OPIOID INDUCED ENDOCRINOPATHIES

Ernesto J. Solá-Sánchez, MD.

Board Certified in Internal Medicine and Endocrinology

San Juan City Hospital Endocrinology Section

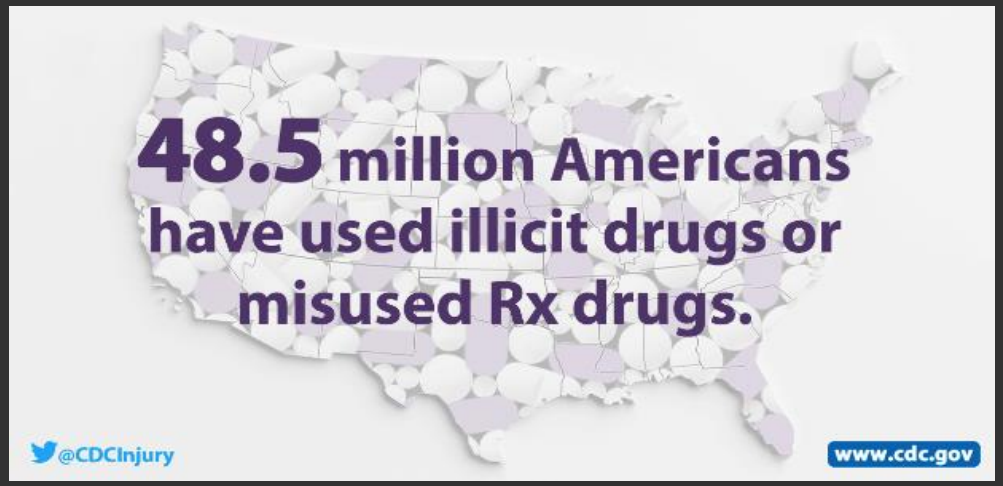
Disclosures

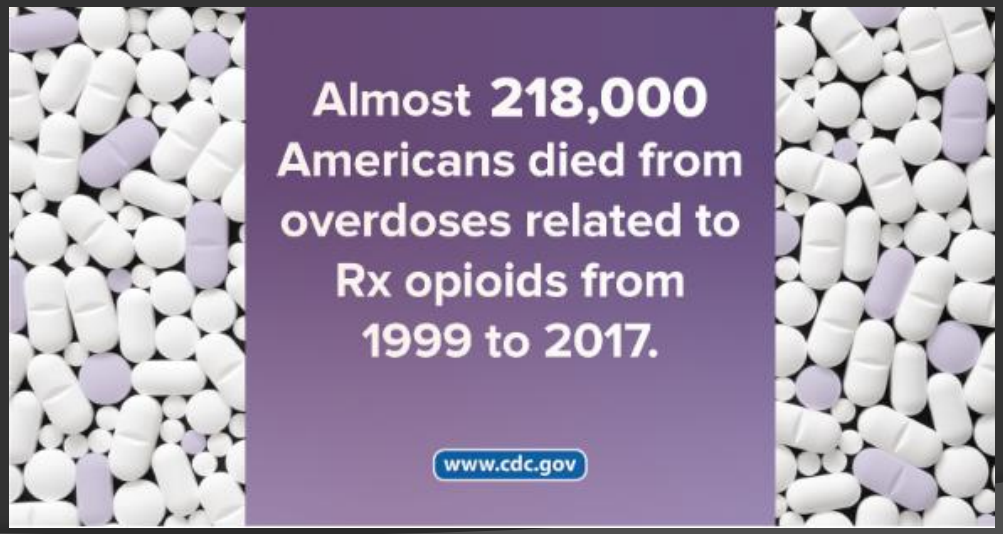
- There is no conflict of interest

Objectives:

- Understanding the opioids epidemic
- Types of opioids
- Opioids induced neuroendocrine disfuction
- Clinically significant pathologies
- Proposed diagnostic algorithms
- Review of treatment alternatives
- My personal reflexion

