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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  - www.LongevityMD.net
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”

United States: 1/3 Obese (Body Mass Index > 30 kg/m²); 1/3 Overweight (BMI 25-29.9)

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

Hypothalamus

GnRH

Pituitary

LH and FSH

Testosterone

Testes

Estrogen and Progesterone

Ovaries

+ + +

− − −
HORMONES DECLINE WITH AGING - Men

Free Testosterone Index

DHEA-S

IGF-I

DHEA-S = dehydroepiandrosterone-sulfate

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

Hormones Decline with Aging - Women

Levels of Estradiol (and Progesterone) Are Low in Menopause

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)

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 $P < 0.001$
## ANDROPause

### Symptoms & Signs

<table>
<thead>
<tr>
<th>PHYSICAL-METABOLIC</th>
<th>PSYCHOLOGICAL</th>
<th>SEXUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ muscle mass &amp; strength</td>
<td>Depressed mood</td>
<td>↓ Libido</td>
</tr>
<tr>
<td>↓ bone mineral density</td>
<td>Diminished energy, sense of vitality, well-being</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Impaired cognition, memory</td>
<td>↓ spontaneous erections</td>
</tr>
<tr>
<td>↑ Body Fat or Body Mass Index</td>
<td></td>
<td>↓ intensity of orgasm</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.”


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

Cicero 1975, 1980; Mendelson 1975; Khan 1990; Genazzani 1993; Abs 2000; Schmittner 2005
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)
**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)

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

*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*
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.”

Bliesener ibid
### Methadone & Buprenorphine (2)

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

BDI = Beck Depression Inventory; BMI = Body Mass Index

## TESTOSTERONE

### Methadone & Buprenorphine (2)

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

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

Hallinan R *ibid*
### International Index of Erectile Function

<table>
<thead>
<tr>
<th></th>
<th>Methadone N = 53</th>
<th>Buprenorphine N = 14</th>
<th>Maximum Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IIEF total mean</strong></td>
<td>50.4*</td>
<td>61.4*</td>
<td>75</td>
</tr>
<tr>
<td><strong>Erectile function mean</strong></td>
<td>22.1</td>
<td>26.6</td>
<td>30</td>
</tr>
<tr>
<td><strong>Erectile Dysfunction</strong> (&lt; 25)</td>
<td>52.8%</td>
<td>21.4%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Orgasmic Function</strong></td>
<td>7.1</td>
<td>8.2</td>
<td>10</td>
</tr>
</tbody>
</table>

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

Hallinan, *ibid*
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.”

Hallinan, ibid
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)

Daniell HW. J Pain. 2006
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

Daniell HW. J Pain. 2006
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.”

Pedrazzoni M *et al.* Effects of chronic heroin abuse on bone and mineral metabolism. *Acta Endocrinol (Copenh).* 1993
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 Absorptiometry
**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

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

TESTOSTERONE REPLACEMENT THERAPY:  

Men

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

Morning Total Testosterone

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

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)

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

Follow-Up

Normal Testosterone

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)

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

BPH=Benign Prostatic Hypertrophy, LH=luteinizing hormone, FSH=follicle stimulating hormone, PSA=prostate specific antigen, DXA Bone Density Scan,CBC=complete blood count, HCG=human chorionic gonadotropin, rhHCG=recombinant human HCG

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 undecanooate 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

Endocrine Society J Clin Endo Metab 2006
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

medi-cal.ca.gov accessed July 30, 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.
Conclusions

- 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.
• 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.
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.
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.
Conclusions

• 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?

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