

# **ENDOCRINE FUNCTION AND OPIATE THERAPY**

*Focus on Gonadal Hormones*

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**PAIN AND ADDICTION WORKSHOP**

**October 7, 2009-San Francisco**

# FINANCIAL DISCLOSURE

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# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Outline*

- Hormone declines (“pauses”) with aging
- Hormone declines & morbidity/mortality
- Sex hormone changes, libido, erectile function, menstrual changes
  - Heroin, Methadone, Buprenorphine
- Bone Density changes and opiates
- Prolactin
- Testosterone Treatment (men)

# LONGEVITY

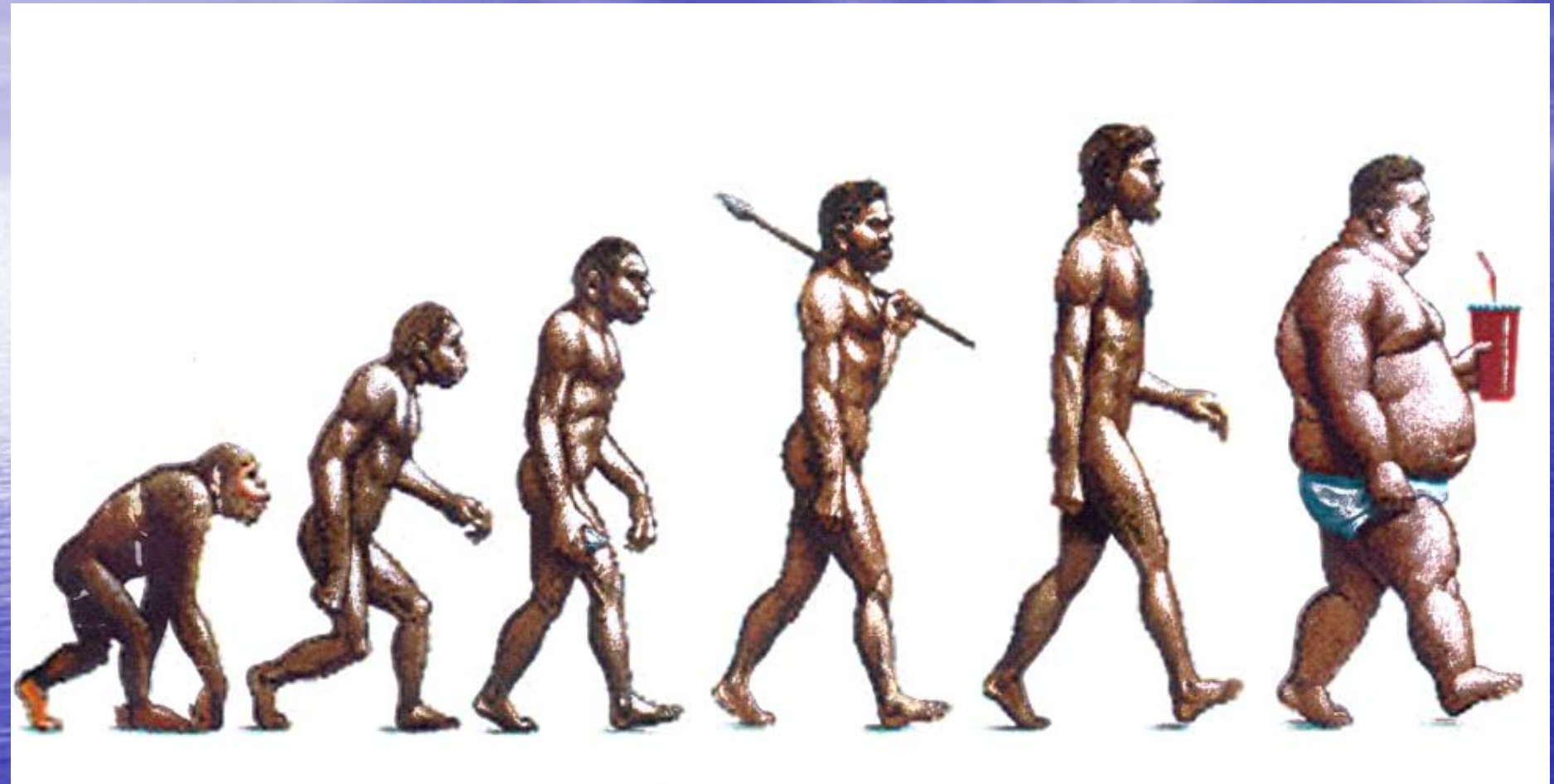
## *Human*

- “Americans Are Living Longer, But Not Necessarily Healthier”

Elliott VS, *American Medical News*, Oct. 27, 2003.

