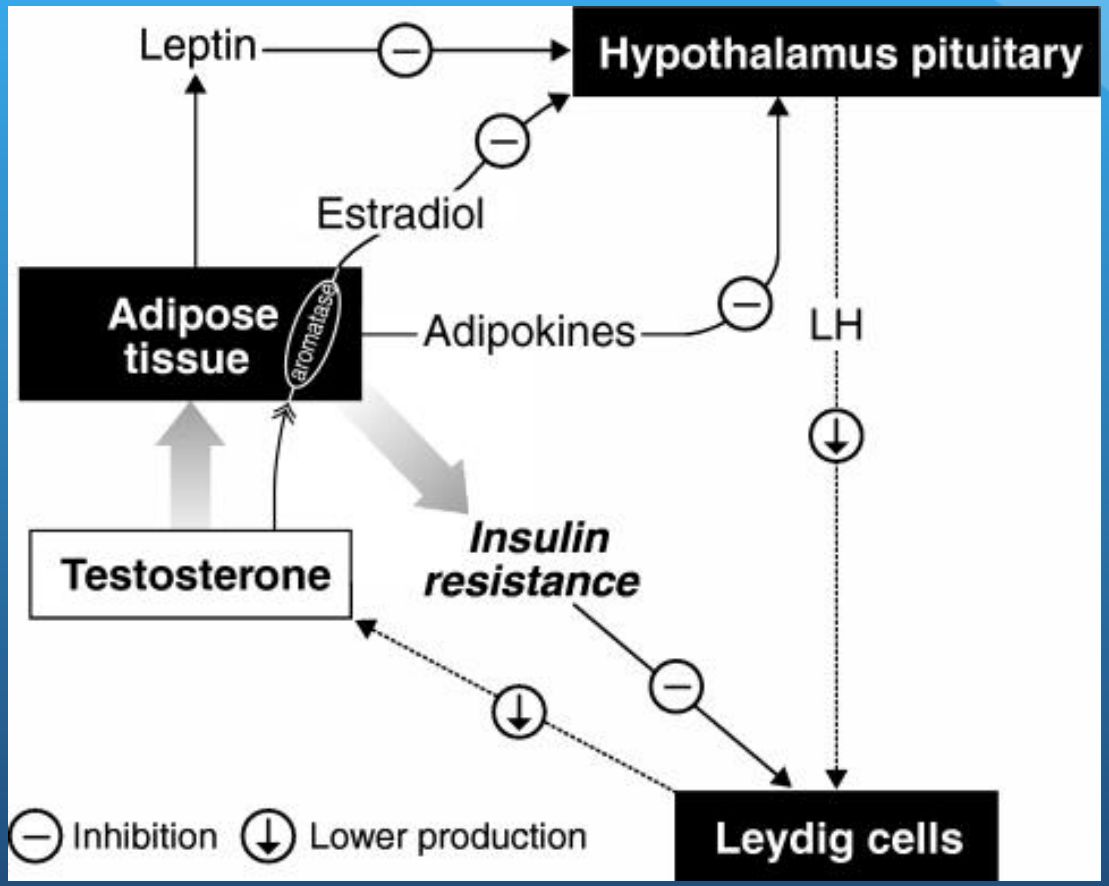
Insulin Resistance cause Low T



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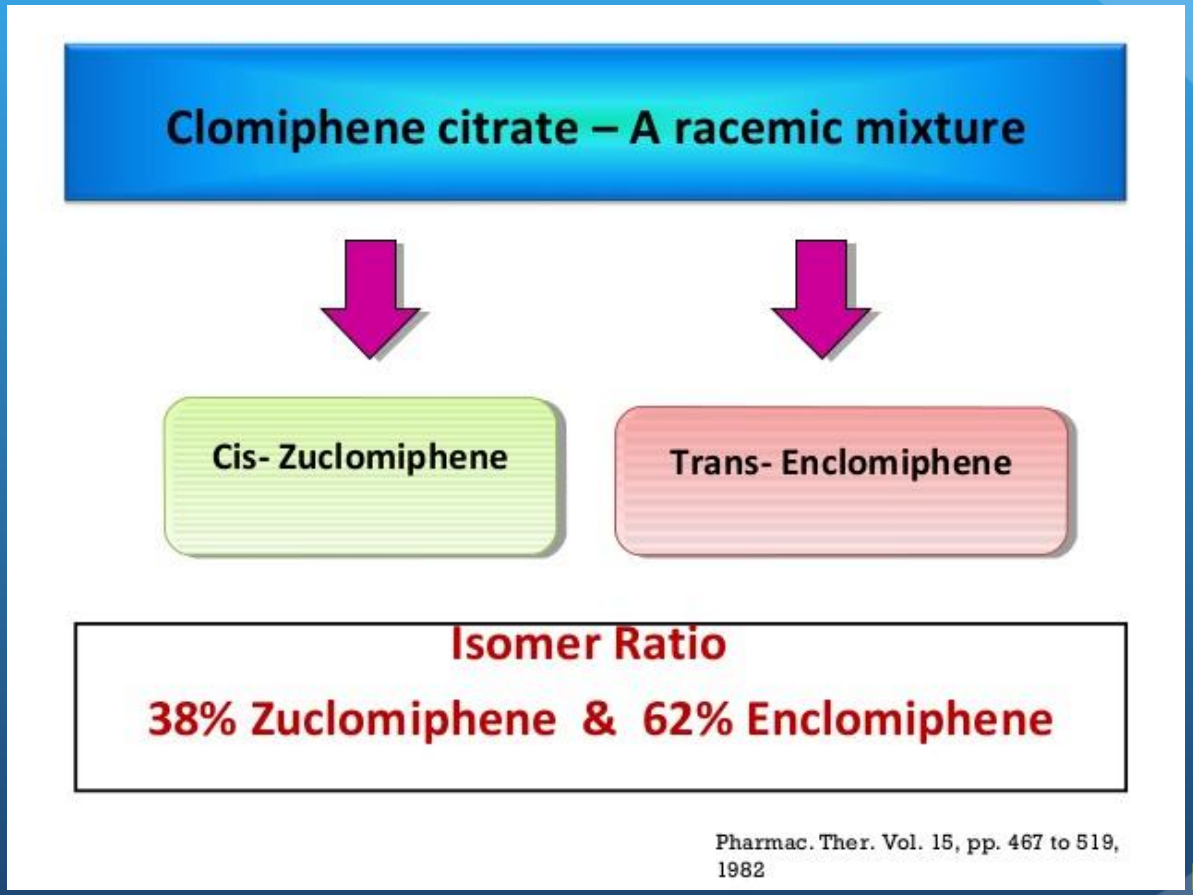
Clomid or Clomiphene

- Clomiphene citrate (CC) is frequently used off-label for the treatment of hypogonadism
- SERM -selective estrogen receptor modulator
- Increases the release of LH and FSH



Clomiphene is a mixture of two isomers: zuclomiphene and enclomiphene



Clomid or Clomiphene

Dadhich P, et al. Indian J Urol. 2017 Jul-Sep; 33(3): 236-240.

- 2017 Study
- **Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men**
- N = 75
- All with a Testosterone level less than 300 ng/dl

	Clomid	Testosterone
Baseline	235	281
3-5 months later	438	541



CLOMIPHENE CITRATE IN THE TREATMENT OF IDIOPATHIC OR FUNCTIONAL HYPOGONADOTROPIC HYPOGONADISM IN MEN

- Clomiphene was initially prescribed at doses between 25 mg 3 times a week and 50 mg/day
- Liel Y. Endocr Pract. 2017 Mar;23(3):279-287

- At 6 to 8 weeks mean basal total-testosterone increased from 219 ng/dL to 556 ng/dL (P<.0001)
- 1 complaint of transient breast tenderness



Outcomes of clomiphene citrate treatment in young hypogonadal men

- N = 86
- Testosterone < 300 ng/dl
- Dosing 25 mg every other day (70%) and titrated to 50 mg every other day (30%)
- 19 months