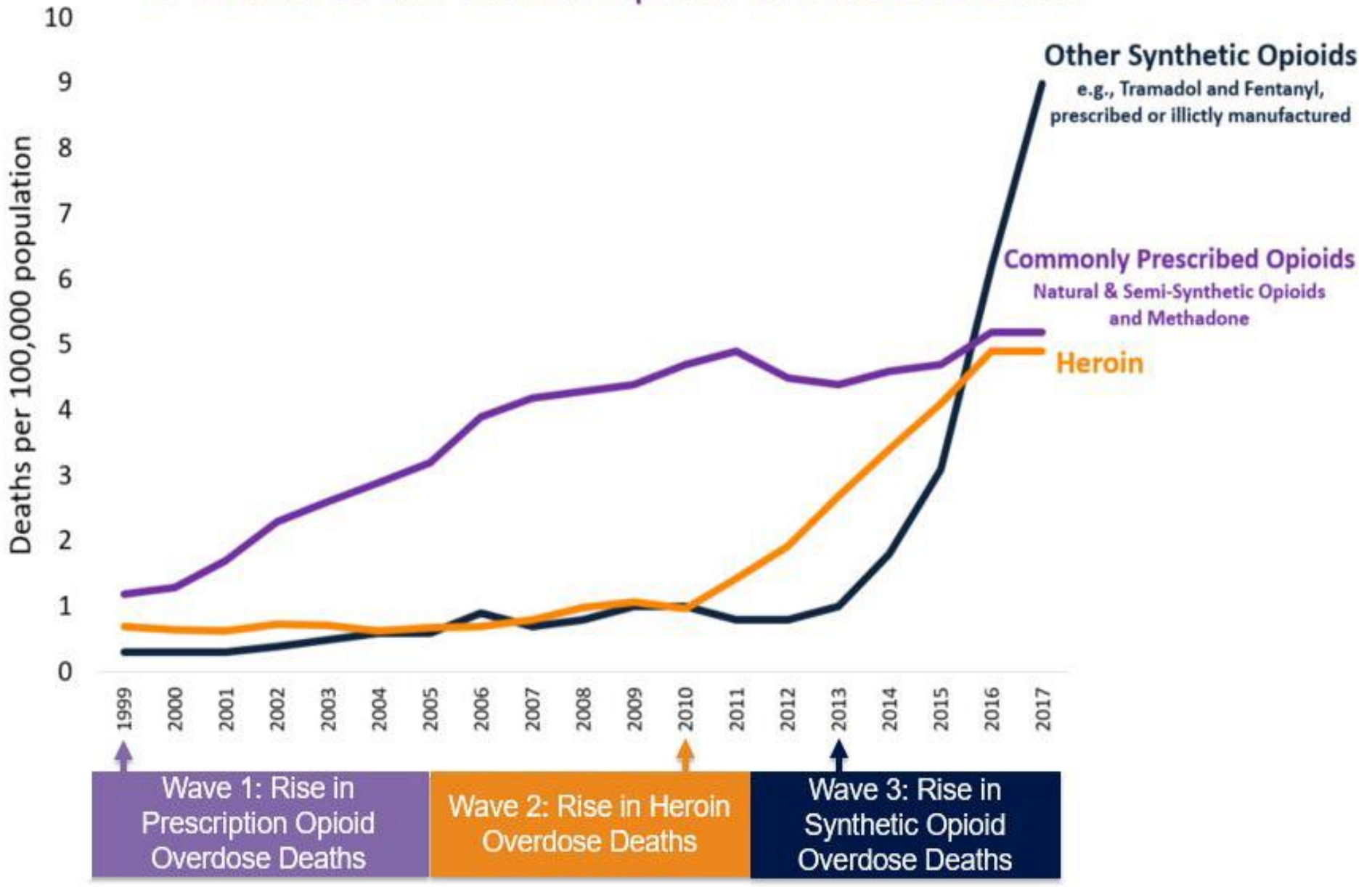
Understanding the Epidemic





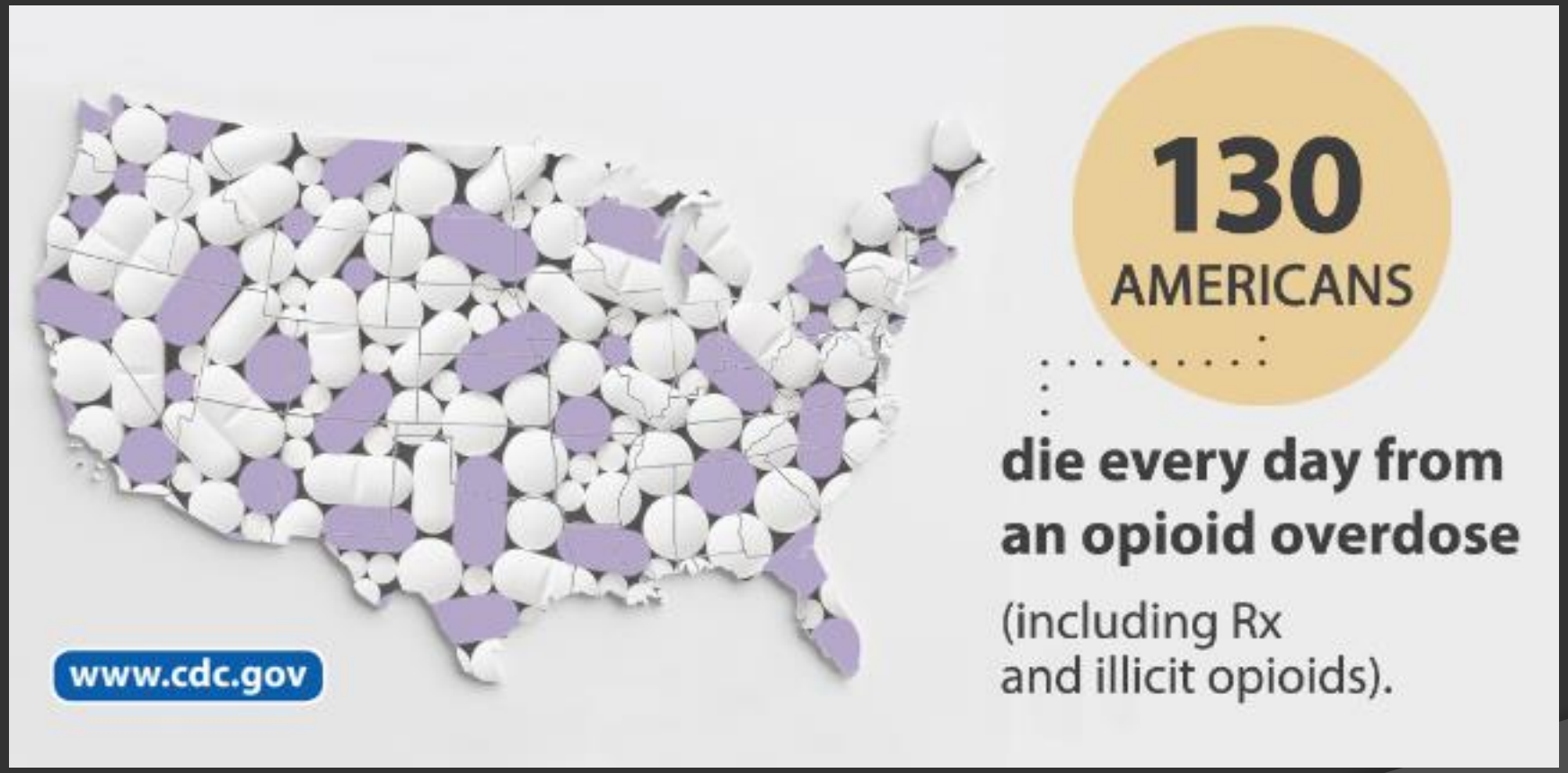
- From 1999 to 2017, more than 700,000 people have died from a drug overdose.
- Around 68% of the more than 70,200 drug overdose deaths in 2017 involved an opioid.