<http://www.ama-assn.org/amednews/2003/10/27/hll11027.htm>

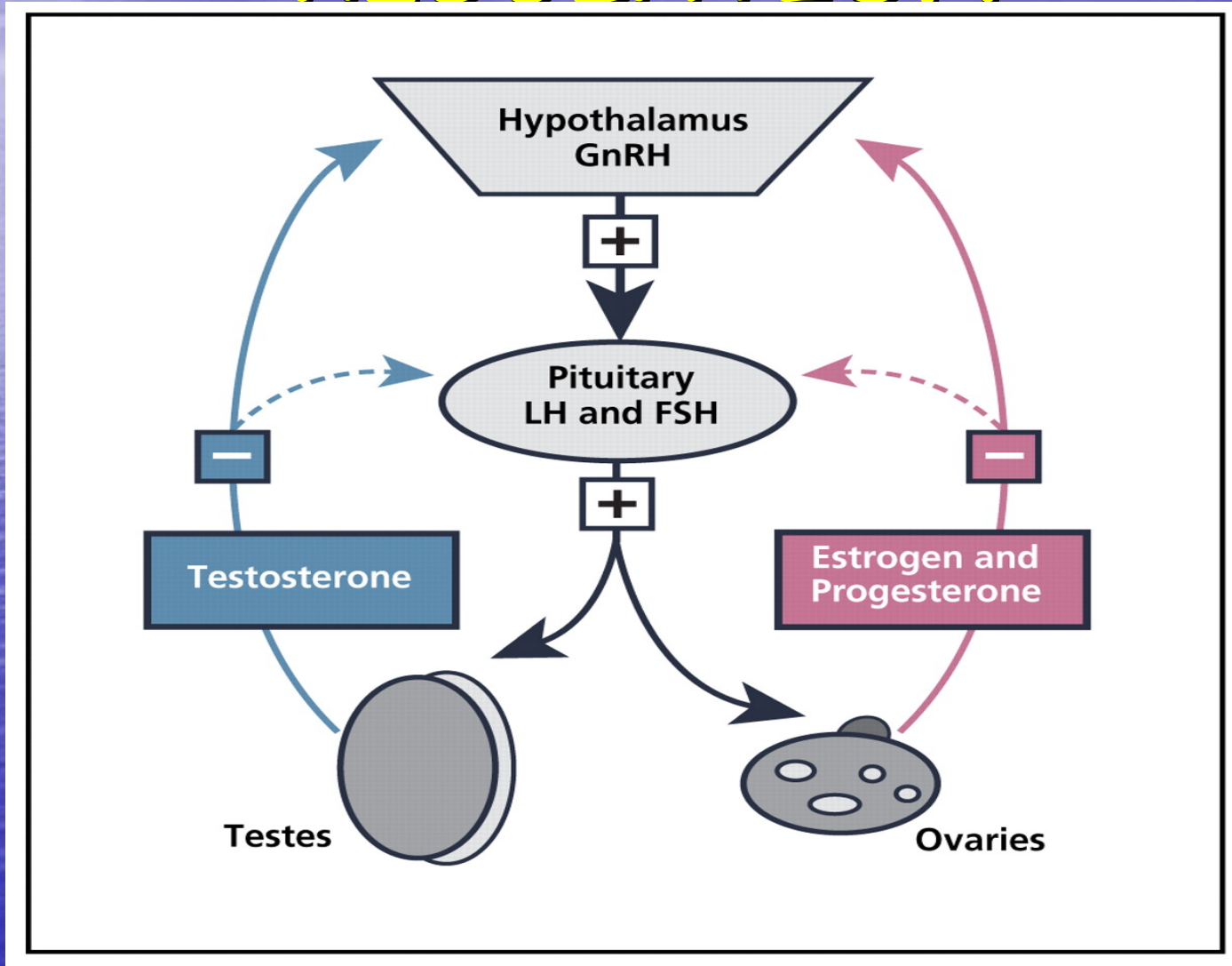
# ASCENT OF HUMANS



United States: 1/3 Obese (Body Mass Index  $> 30 \text{ kg/m}^2$ ); 1/3 Overweight (BMI 25-29.9)

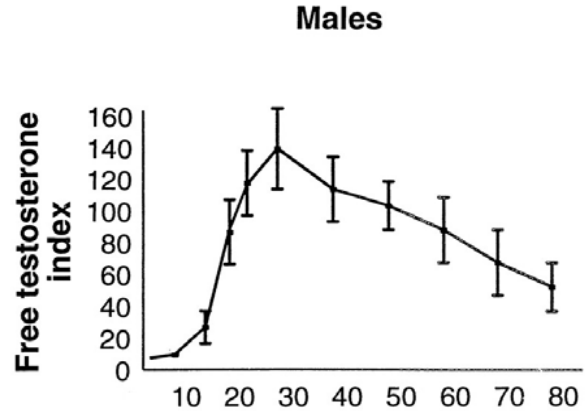
US Department of Health and Human Services, Centers for Disease Control and Prevention, 2006

# GONADAL HORMONE REGULATION

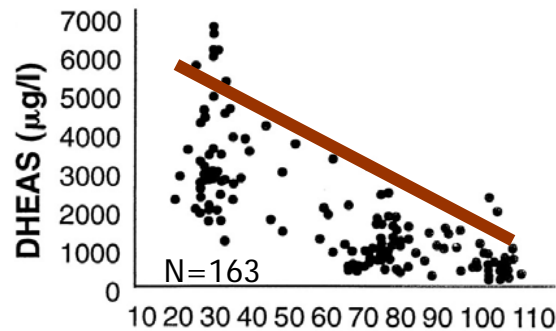


# HORMONES DECLINE WITH AGING-*Men*

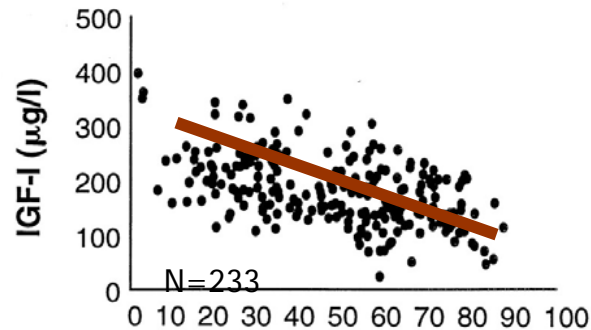
Free  
Testosterone  
Index



DHEA-S



IGF-I



Age (years)

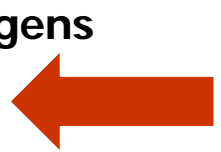
DHEA-S=  
dehydroepiandrosterone-  
sulfate

IGF-1= insulin-like  
growth factor-1 or  
somatomedin)

Lamberts SW *et al.*  
The endocrinology of  
aging. *Science*. 1997

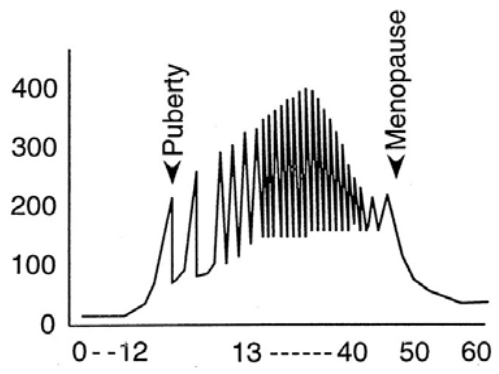
# HORMONES DECLINE WITH AGING - *Women*

Levels of Estradiol (and Progesterone) Are Low in Menopause



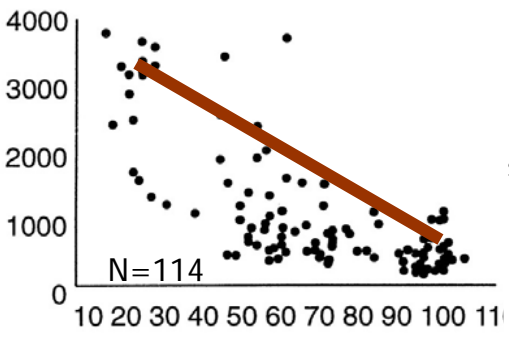
Females

Estrogens excreted in urine (µg/24 hours)



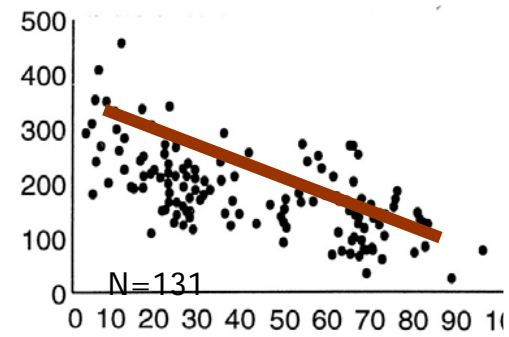
Estrogens

DHEAS (µg/l)



DHEA-S (dehydroepiandrosterone-sulfate)

IGF-I (µg/l)



IGF-1 (somatomedin; insulin-like growth factor-1)

Age (years)

Lamberts SW *et al.* The endocrinology of aging. *Science*. 1997 Oct 17;278(5337):419-24.