	Baseline	Treatment
Total T ng/dl	192	485
Free T pg/ml	22	95

- Katz DJ JU Int. 2012 Aug;110(4):573-8. doi: 10.1111/j.1464-410X.2011.10702

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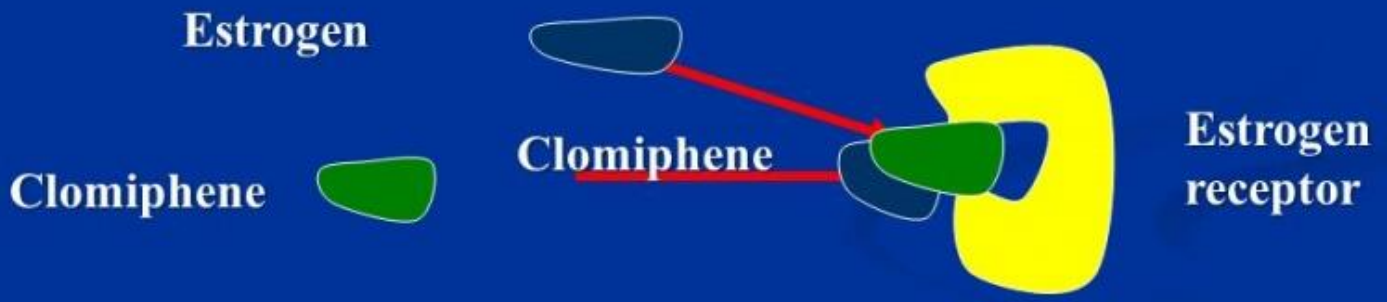
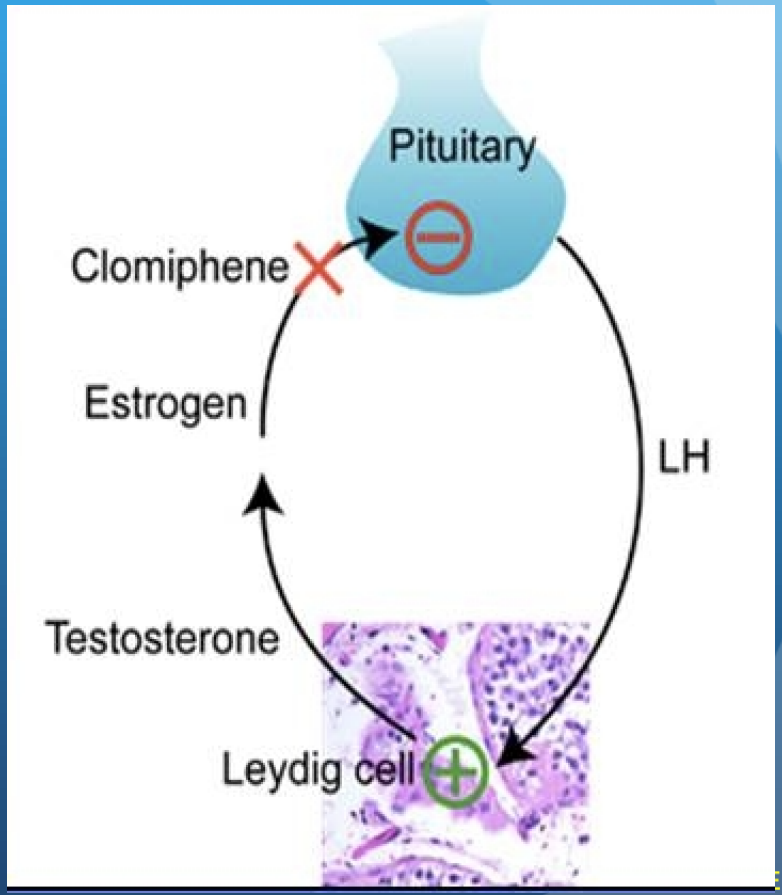
Clomiphene: Mechanism of Action



Structurally like estrogen, it binds to brain receptors where estrogen normally attaches, fooling body into thinking E2 is too low

Clomiphene or Clomid

- Competitively binds to estrogen receptors on the hypothalamus and pituitary
- The pituitary sees less estrogen and makes more LH, increasing T production by the testis



Clomiphene or Clomid

- Half life is 5 days
- Approved by the FDA in 1967
- Approved by the FDA in 1976 to treat female infertility
- Dose in women 25 mg to 250 mg (generally 50-100 mg)



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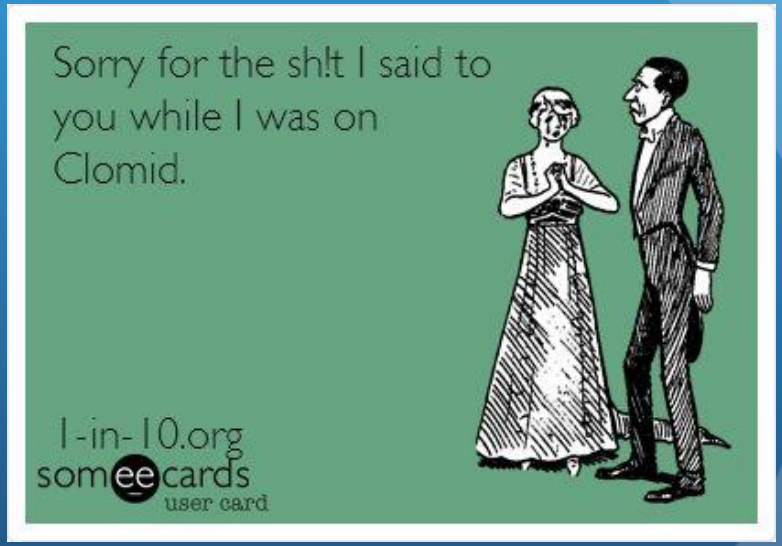
Clomiphene Side effects

- Visual disturbances, including blurred or double vision, scotomata, and light sensitivity, generally are uncommon (<2% prevalence) and reversible
- anxiety, decreased appetite, and depressed mood

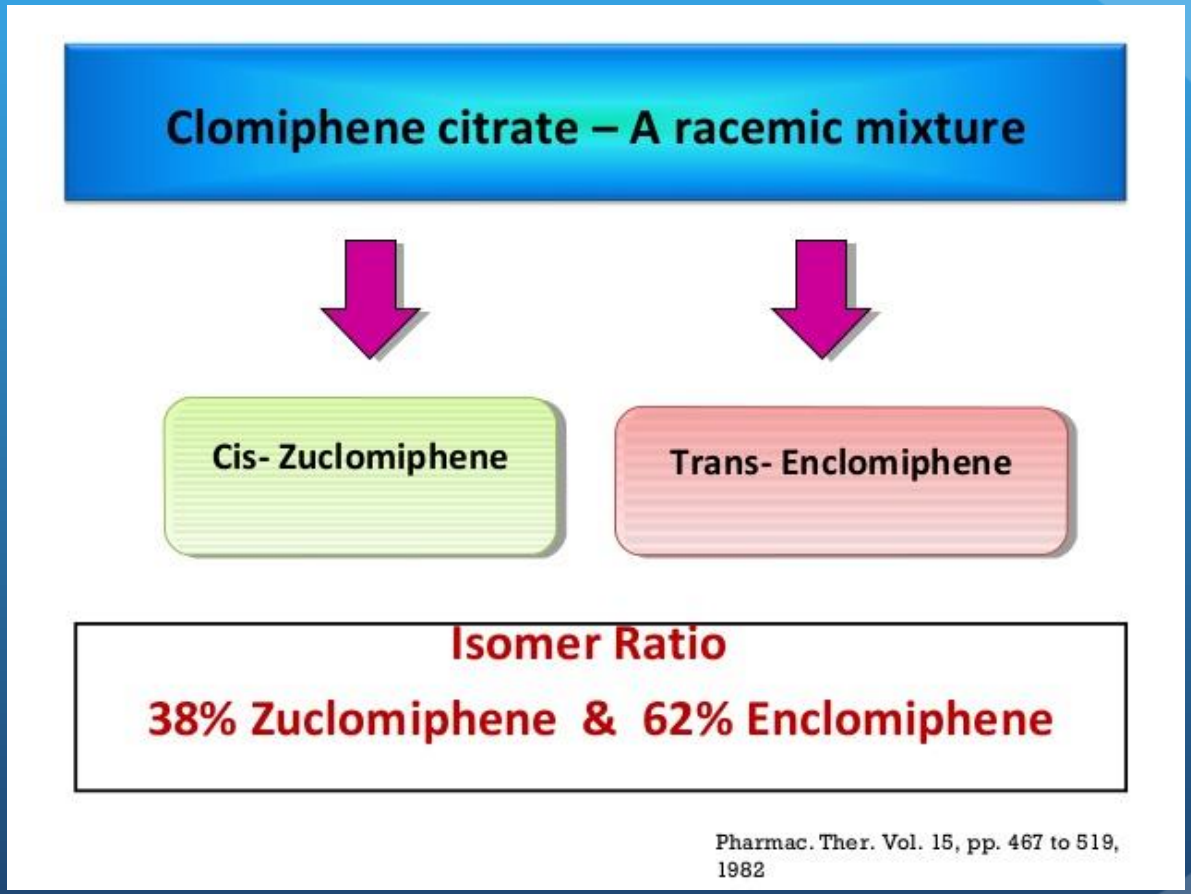


Clomiphene or Clomid

- Dosing in Men (off label)
- 25 to 50 mg three times a week to every 3 days
- Try to use the lowest dose



Enclomiphene – isomer of Clomiphene



Zuclomiphene

Fortenot GK, et al. BJU Int. 2016 Feb;117(2):344-50. doi: 10.1111/bju.13244
Glasier et al. Hum Reprod. 1989 Apr;4(3):252-6.

ER agonist

↓

Opposes the action of Enclomiphene

↓

Lowers Testosterone levels



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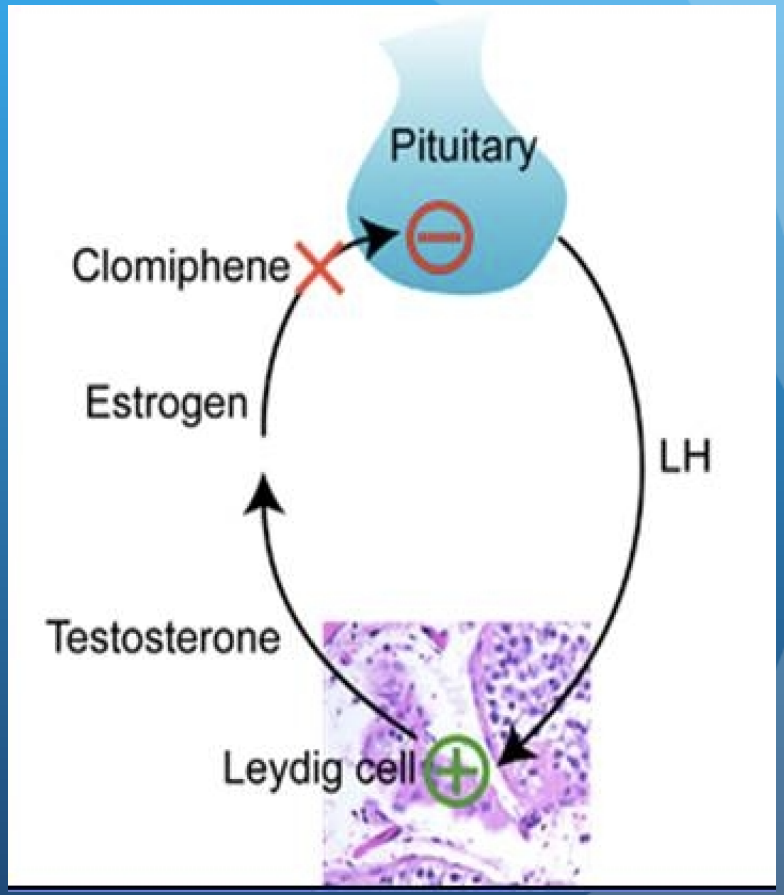
Enclomiphene

- SERM- Selective Estrogen Receptor Modulator
- Increases LH and FSH
- Increase Testosterone



- Rodriguez K, et al. Expert Opin Pharmacother. 2016 August ; 17(11): 1561-1567.