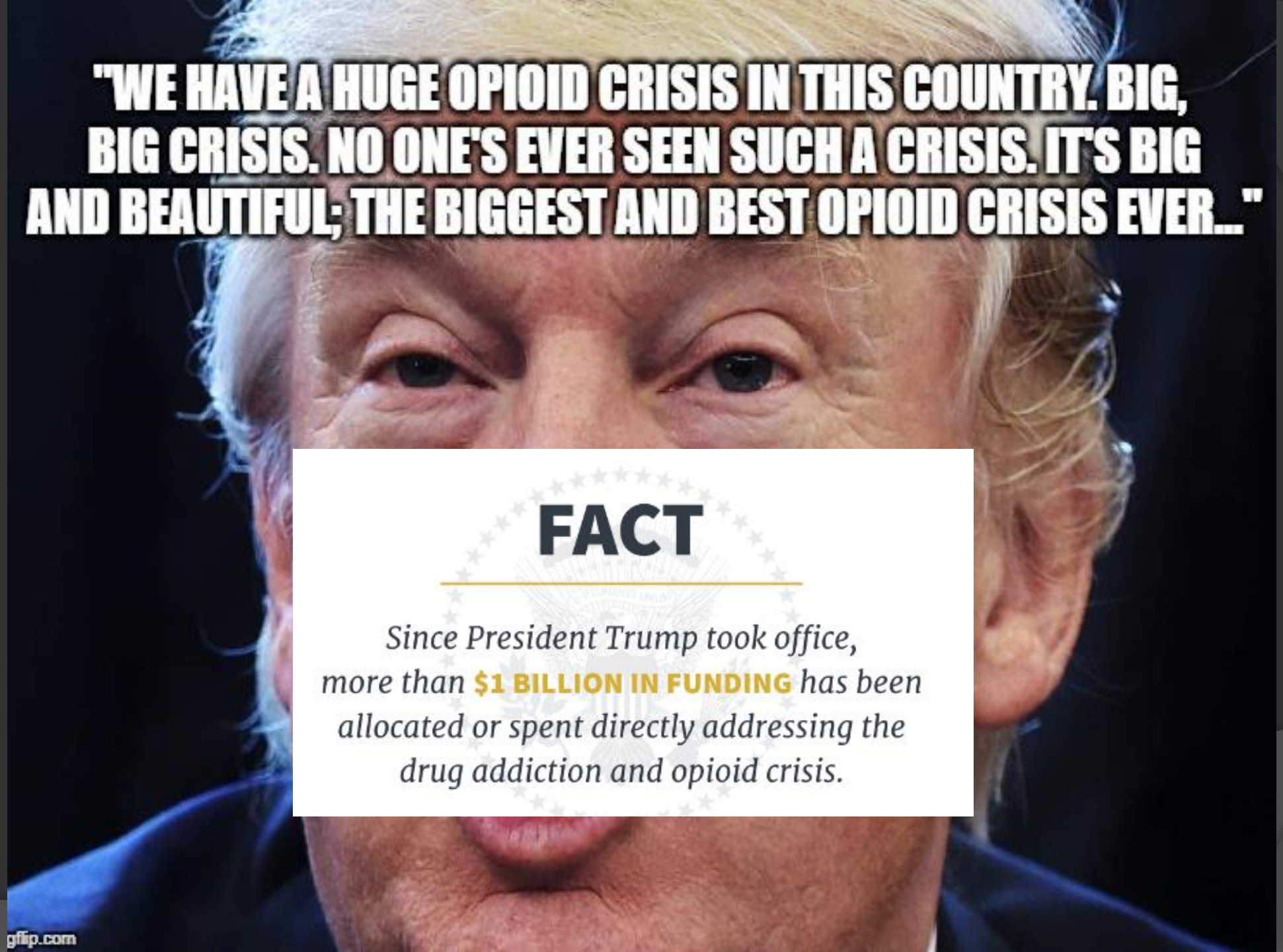
3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

Public Health Emergency!




"WE HAVE A HUGE OPIOID CRISIS IN THIS COUNTRY. BIG, BIG CRISIS. NO ONE'S EVER SEEN SUCH A CRISIS. IT'S BIG AND BEAUTIFUL; THE BIGGEST AND BEST OPIOID CRISIS EVER..."
FACT
Since President Trump took office, more than $1 BILLION IN FUNDING has been allocated or spent directly addressing the drug addiction and opioid crisis.
gflip.com

At a Glance

- Opioids can lead to addiction and even death, but they also have multiple effects on the endocrine system.
- Most notably, opioids can suppress the hypothalamo/pituitary/gonadal system and in the long term, can reduce bone mineral density.
- Physicians and patients should be aware of this problem and not shy away from discussing potential opioid-induced endocrinopathies.