# MENOPAUSE SYMPTOMS

- Hot Flashes
- Excess Sweats
- Insomnia
- Headache
- Depression
- Other: Irritability, Lack of Concentration, Nervousness, Dizziness, Joint Pain, Tremor

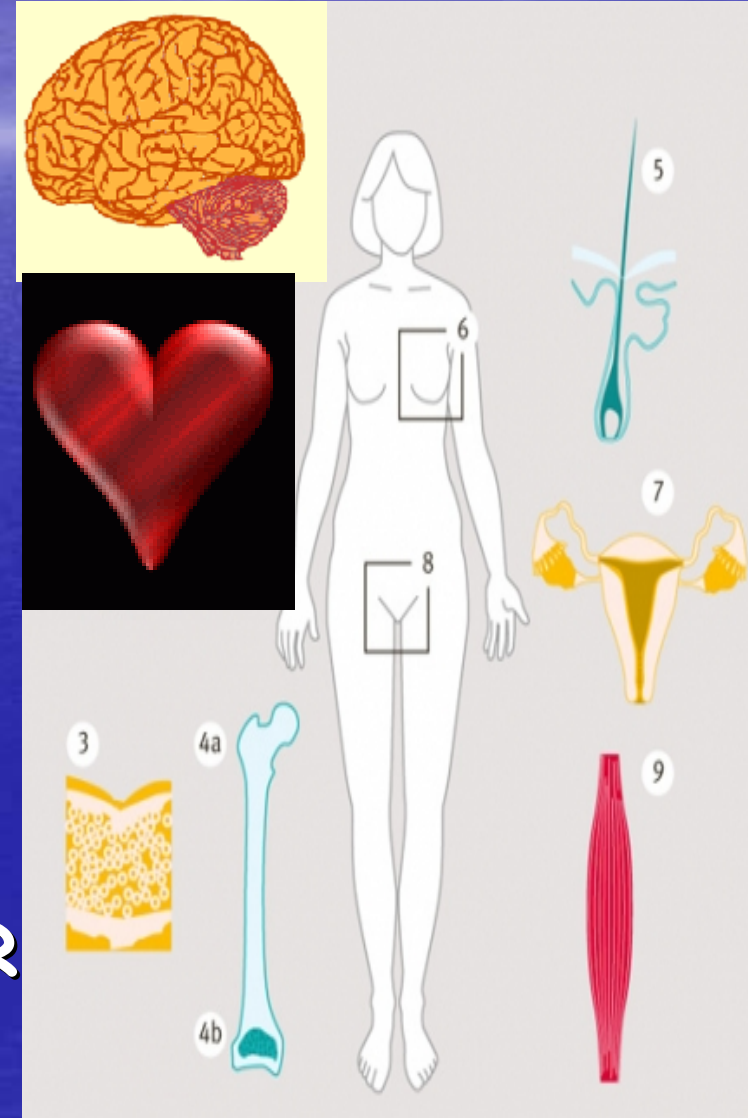
Kupperman HS, Contemporary therapy of the menopausal syndrome.  
*JAMA* 1959.

# FEMALE MENOPAUSE

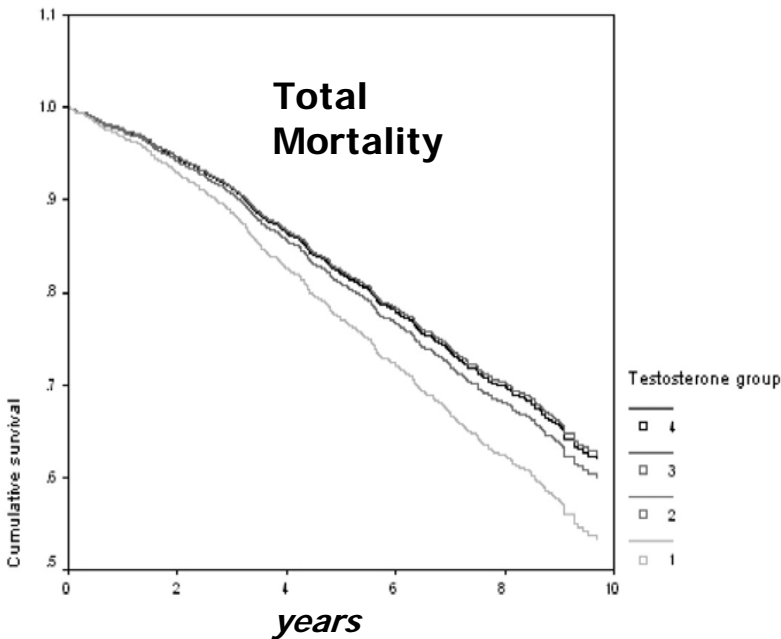
## *Benefits of Bio-Identical Hormone*

### *Replacement*

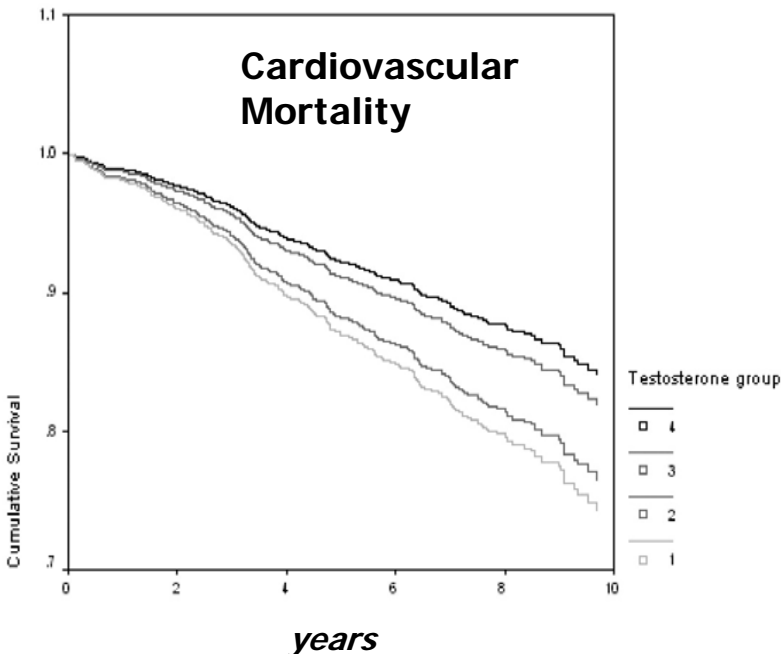
- LIFE EXPECTANCY
- BRAIN  
*cognition, memory, mood, libido*
- HEART, BLOOD VESSELS
- BONE (including teeth)
- WAIST CIRCUMFERENCE
- SKIN, HAIR
- BREAST
- UTERUS - VAGINA - BLADDER
- MUSCLE - ADIPOSE (FAT)



A



B



# TESTOSTERONE

## *Life Expectancy-EPIC*

10-year survival: 11,606 men  
 An increase of 173 ng/dl  
 testosterone associated with  
 0.81 (CI 0.71-0.92,  $p < 0.01$ )  
 adjusted odds ratio for  
 mortality

Multivariate-adjusted  $P < 0.001$

Khaw, K.-T. *et al.* Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 2007.