Enclomiphene

- Half life is 10 hours
- Maximum serum drug concentration after a single dose of enclomiphene was achieved 2-3 hours after drug ingestion



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Enclomiphene 12.5 mg or 25 mg

- Enclomiphene resulted in increased morning serum Testosterone similar to those obtained with a topical T gel
- Wiehle et al. Fertil Steril. 2014 Sep;102(3):720-7. doi: 10.1016
- Follicle-stimulating hormone and LH were increased with enclomiphene, and sperm counts were conserved.



Enclomiphene versus Clomiphene

- Enclomiphene has a shorter half life of 10 hours versus Clomiphene half life of 5 days
- Enclomiphene is the active part of Clomiphene
- Clomiphene has zuclomiphene which is estrogen agonist



Enclomiphene- Androxal

- Currently not FDA approved in the USA
- Seeing FDA approval in Europe
- Increase in Testosterone lasted 7 days after stopping enclomiphene



Enclomiphene

- Not FDA approved in the US
- Doses 12.5 mg to 25 mg
- Off label use – start with 12.5 mg Monday to Friday
- Give the Pituitary a holiday



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HCG – Human Chorionic Gonadotropin

- Discovered in 1930
- Pregnancy test- hCG can be detected in urine or blood after implantation, which occurs six to twelve days after fertilization



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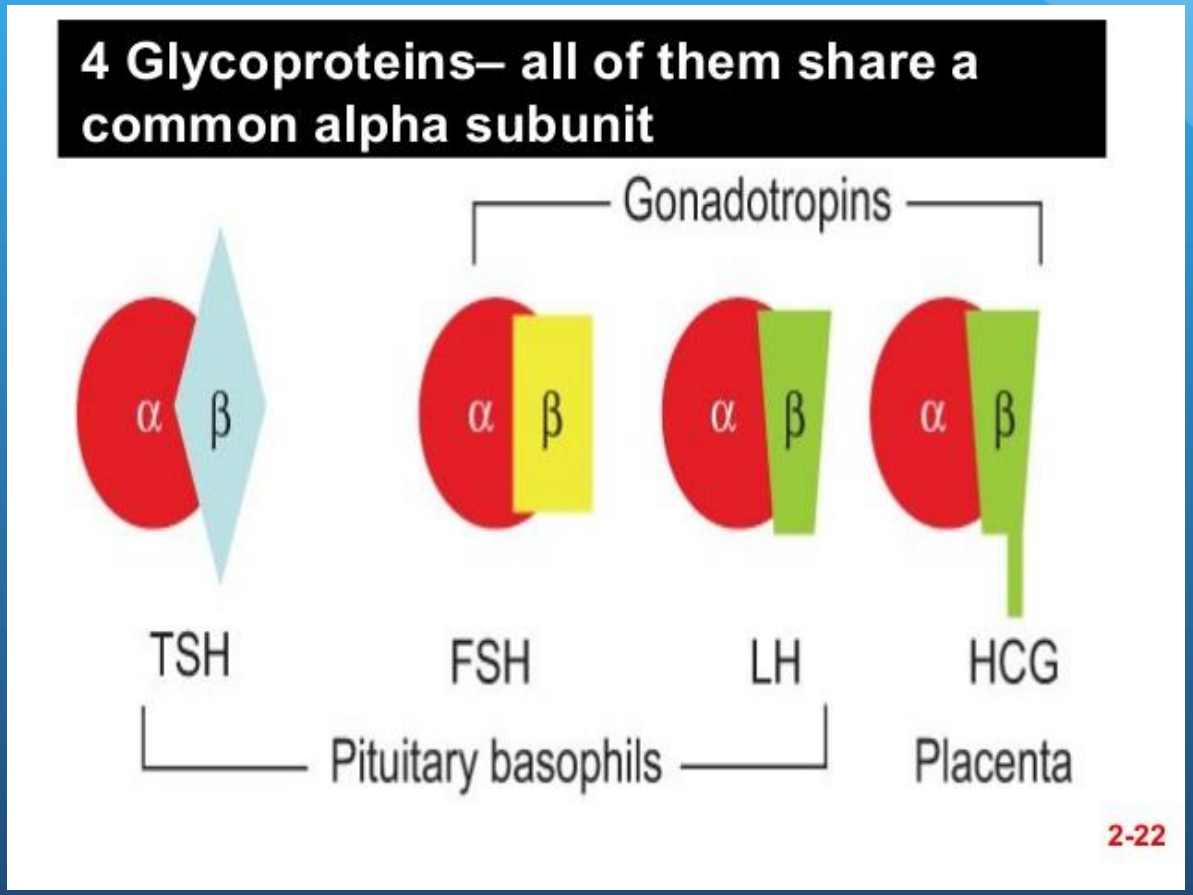
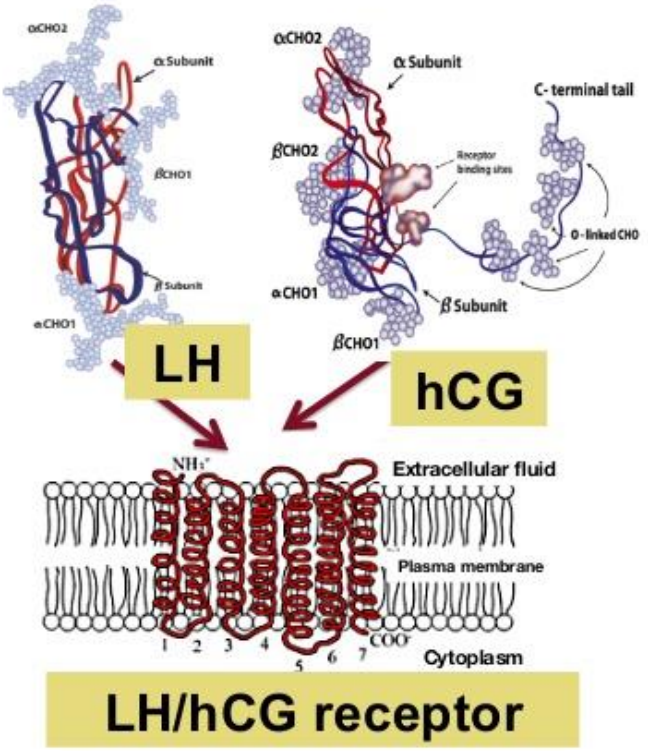
HCG – Human Chorionic Gonadotropin



HCG – Human Chorionic Gonadotropin

Sharing the same α subunit and 81% of AA residues of β subunit, LH and hCG bind to the same receptor



Adapted from: Leao & Esteves.
Clinics 2014; 69(4): 279–293.

HCG – Human Chorionic Gonadotropin

Lipsett M, et al 1966 Reccent Progr. Hormone Res. 22:245
Steelman SL, et al. 1953 Endocrinology 53: 604

1930
- Discovery of HCG

1953
- FSH increases with HCG

1966
- HCG for Leydig cell function



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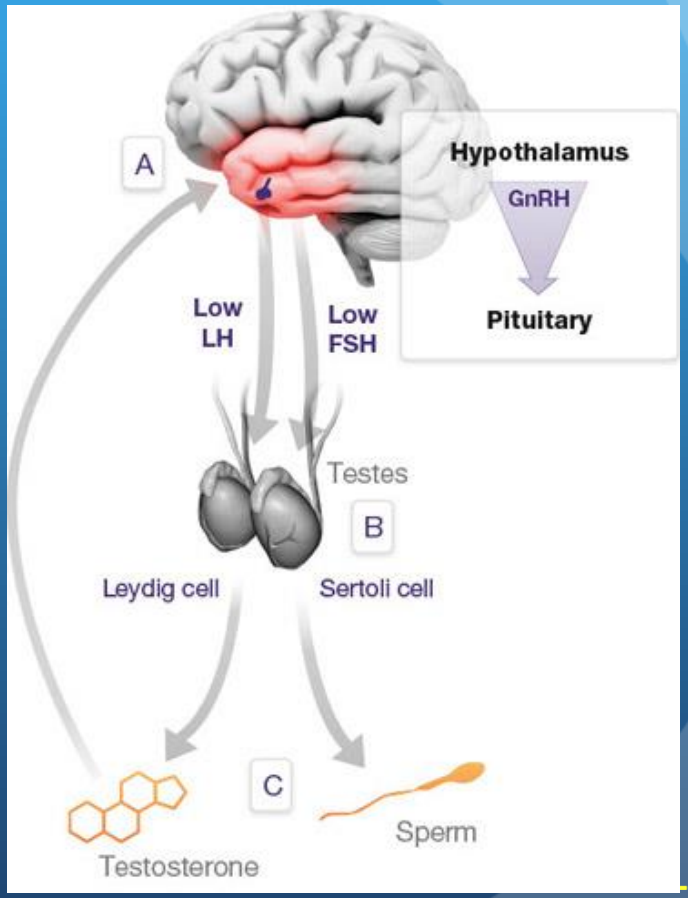
HCG – Human Chorionic Gonadotropin

- 1968 - HCG was used to treat secondary hypogonadism

- Knorr D. 1968 Testosterone excretion in boys treated with HCG for cryptorchidism. Testosterone, 1st edition 190



HCG – Human Chorionic Gonadotropin

- Study in 1974 showed in 6 men with Low FSH and LH that did not respond to Clomiphene for 12 weeks
- HCG 5000 Units IM daily for 4 days then 3 times a week x 12 weeks
- Treatment with human chorionic gonadotropin (HCG) increased levels of plasma testosterone to normal adult male values in all 6 men
- 6 weeks after stopping HCG, testosterone level dropped to undetectable levels

- Weinstein R, et al. J Clin Invest. 1974 Feb;53(2):408-15.

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HCG – Human Chorionic Gonadotropin

- Retrospective study of 223
- Congenital Hypogonadotropic hypogonadism (deficiency or dysfunction of GnRH)
- Liu Z, et al. Medicine Volume 95, Number 9, March 2016

Kallmann's syndrome

- Anosmia, small testes, cryptorchidism, color blindness, *hypogonadotropic hypogonadism*
  - GnRH secretion failure by hypothalamus causing testicular failure



HCG – Human Chorionic Gonadotropin

- HCG 2000- 5000 U -IM 2 times a week x 6 months then followed
- HMG (Human menopausal gonadotropin) 75-150 U- IM 2 times a week
- Adverse events- < 10% Acne, Gynecomastia

	Baseline	> 6 months
Testosterone	26 ng/dL	432 ng/dL
Testicular size (ml)	2.1 ml	8.1 ml

- Liu Z, et al. Medicine Volume 95, Number 9, March 2016

HCG – Increase Penis size

- 20 males with idiopathic hypogonadotrophic hypogonadism with micropenis
- HCG 1500 -2000 IU IM times a week x 8 weeks
- Avg age of 18.9 years old

	Baseline	24 weeks
Testosterone	90 ng/dL	558 ng/dL
Penile length cm flaccid	3.39 cm	5.14 cm

- Kim, Sun Ouck, et al Chonnam Med J. 2011 Apr; 47(1): 39-42.

HCG not working

- Defective testicles- mutations in certain genes, such as FGFR1 and KAL1 have a direct impairment on testicular development and spermatogenesis.
- HCG (recombinant versus urine collected from pregnant women)- batch to batch inconsistencies and impurities

- Biffoni M, Marcucci I, Ythier A, et al. Effects of urinary gonadotrophin preparations on human in-vitro immune function. Hum Reprod. 1998;13:2430–2434.
- Cotton L, Gibbs GM, Sanchez-Partida LG, et al. FGFR-1 [corrected] signaling is involved in spermiogenesis and sperm capacitation. J Cell Sci. 2006;119(Pt 1):75–84.
- Salenave S, Chanson P, Bry H, et al. Kallmann's syndrome: acomparison of the reproductive phenotypes in men carrying KAL1 and FGFR1/KAL2 mutations. J Clin Endocrinol Metab.2008;93:758–763.

HCG dosing

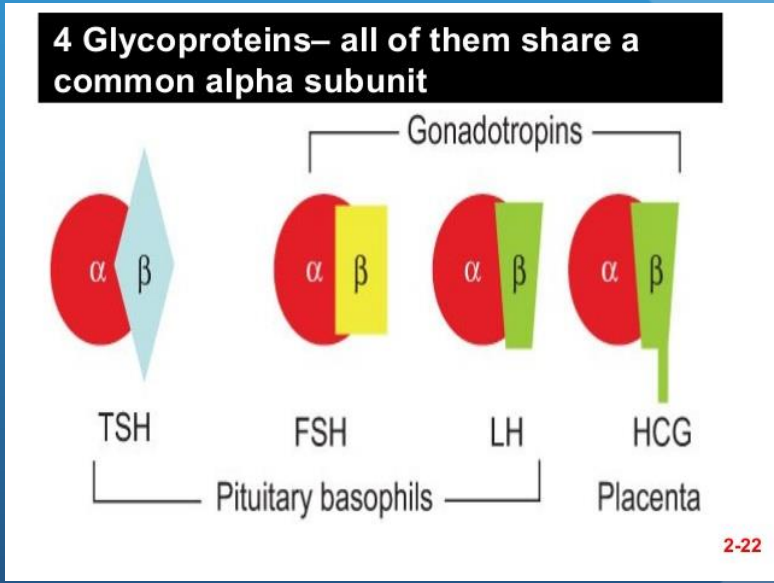
- 500 units to 1000 units Sq daily for 5 days then Monday, Wed and Friday
- Recheck testosterone in 2 weeks
- Increase HCG to 2500 units SQ 3 times/ week



HCG concern w/ Prostate cancer

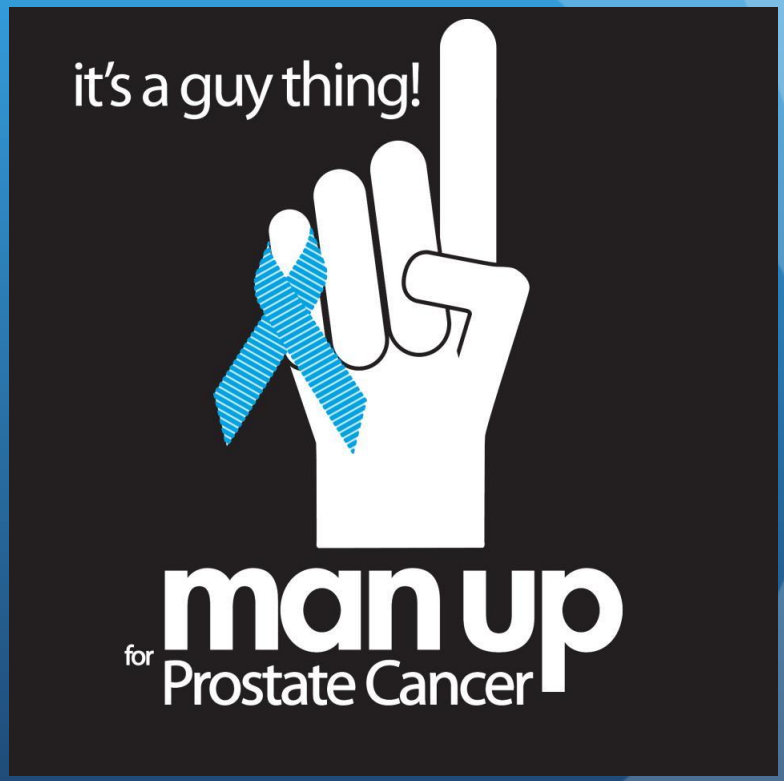
- The presence of HCG- ß in prostatic adenocarcinoma identifies a population of patients with a poor prognosis

- *Sheaff MT, et al. beta hCG as a prognostic marker in adenocarcinoma of the prostate. J Clin Pathol. 1996; 49: 329-332.*



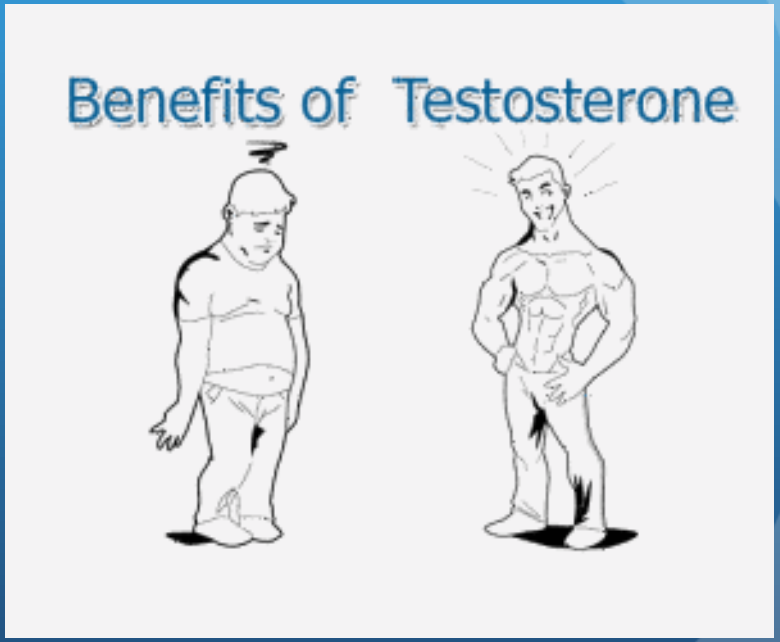
HCG concern w/ Prostate cancer

- **Beta HCG down-regulates E-cadherin and promotes human prostate carcinoma cell migration and invasion. (in vitro)**
- **Wu W, Walker AM** Cancer. 2006 Jan 1;106(1):68-78.