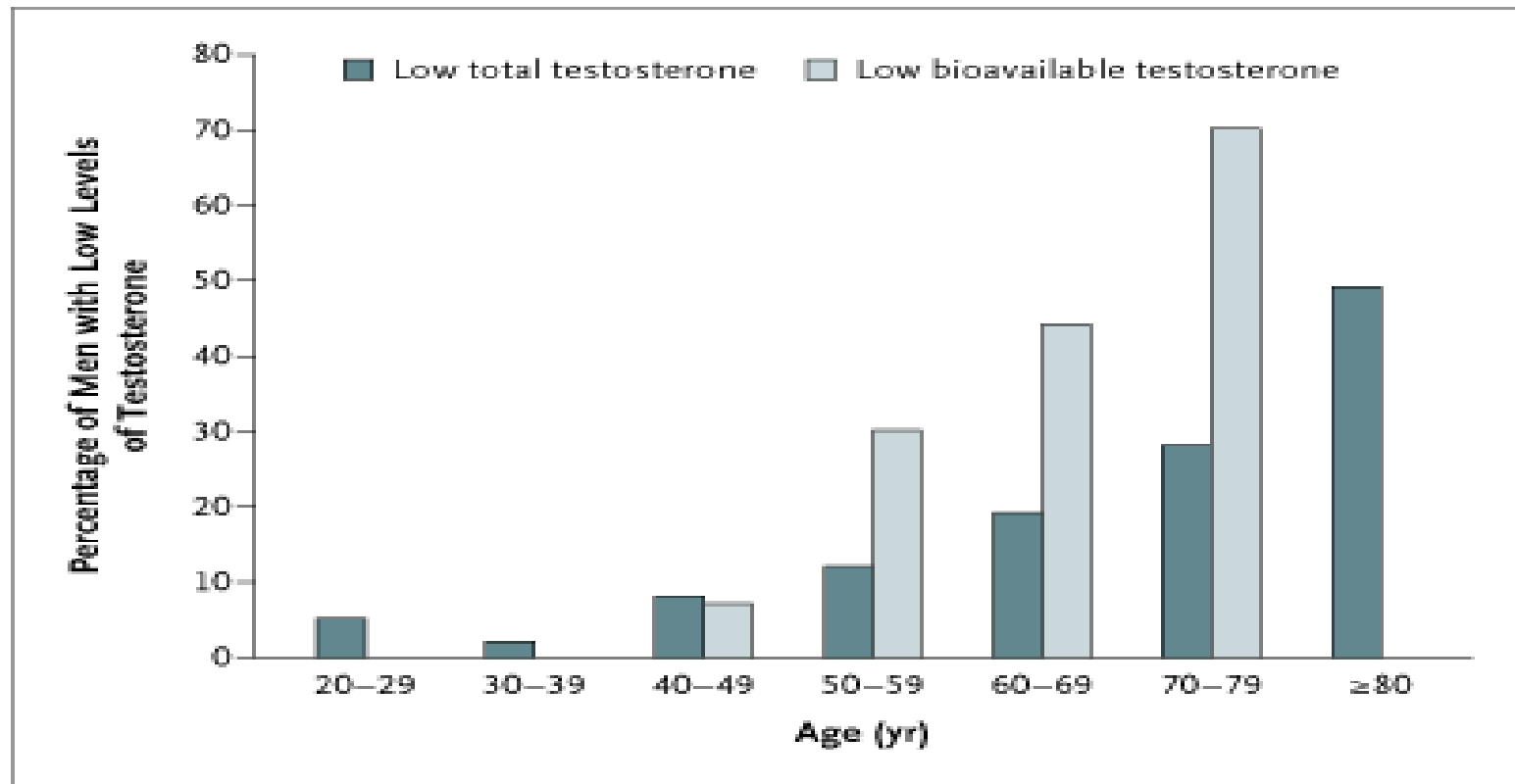
# ANDROPAUSE

## *Symptoms & Signs*

PHYSICAL-METABOLIC	PSYCHOLOGICAL	SEXUAL
↓ muscle mass & strength	Depressed mood	↓ Libido
↓ bone mineral density	Diminished energy, sense of vitality, well-being	Erectile dysfunction
Gynecomastia	Impaired cognition, memory	↓ spontaneous erections
↑ Body Fat or Body Mass Index		↓ intensity of orgasm
Fatigue	Bhasin S. Endocrine Society Clinical Practice Guideline, <i>J Clin Endocrinol Metab</i> 2006; Am. Assoc. Clin. Endo. Hypogonadism Task Force, <i>Endocr Pract.</i> 2002; Amer. Urol. Assn. 2002 in Rhoden E <i>et al. N Engl J Med</i> 2004.	
Anemia		
Frailty		

# LOW TESTOSTERONE

## *By Age-Men*



Rhoden EL *et al.* Risks of testosterone-replacement therapy and recommendations for monitoring. *New England Journal of Medicine* 2004 January.