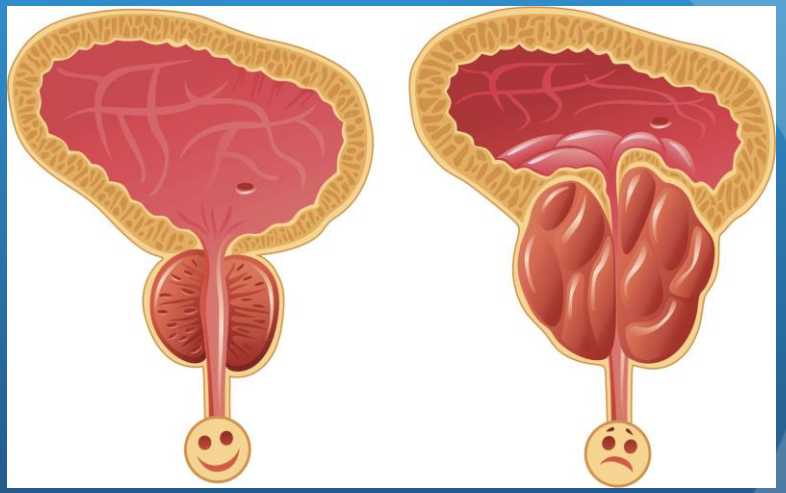
Is there a new therapy?

- Improve on Testosterone action
- Increase physical activity
- Improve on bone health



Is there a new therapy?

- Improving on testosterone action without breaking down to E2 or DHT
- Without affecting the prostate
- Without affecting cardiovascular outcomes



New Therapy – SARM
Selective androgen receptor modulator

- Many companies have been trying to develop a SARM to treat muscle wasting and functional limitations associated with chronic illness and aging
- In animal models LGD-4033 has demonstrated anabolic activity in bone and muscle without affecting the prostate



- Basarua et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95

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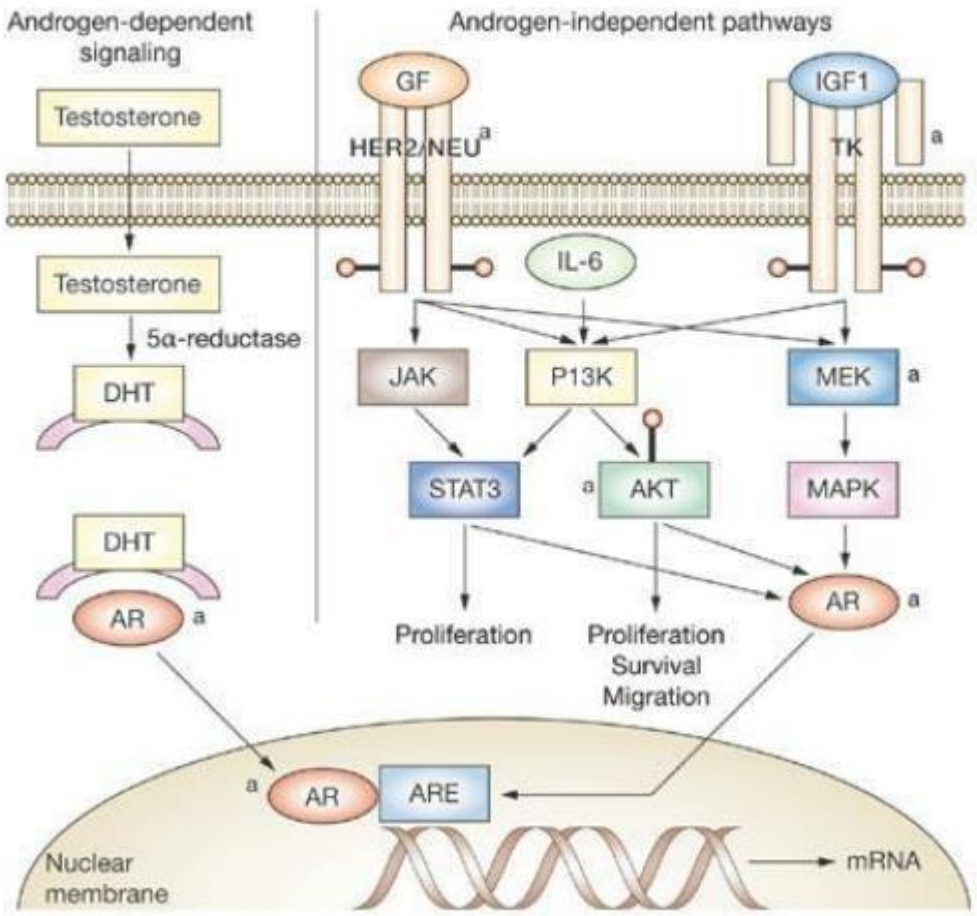
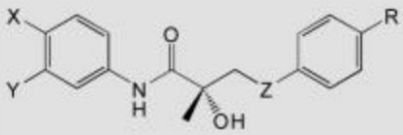
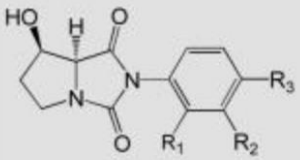
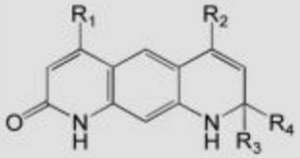
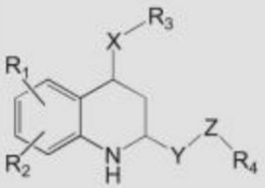
Androgen Receptor Signaling



4 General classes of SARM

Bhasin S, et al. Nat Clin Pract Endocrinol Metab. **2006** Mar; 2(3): 146–159.

CHEMOTYPE	GENERAL CHEMICAL STRUCTURE	IDENTITY OF LEAD MOLECULE	COMPANY	STAGE OF DEVELOPMENT
Aryl propionamide analogues		Ostarine Andarine	GTx Inc. Ortho Biotech	Phase I Phase I
Bicyclic hydantoin analogues		BMS564929	BMS	Phase I
Quinoline analogues		LGD2226	Ligand Pharmaceuticals TAP	Phase I
Tetrahydro-quinoline analogues		S-40503	Kaken (Japan)	Preclinical discovery

New therapy- SARM

Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95

- LGD-4033 is a novel nonsteroidal oral SARM that binds to androgen receptor with high affinity

- 76 healthy men (21-50 years old)
- Placebo controlled randomized to placebo or 0.1, 0.3 or 1 mg LGD-4033
- 21 days
- Study went 5 weeks after treatment



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New Therapy – SARM
Selective androgen receptor modulator

- Previous phase I single ascending-dose study had established the safety of up to 22 mg LGD-4033
- Half life of 30 hours
- Serum LGD-4033 concentrations were nearly threefold higher on day 21 than on day 1

- Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95



New therapy- SARM

Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95

- Increase in LBM averaged 1.21 kg at the 1.0 - mg dose (p = 0.047 vs placebo)
- Stair - climbing speed and power revealed a trend toward dose-related improvement but these changes did not achieve statistical significance
- LGD-4033 was safe and well tolerated at all doses



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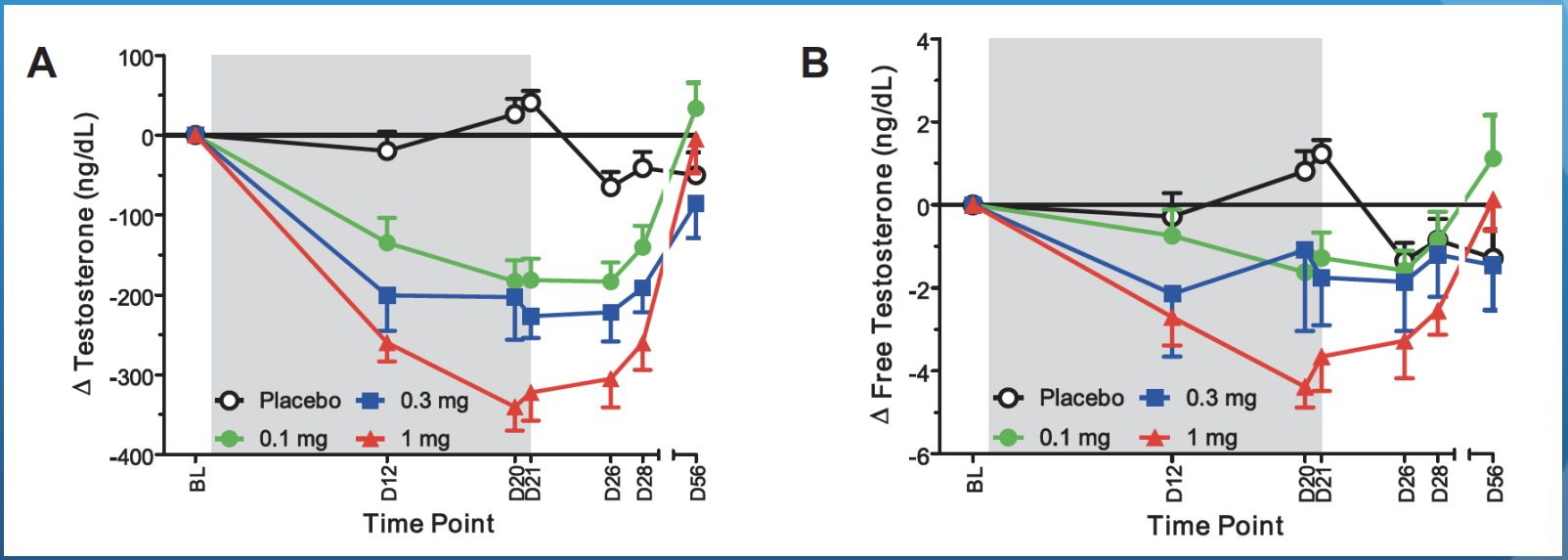
Treatment Group*	Mean (*SD*) Baseline	Mean (*SE*) Change From Baseline	
		Day 21	Day 56
Total cholesterol (mg/dL)			
Placebo	163.4 (28.1)	−1.6 (2.9)	5.2 (4.2)
0.1 mg	163.3 (33.5)	−10.8 (3.6)	0.4 (5.5)
0.3 mg	168.6 (16.6)	−18.0 (4.8)	6.4 (5.0)
1 mg	175.1 (33.5)	−14.3 (8.1)	0.3 (4.4)
HDL cholesterol (mg/dL)			
Placebo	52.5 (11.8)	−1.7 (1.2)	0.4 (1.8)
0.1 mg	56.1 (17.3)	−1.0 (2.6)	3.5 (2.3)
0.3 mg	50.3 (8.0)	−10.4 (1.4)	0.6 (1.7)
1 mg	49.2 (11.7)	−19.4 (2.1)	−1.1 (3.2)
LDL cholesterol (mg/dL)			
Placebo	92.4 (26.2)	0.9 (2.6)	4.4 (3.7)
0.1 mg	91.0 (29.6)	−5.5 (3.3)	−4.5 (4.9)
0.3 mg	101.5 (15.9)	−2.8 (4.5)	1.7 (3.7)
1 mg	106.8 (31.6)	7.1 (7.1)	4.42 (4.0)
Triglycerides (mg/dL)			
Placebo	92.6 (36.8)	−4.3 (4.7)	1.9 (7.5)
0.1 mg	80.0 (31.0)	−21.4 (8.1)	7.2 (9.1)
0.3 mg	84.4 (26.1)	−24.0 (4.3)	20.8 (8.0)
1 mg	95.4 (39.1)	−10.1 (6.7)	−15.6 (8.0)