# ANDROPAUSE

## *Testosterone: Potential Benefits*

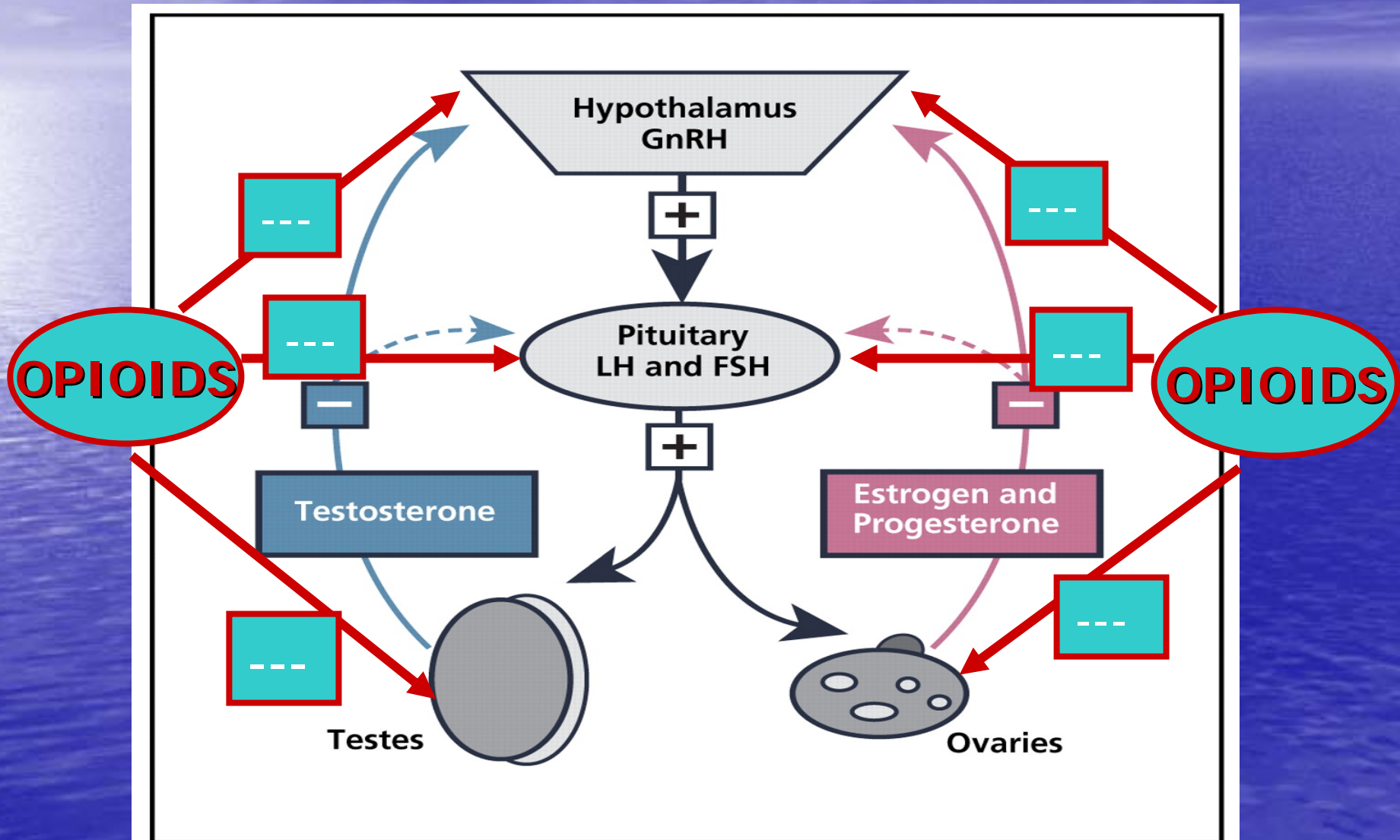
- BRAIN-cognition, mood, libido
- HEART
- BLOOD VESSELS
- BONE
- MUSCLE-ADIPOSE
- WAIST CIRCUMFERENCE
- SKIN
- DIABETES, METABOLIC SYNDROME
- TRIGLYCERIDES
- ERECTILE FUNCTION
- PROSTATE- neutral (rule out baseline carcinoma)
- LIFE EXPECTANCY

# GONADAL FUNCTION

## *Opioids*

- “[Opium] has kept, and does now keep down the population: the women have fewer children than those of other countries...the feeble opium-smokers of Assam...are more effeminate than women.”
  - *Charles Alexander Bruce, "Report on the Manufacture of Tea and on the extent and produc[tion] of the tea plantations in Assam," Calcutta, 1839.*

# GONADAL HORMONE REGULATION - *Opioids*



# GONADAL HORMONES & SEXUAL FUNCTION

## *Heroin, Morphine*

- Men

- Decreased testosterone and LH
- Decreased libido & fertility; erectile dysfunction

- Women

- Decreased LH, estradiol, progesterone (premenopause)
- Decreased LH and FSH (postmenopause)
- Amenorrhea, oligomenorrhea, irregular menses, galactorrhea & decreased libido
- Trend of menstrual cycle normalization with increasing duration of methadone treatment

# SEXUAL FUNCTION & ADHERENCE TO DOSING

## *Other Therapeutics*

- Sexual Dysfunction has been shown to interfere with therapeutic adherence among patients with:
  - Depression (Koutouvidis 1999)
  - HIV-AIDS (Trotta 2003)
  - Hypertension (Rosen 1997)

# GONADAL HORMONES & SEXUAL FUNCTION

## *Methadone*

- Early studies: Mixed results regarding testosterone levels in men on methadone
  - Normal (*Cushman 1973, 1974; Ragni 1988*)
  - LOW (*Azizi 1973; Cicero 1975, N Engl J Med* )
  - Low with higher dosing (*Mendelson 1975*)
    - 80-100 mg daily; normal if 10-60 mg daily
- Sexual behavior inversely associated with methadone dose in men (ejaculation) & women (genital contact, orgasm) (*Crowley 1978*)

# GONADAL HORMONES & SEXUAL FUNCTION

## *Methadone & Buprenorphine (1)*

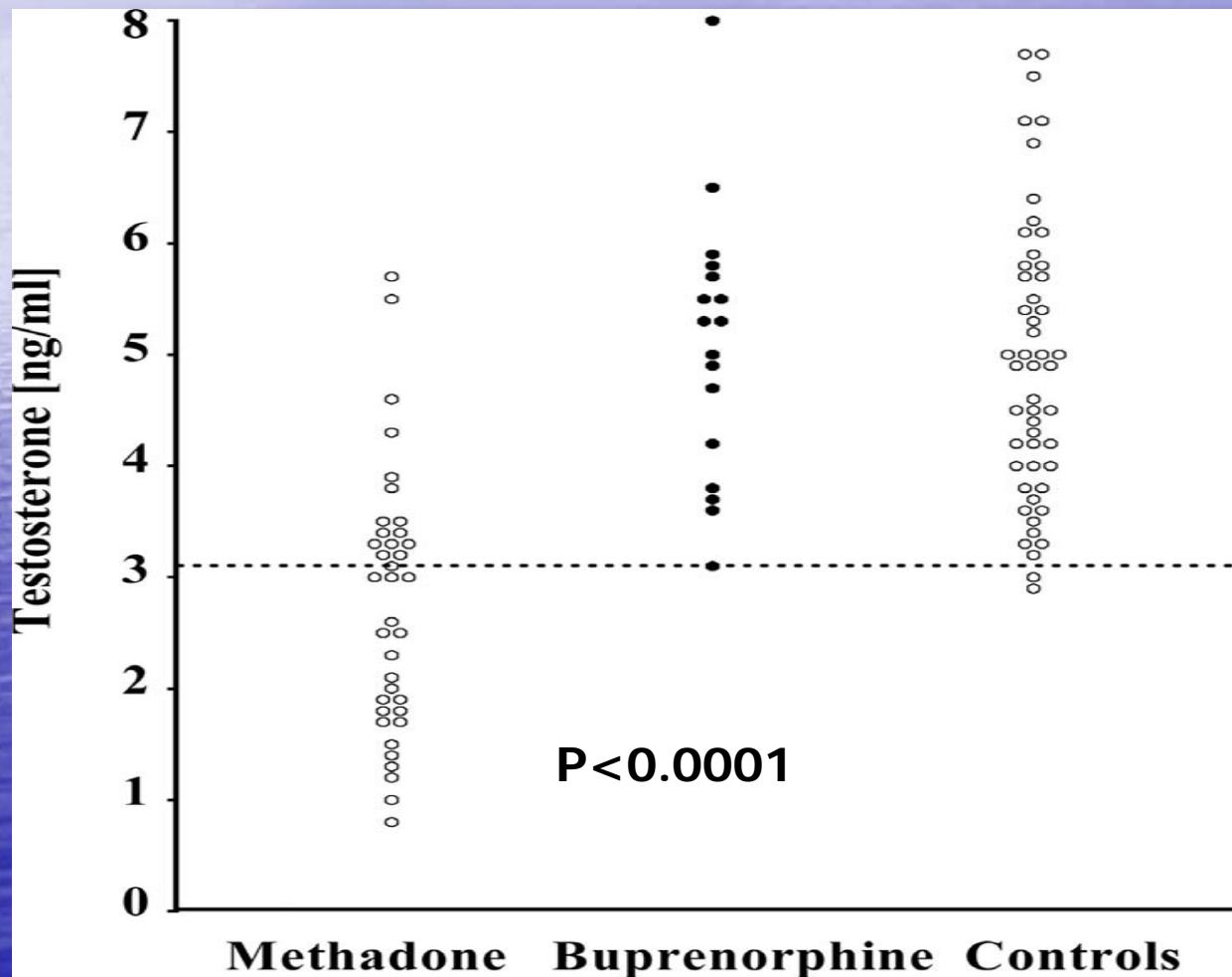
	Methadone N = 37	Buprenorphine N = 17	Controls N = 51
Age, years	37.5	34.7	35.2
Daily dose, mg	88.4 $\pm$ 16	11.2 $\pm$ 4.3	N/A
BDI Score	21.5 $\pm$ 9.7	16.4 $\pm$ 13.0	N/A
<b>Total Testosterone</b> (ng/dL, range 300-1000)	<b>280 <math>\pm</math> 120*</b>	<b>510 <math>\pm</math> 120</b>	490 $\pm$ 130
<b>Free Testosterone</b> (pg/mL, range 8.8-27)	<b>7.8 <math>\pm</math> 2.9*</b>	<b>17.1 <math>\pm</math> 4.8</b>	N/A
Prolactin	8.7 $\pm$ 8.3**	5.0 $\pm$ 2.0	5.2 $\pm$ 1.5