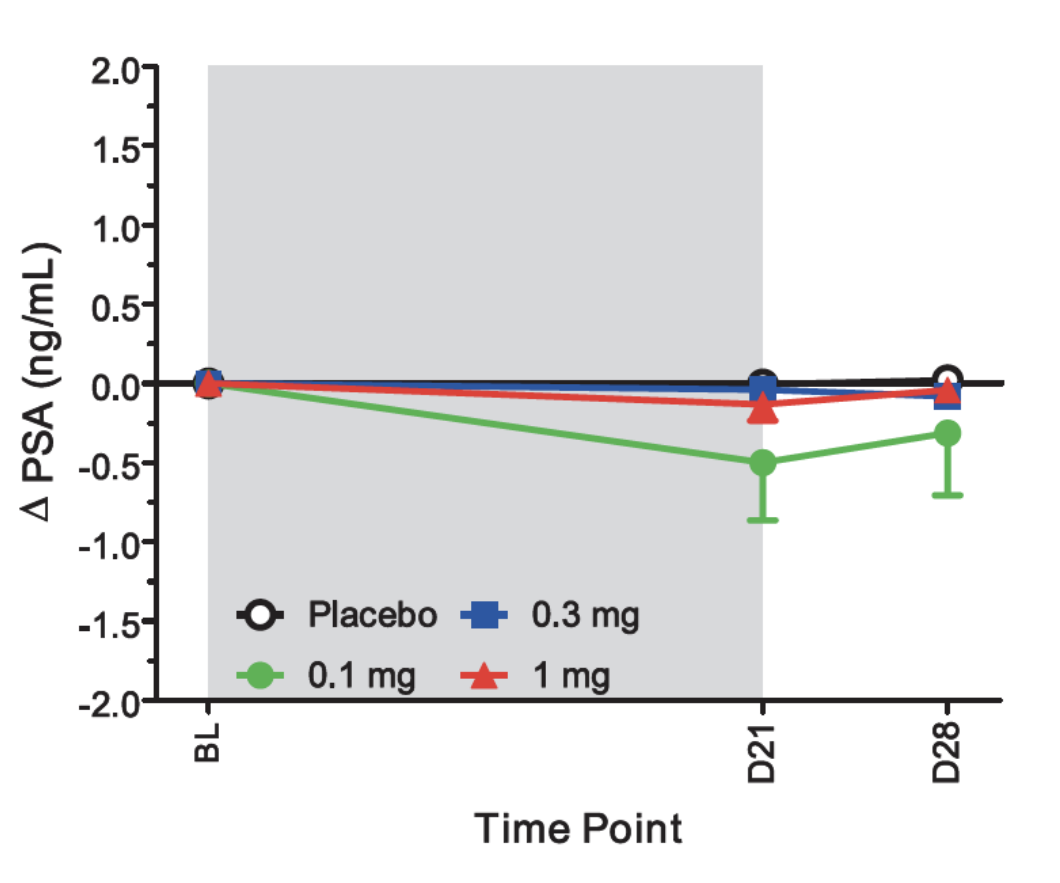
New therapy- SARM

Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95



New therapy- SARM

Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95



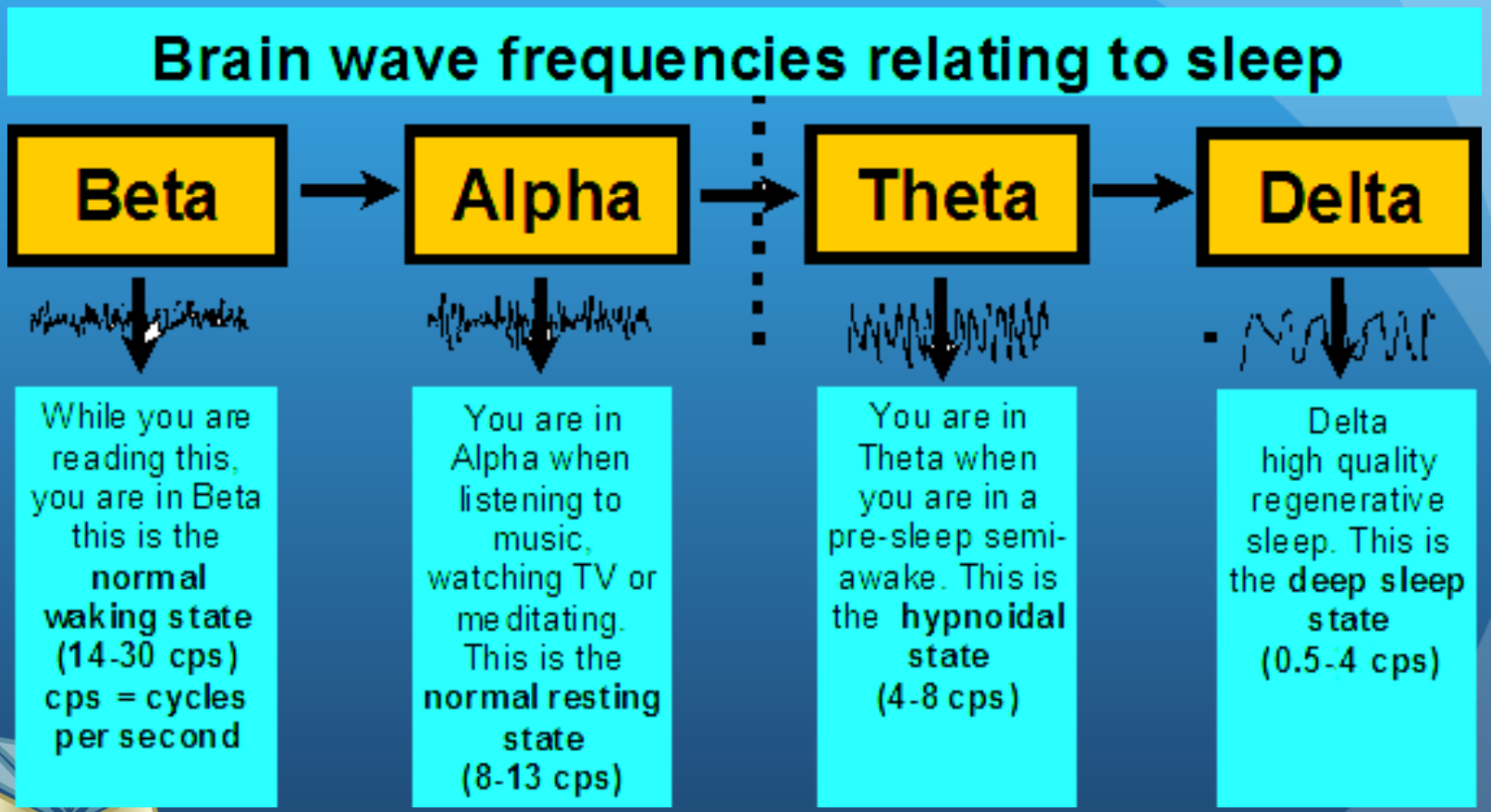
New therapy- SARM

Basaria S. et al. J Gerontol A Biol Sci Med Sci. 2013 Jan;68(1):87-95

- Not FDA approved in the US
- LGD- 4033 Dose 1 mg
- Off label use – 1 mg a day for 21 days then take 5 weeks off since LGD-4033 accumulates
- Monitor the lipids



Delta Wave- Deep Restorative Sleep



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Delta Sleep Induced Peptide

- Delta sleep-inducing peptide was first discovered in 1974 by the Swiss scientist who isolated it from the cerebral venous blood of rabbits in an induced state of sleep

- Kovalzon VM et al. J Neurochem. 2006 Apr;97(2):303-9



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Delta Sleep Induced Peptide (DSIP)

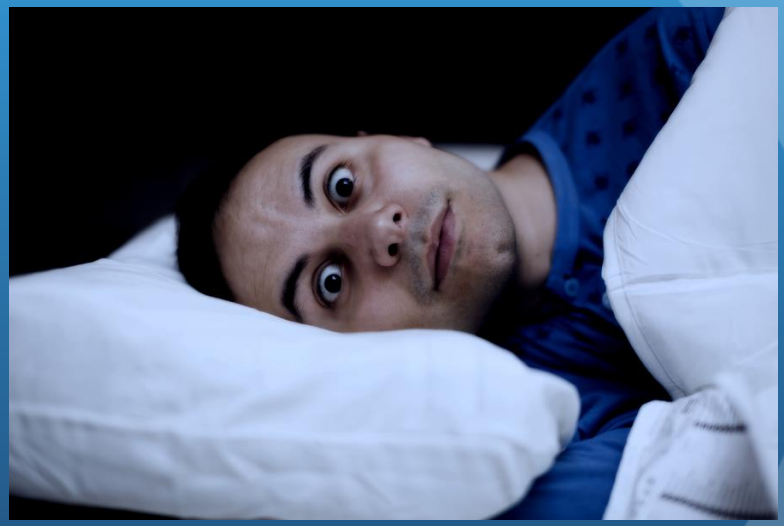
Charnay Y, et al. *Neuroendocrinology.* ***49*** *(2): 169-175*

- 9 Amino Acid Peptide
- It has been found in both free and bound forms in the hypothalamus, limbic system and pituitary
- However the Gene for DSIP and where it is made is still unknown



Delta Sleep Induced Peptide (DSIP) in chronic insomniacs

- DSIP appears to help promote sleep in humans
- Study of 6 chronic insomniacs were given IV DSIP 25 nmoles/kg improved sleep quality
- Schneider-Helmert, D. & Schoenenberger, G.A. Experientia (1981) 37: 913



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Delta Sleep Induced Peptide (DSIP) in Narcolepsy

- Repeated injections of DSIP was given to a 35-year-old male narcoleptic which reduced the frequency of sleep attacks.
- Schneider-Helmert D. Eur Neurol. 1984;23(5):353-7



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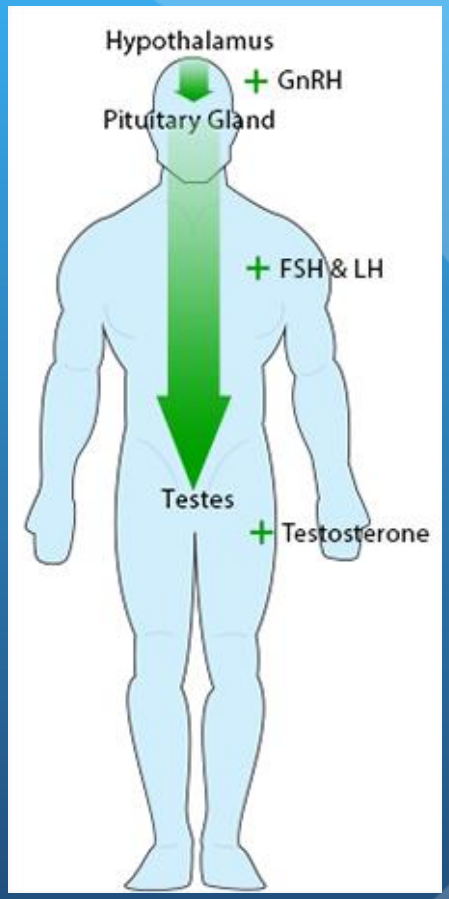
Delta Sleep Induced Peptide (DSIP) on LH

- In rat studies DSIP has been shown to increase LH
- DSIP-may activate the hypothalamic neural circuitry responsible for stimulation of LH release reported to occur during sleep.



- Sahu A, et al. Life Sci. 1987 Mar 23;40(12):1201-6.

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Delta Sleep Induced Peptide

200 mcg sq qhs for 2 weeks

	LH	Testosterone ng/dL
Baseline	7.1	370
DSIP 200 mcg	11	416



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Delta Sleep Induced Peptide

200 mcg sq qhs for 2 weeks

	LH	Testosterone ng/dL
Baseline	2.9	776
DSIP 200 mcg	7.5	1040



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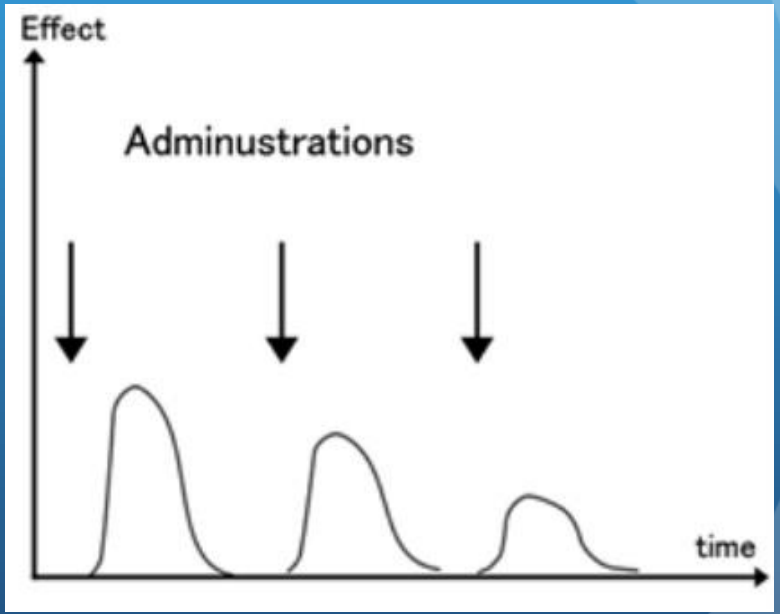
Delta Sleep Induced Peptide

- To prevent tachyphylaxis it is best to give the hypothlamus a break.
- 3 to 5 nights a week
- 100 mcg to 800 mcg Subcutaneous at bedtime



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Puberty begins with a Kiss

Rhie YJ, et al.*Annals of Pediatric Endocrinology & Metabolism.* ***18*** *(2): 55-59.*

- Kisspeptin is a neuroendocrine peptide than stimulates the release of Gonadotropin Releasing Hormone (GnRH) and is involved in the start of puberty



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Kisspeptin

Lee JH et al., *Journal of the National Cancer Institute*. ***88*** *(23): 1731-7*

- Kisspeptin is a peptide that is encoded by the KISS1 gene
- Originally identified as a human metastasis suppressor gene for melanoma and breast cancer metastasis
- KISS1 gene was discovered in Hershey, Pennsylvania in 1966



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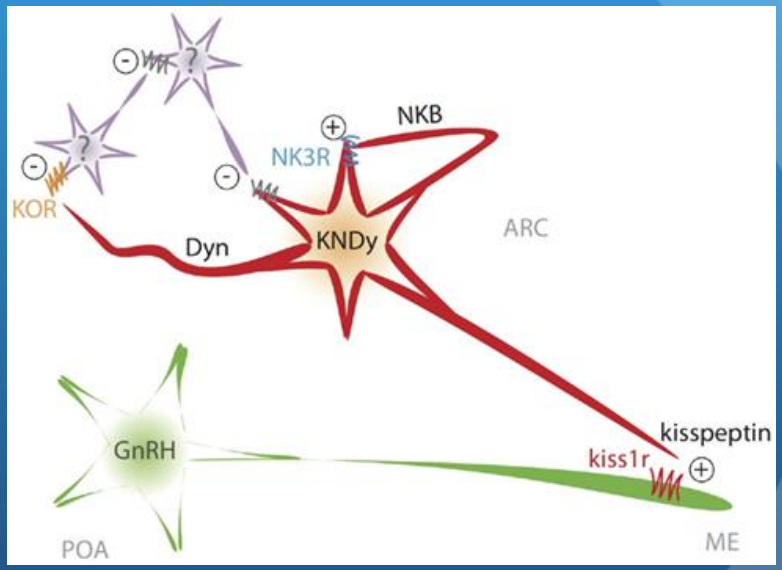
Kisspeptin- Released from KNDy

Pasquier J, et al. *Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors". Journal of Molecular Endocrinology.* ***52*** *(3): T101–17.*

- Kisspeptin is released together with two other hormones, neurokinin B and dynorphin.
- Consequently, the nerve cells making kisspeptin, dynorphin and neurokinin B are popularly referred to as KNDy



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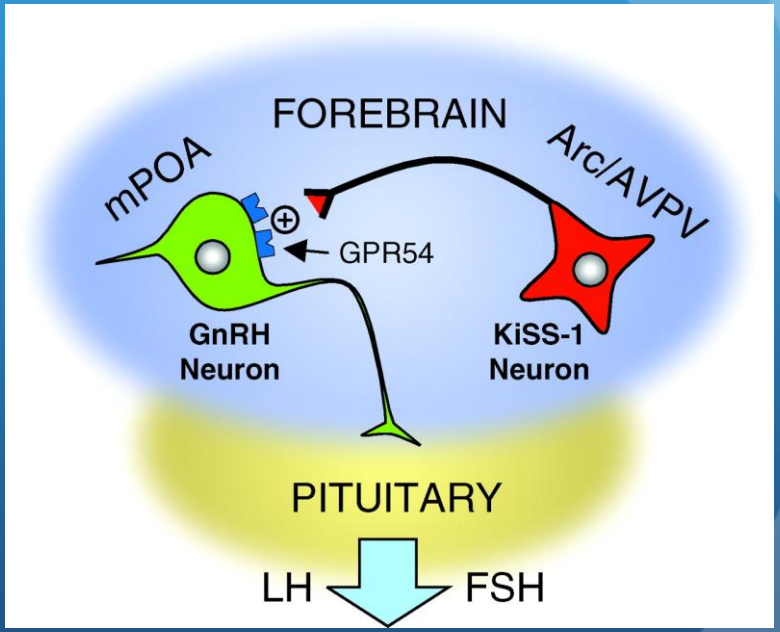
Kisspeptin increases LH and FSH