\*P<0.0001: \*\*P<0.05:

Bliesener, N. *J Clin Endocrinol Metab* 2005

# TESTOSTERONE

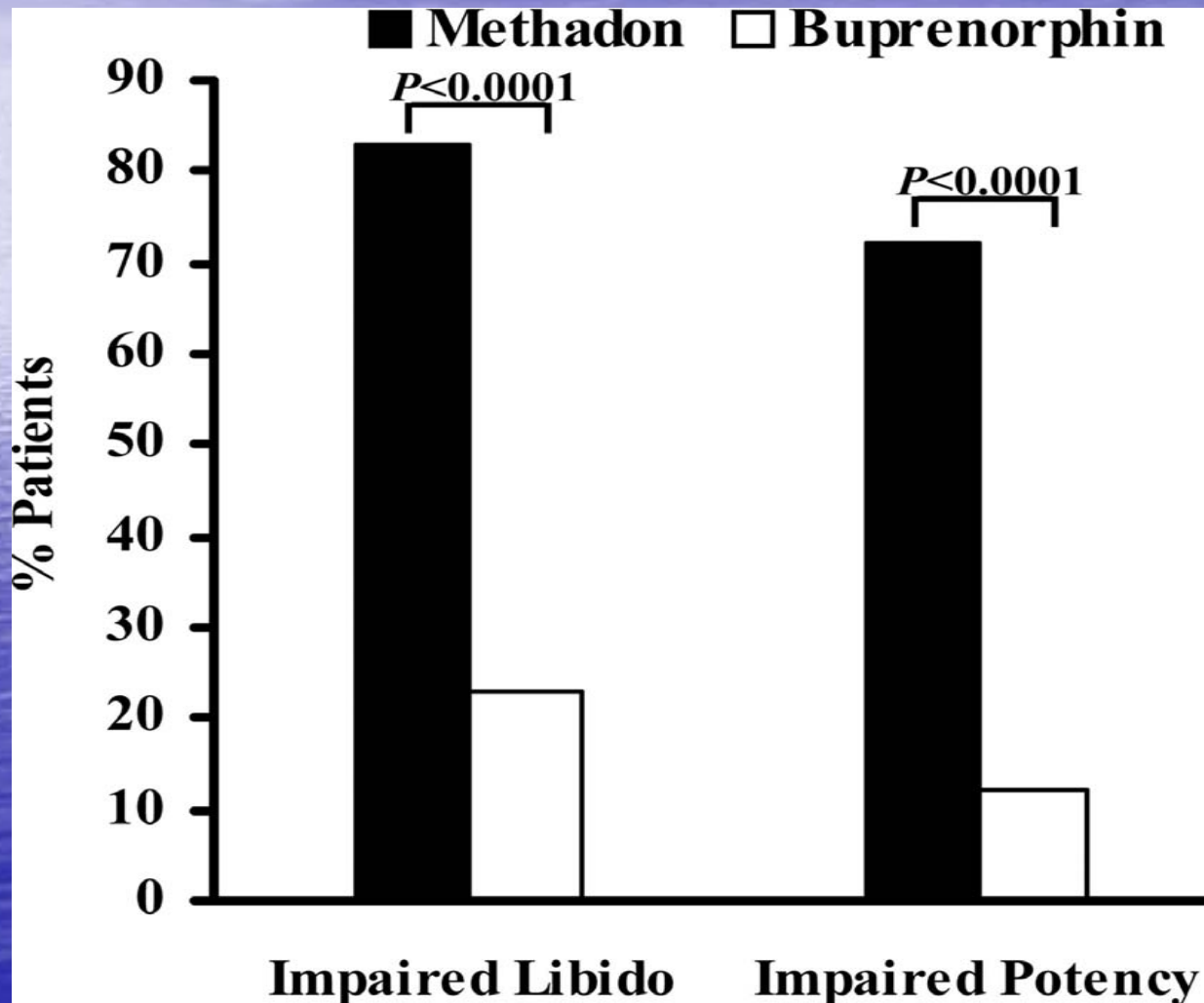
## *Methadone & Buprenorphine (1)*



Bliesener *ibid*

# SEXUAL DYSFUNCTION

## *Methadone & Buprenorphine (1)*



Bliesener *ibid*

# GONADAL HORMONES & SEXUAL DYSFUNCTION

## *Methadone & Buprenorphine (1)*

- Conclusions: "Buprenorphine
  - In contrast with high-dose methadone, seems not to suppress testosterone in heroin-addicted men.
  - Less frequently related to sexual side effects
  - Might therefore be favored in the treatment of opioid dependence to prevent patients from the clinical consequences of methadone-induced hypogonadism."

# GONADAL HORMONES & SEXUAL DYSFUNCTION

## *Methadone & Buprenorphine (2)*

	Methadone N = 84	Buprenorphine N = 19	P value
Age, mean years	38.3 ± 8.2	35.0 ± 5.6	0.103
Daily dose, mean mg	106 ± 70	10.2 ± 7.5	N/A
<b>Duration Treatment</b>	<b>67 months</b>	<b>26 months</b>	<b>0.009*</b>
BMI, mean	24.6	23.9	0.560
BDI, mean	17.2	17.0	0.944
HCV antibody	78.6%	57.9%	0.061
Chronic HCV	54.8%	52.6%	0.793

BDI = Beck Depression Inventory;  
BMI = Body Mass Index

Hallinan R *et al.* *J Sex Med.* 2008

# TESTOSTERONE

## *Methadone & Buprenorphine (2)*

	Methadone N = 84	Buprenorphine N = 19	P value
<b>Total Testosterone</b> Mean (Range 433- 1,300 ng/dL)	<b>418 ± 252</b>	<b>668 ± 314</b>	<b>0.001*</b>
<b>Free Testosterone</b> Mean (Range 45-127 pg/mL)	<b>37 ± 29</b>	<b>56 + 48</b>	<b>0.037*</b>
<b>Prolactin, Mean</b> (Range 1-15 ng/L)	<b>6.9 ± 4.7</b>	<b>10.2 ± 11.3</b>	<b>0.092</b>

No significant difference: tobacco, alcohol,  
benzodiazepine, cannabis stimulants, heroin

Hallinan R *ibid*

# SEXUAL DYSFUNCTION

## *Methadone & Buprenorphine (2)*

<b><i>International Index of Erectile Function</i></b>	<b>Methadone N = 53</b>	<b>Buprenorphine N = 14</b>	<b>Maximum Score</b>
<b>IIEF total mean</b>	<b>50.4*</b>	<b>61.4*</b>	<b>75</b>
<b>Erectile function mean</b>	<b>22.1</b>	<b>26.6</b>	<b>30</b>
<b>Erectile Dysfunction (Erectile Dysfunction <math>\leq</math> 25)</b>	<b>52.8%</b>	<b>21.4%</b>	<b>N/A</b>
<b>Orgasmic Function</b>	<b>7.1</b>	<b>8.2</b>	<b>10</b>

Multivariate Analysis: IIEF and Erectile Function Scores each significantly associated with Total Testosterone, BDI, and Age. (Currently partnered men only)

Hallinan, *ibid*

# GONADAL HORMONES & SEXUAL DYSFUNCTION

## ***Methadone & Buprenorphine (2)***

- Conclusions: Men on methadone maintenance treatment, but not buprenorphine, have a high prevalence of Erectile Dysfunction, related to hypogonadism [low testosterone] & depression.
- **Practitioners should screen for sexual dysfunction in men receiving opioid replacement treatments.**
- Future studies: dose reduction, androgen replacement, depression treatment, and choice of opioid."

# OPIOID-INDUCED ANDROGEN DEFICIENCY IN MEN

## *Testosterone Replacement*

- 23 men with OPIAD (OPioid-Induced Androgen Deficiency)
- 24-week, open-label pilot study
- Testosterone patch 5 mg/ day: first 12 weeks, then 7.5 mg/ day second 12 weeks
- Early withdrawal: 4 non-compliance; 2 skin irritation; 1 hepatitis C treatment (16 completers)

# OPIOID ANDROGEN DEFICIENCY IN MEN

## *Testosterone Replacement*

- Results: Free testosterone significantly increased from baseline
  - (28.5 pg/mL → 120 pg/mL;  $p < 0.001$ )
- Total testosterone increased significantly
- Significant improvements in libido, sexual function, depression, hematocrit ( $p < 0.001$ )
- Mild decrease in pain score ( $p < 0.05$ )
- Opioid usage did not change

# BONE DENSITY

## *Heroin Addiction (1)*

- 13 male chronic heroin users, 22 control patients
- Results: DXA Bone Density Scan significantly lower density in heroin patients vs. controls ( $p < 0.05$ )
- Testosterone and Luteinizing Hormone significantly lower in heroin patients ( $p < 0.01$ )
- Conclusion: "Chronic opioid use may be associated with altered bone metabolism and reduced trabecular bone mass, attributable, at least in part, to gonadal deficiency."

# BONE DENSITY

## *Methadone Therapy (2)*

- Cross-sectional study of 92 patients in Methadone Maintenance Treatment program (Boston Medical Center)
- Risks: tobacco 91%, heavy alcohol 52%, HIV 28%
- Results: Abnormal DXA Bone Scan in **83%**
  - **Osteoporosis 35%; Osteopenia 48%**
- None were aware of previous bone diagnosis

DXA=Dual Energy X-Ray Absorbtiometry

Kim TW *et al.* Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend.* 2006

# BONE DENSITY

## *Methadone Therapy (2)*

- Significant predictors of low bone density:
  - Male gender ( $p < 0.001$ );
  - Lower weight ( $p = 0.009$ );
  - Heavy alcohol use ( $p = 0.02$ )
- Conclusion: “Efforts to increase awareness of low bone mineral density in methadone maintenance patients should be considered so that effective treatment may be employed to lower future fracture risk.”