- Kisspeptin interacts with the KISS1 receptor or the GPR54 receptor
- Kisspeptin stimulates the release of GnRH and thus increase LH and FSH



- Rhie YJ, et al.*Annals of Pediatric Endocrinology & Metabolism.* ***18*** *(2): 55-59*

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Kisspeptin
Stimulates
GnRH
LH/FSH
Gonadotropins
Gonads
> Sexual development
> Gametogenesis
Baronerocks.com
I'm Gonna rock n Roll all night and get Puberty every day!
©2010 Alberto Cabello from Vitoria Gasteiz (Gene Simmons (KISS)) [CC BY 2.0 (http://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons

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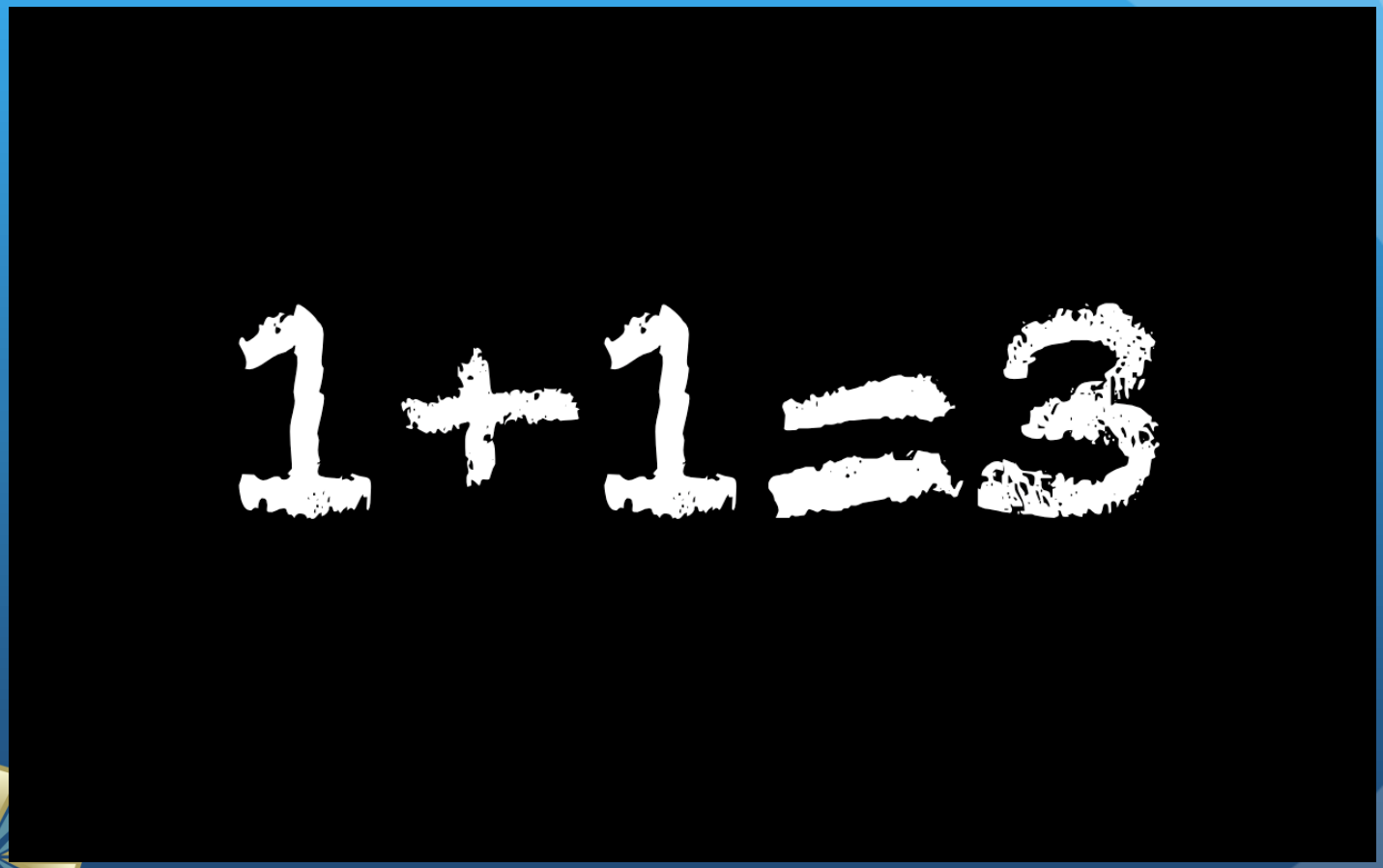
Kisspeptin initiates Puberty



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Kisspeptin levels w/ hypogonadism

Masato Kotani et al. Endocrine Journal 2014, 61 (11), 1137-1140

	fmol/ml
Normal controls (7 men)	12
Kallman's syndrome	43
Azoospermia (elevated FSH and LH)	41
Hypergonadotropic hypogonadism	323
Hypogonadotropic hypogonadism	6



Kisspeptin 54 increases testosterone

- Double blind placebo controlled crossover study
- N = 6
- 90 minute infusion 4 pmol/kg x min
- LH increased from 4.2 to 10.8
- Testosterone increased from 625 ng/dl to 718 ng/dl ($p < 0.001$)
- Dhillo WS, et al. J Clin Endocrinol Metab. 2005 Dec;90(12):6609-15.



Response to Kisspeptin -54 is preserved in 60 year old men (Older men)

- 5 men 60 years old compared to 5 men 29 years old
- 3 hour intravenous infusion kisspeptin-54 0.1, 0.3, 1.0 nmol/kg/h
- Abbara A, et al. Neuroendocrinology. 2018 Mar 15. doi: 10.1159/000488452

- Dose dependent
- LH and FSH response to Kisspeptin was preserved
- Testosterone increased with Kisspeptin but less compared to younger men (age of 29)



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Kisspeptin -10 increases Testosterone

- Kisspeptin-10 is the minimal kisspeptin sequence with full intrinsic bioactivity
- Infusion of kisspeptin-10 at 4 μg/kg · h for 22.5 hours
- George JT et al. Clin Endocrinol Metab. 2011 Aug;96(8):E1228-36

- Elicited an increase in LH from 5 to 21
- Increase in Testosterone from 478 ng/dl to 692 ng/dl ($p < 0.001$)
- Also increased LH pulse frequency



Kisspeptin- 10 in Type 2 Diabetics

- 5 men with low testosterone and with type 2 diabetes were compared to 7 healthy men
- Age is 33.6 years old
- BMI of 40.6
- George JT, et al. Clin Endocrinol (Oxf). 2013 Jul;79(1):100-4.



- Intravenous infusion of kisspeptin-10 (4 mcg/kg/h) was administered for 11 hours
- Increase in LH from 3.9 to 20.7 IU/l
- Increase in Testosterone from 245 to 329 ng/dl

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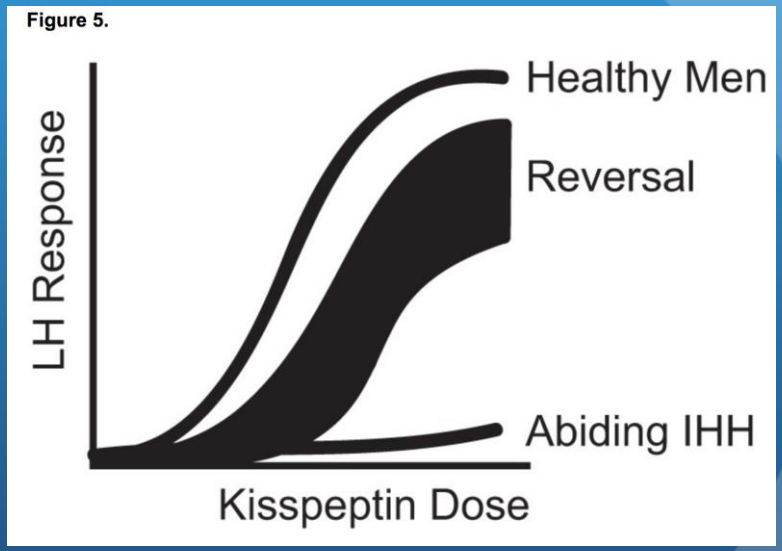
Response to Kisspeptin for idiopathic hypogonadotropic hypogonadism (IHH)

- LH response to iv boluses of kisspeptin (0.24–2.4 nmol/kg)
- In the future Kisspeptin may be used to access and to treat hypogonadotropic hypogonadism



- Lippincott MF, et al. J Clin Endocrinol Metab. 2016 Aug; 101(8): 3061–3069

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Summary

- For Men consider Clomiphene 25 to 50 mg three times a week to every 3 days
- For Men Enclomiphene Off label use – start with 12.5 mg Monday to Friday
- For Men HCG - 500 units to 1000 units Sq daily for 5 days then Monday, Wed and Friday
- For Men LGD –4033: Off label use- 0.5 mg a day for 30 days then take 30 days off since LGD-4033 accumulates



Summary

- Delta Sleep Induced Peptide –100 mcg to 800 mcg subcutaneous at bedtime. Use it 3- 5 nights a week
- Kisspeptin is an exciting new peptide that regulates GnRH and will have a lot of therapy in men and in women
- First Step is Weight Loss
- Recommend to use therapy that stimulates the production of testosterone before using exogenous testosterone



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