Kim *ibid*

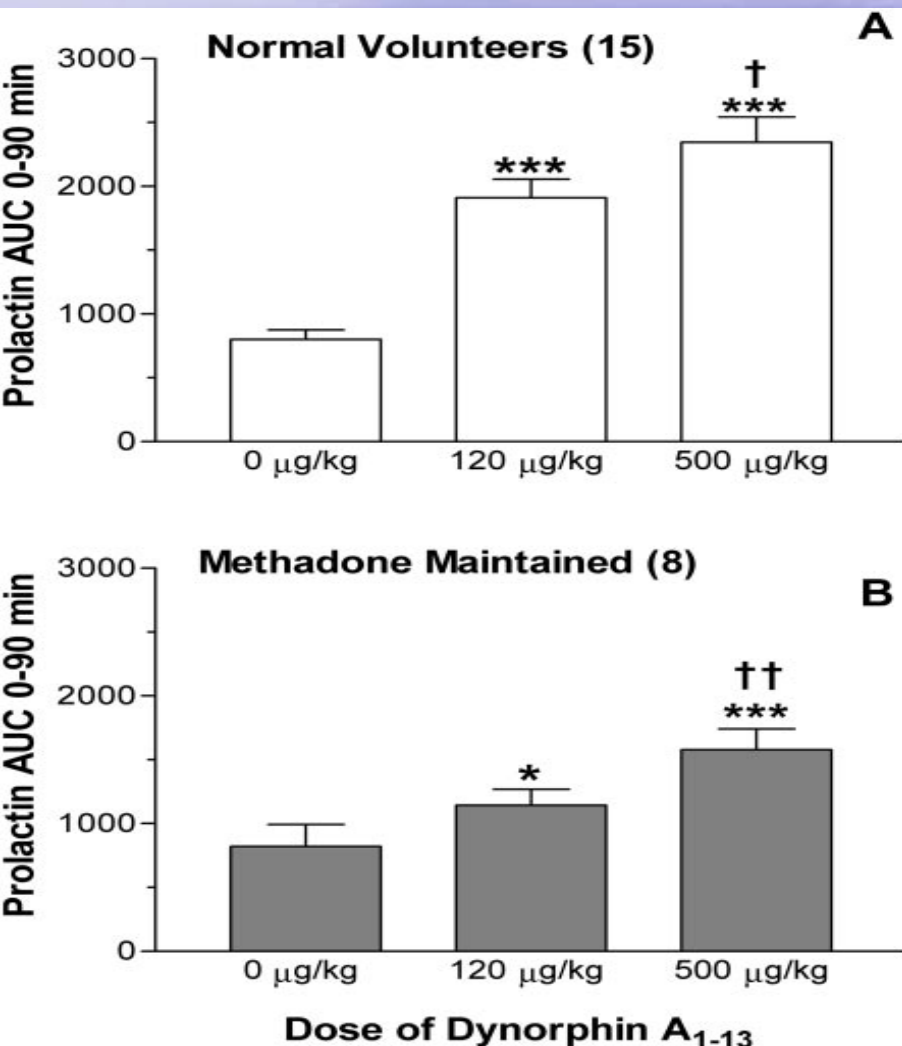
# OPIATES & PROLACTIN

## *Dynorphin A (1)*

- Opiate & opiate antagonists increase prolactin, alter its circadian rhythm.
- Hyperprolactinemia associated with:
  - Galactorrhea, osteoporosis/osteopenia, GnRH inhibition
  - Women: amenorrhea, oligomenorrhea, infertility, galactorrhea, decreased libido, vaginal dryness
  - Men: Decreased libido, impotence, premature ejaculation, erectile dysfunction, oligospermia

# OPIATES & PROLACTIN

## *Dynorphin A (1)*



Dynorphin A significantly increased prolactin levels in normal volunteers and in methadone maintained patients, though blunted. Mechanism: decreased dopaminergic tone.

Bart G *et al.* J Pharmacol Exp Ther. 2003 Aug. Kreek MJ *et al.* J Pharmacol Exp Ther. 1999 Jan.

# TESTOSTERONE REPLACEMENT THERAPY: Men

History & Physical Exam (symptoms & signs) consistent with Andropause

Morning Total Testosterone

Normal Testosterone

Low Total Testosterone (< 300 ng/dL) or  
Low Free Testosterone (< 5 ng/dL)

Follow-Up

Confirmed Low Total or Free Testosterone;  
Rule Out: Sleep Apnea, Prostate Symptoms (BPH).  
Evaluate for: Increased Iron, Increased Prolactin,  
Low LH & FSH, "Treatable" Illness (Diabetes, Obesity, HIV),  
(Baseline CBC, PSA, Prostate Exam, DXA, ?Estradiol)

Normal  
Testosterone,  
LH, FSH

Treat with Testosterone and Monitor  
If Low LH & FSH, ?Treat with HCG or rhHCG

*JCEM 2006*

# TESTOSTERONE REPLACEMENT DOSING: Men

- Testosterone cypionate or enanthate, 75-100 mg intramuscularly once weekly (200 mg/cc)
- 1% Testosterone topical gel, 5-10 grams daily, applied over covered area of skin
- 10% Testosterone topical gel, 1 gram daily or BID, applied over covered skin  
*(\*\*compounded only)*
- Testosterone undecanoate 1,000 mg intramuscular, 2 doses 4 weeks apart, then every 3 months *(\*\*Europe, phase III in US)*

# TESTOSTERONE THERAPY:

## *Men-Ongoing Monitoring*

- 2-3 Months after Starting Therapy & Annually
  - Testosterone, Total & Free; adjust dosing as needed (target mid-normal range)
  - CBC (If hematocrit >54%, stop testosterone, phlebotomy to normal Hct, then restart lower dose, evaluate for hypoxia and sleep apnea)
  - PSA (Refer to Urology if >4.0 ng/ml or if increase > 1.4 ng/ml in 12 months)
  - ?Estradiol level
  - Digital prostate exam at 3 months and annually (Refer to Urology if nodule)
  - Repeat DXA scan if baseline was abnormal

# BIO-IDENTICAL GONADAL HORMONES

## *California Medi-Cal*

- Estradiol oral tablets, patches (weekly, twice-weekly), vaginal tablet, vaginal ring
- Estradiol cypionate injection
- Progesterone injection
- Testosterone cypionate injection
- Testosterone, aqueous suspension for injection
- Testosterone in oil for injection
- ?Testosterone topical gel

# SF Gate-SF Chronicle

*Letter to the Editor: Feb 13, 2009*

- "See Testosterone For All It Is - Not Just A Male Sex Hormone"
- "It is time for men (and their spouses, partners and physicians) to become aware that testosterone in men is not just a sex hormone but a total body hormone, essential for normal psychological and physical functioning and to help offset risks for chronic life-threatening diseases."  
--H.S. Bartnof, M.D.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-1*

- There are several (but not all) cohort studies indicating that low testosterone levels in men are associated with shorter life expectancy.
- Low testosterone in men is associated with increased morbidity and several biologic parameters that increase the risk of morbidity and mortality.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-2*

- Studies of hypogonadal men treated with testosterone replacement therapy indicate improvements in risk factors for morbidity and mortality, in addition to increased quality-of-life, including increased libido, erectile function, and orgasm.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-3*

- Bio-Identical Hormone Replacement Therapy in women has potential benefits for many body organs and functioning: brain, libido, sexual response, heart, blood vessels, bone (& teeth), muscles, breast, uterus, vagina, skin, and urinary bladder.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-4*

- In men, opioid therapy is associated with a decline in luteinizing hormone and testosterone, leading to decreased libido and erectile function and a decrease in bone density.
- In women, opioid therapy is associated with decreased LH & estrogen, menstruation changes, decreased libido, sexual functioning, and fertility.
- Methadone replacement therapy in men may be associated with a worsened decline in testosterone and libido than buprenorphine replacement.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-5*

- Options for opioid-induced gonadal dysfunction and symptoms may include dose reduction, changing to buprenorphine, and testosterone replacement therapy in men.
- Additional studies are needed in men.
- Studies are needed in women who have been prescribed opioid therapy to determine the potential benefits of HRT, including estrogen, progesterone, & androgen (DHEA, testosterone) replacement therapy.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

## *Conclusions-6*

- Practitioners who prescribe opioid therapy need to be aware of potential endocrine adverse effects.
- Practitioners should strongly consider screening patients by history, laboratory parameters and imaging (DXA bone scan) and consider hormone replacement therapy when indicated to improve quality-of-life, morbidity and probable premature mortality.

# ENDOCRINE FUNCTION AND OPIATE THERAPY

- Thank you.
- Questions?
  
- Harvey S. Bartnof, M.D.
  - 415-986-1300
  - [www.LongevityMD.net](http://www.LongevityMD.net)
- [DrBartnof@DrBartnof.com](mailto:DrBartnof@DrBartnof.com)