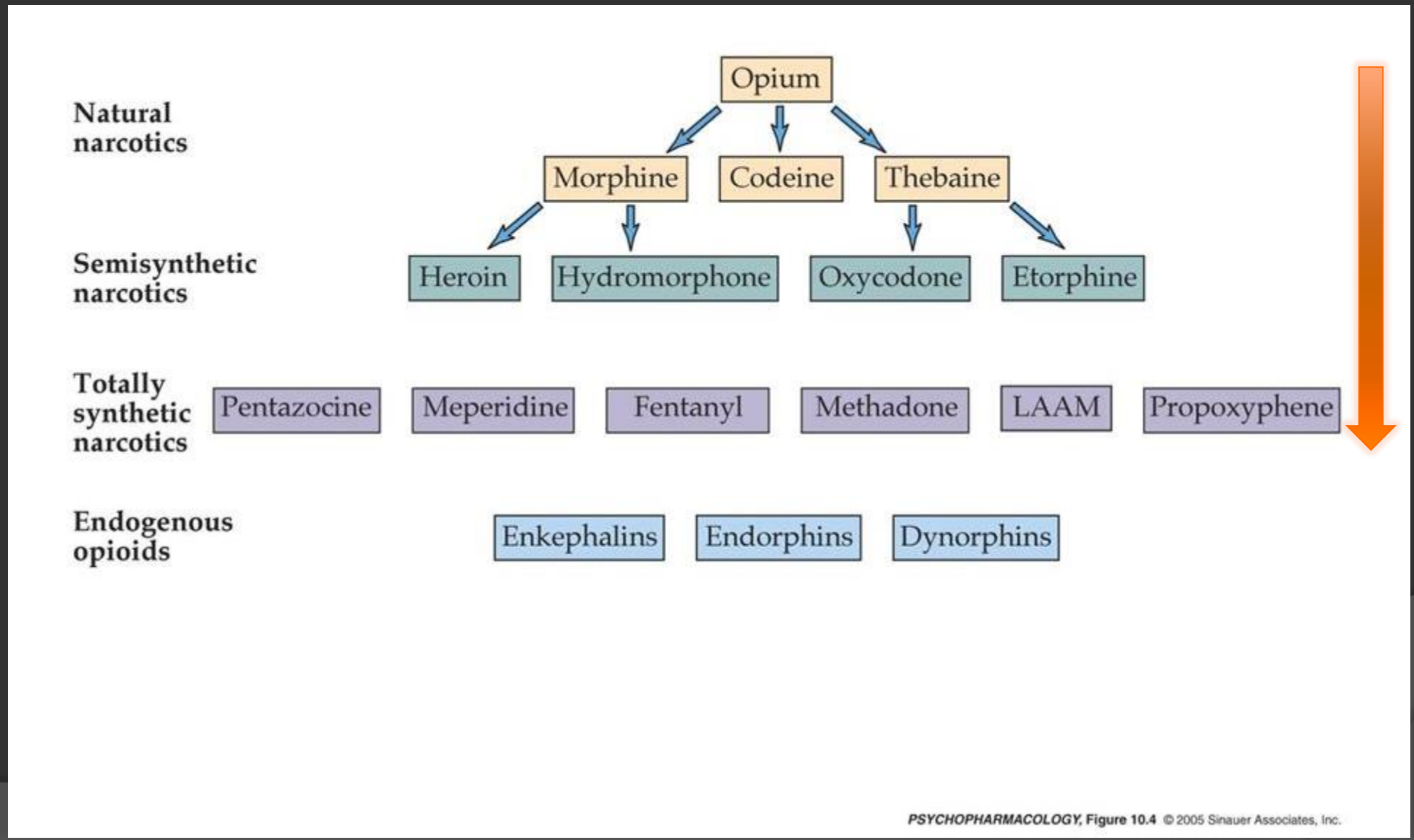
Opioid-Induced Endocrinopathies

patients and clinicians need to know about the insidious effects of these drugs and the potential steps to combatting these often-severe conditions.

"It seems that awareness of the endocrine effects of opioids amongst healthcare professionals prescribing or looking after patients on these agents is rather limited and possibly this is one of the reasons the problem has not been addressed in an effective way in clinical practice." – Niki Karavitaki, MSc, PhD, FRCP, University of Birmingham, United Kingdom

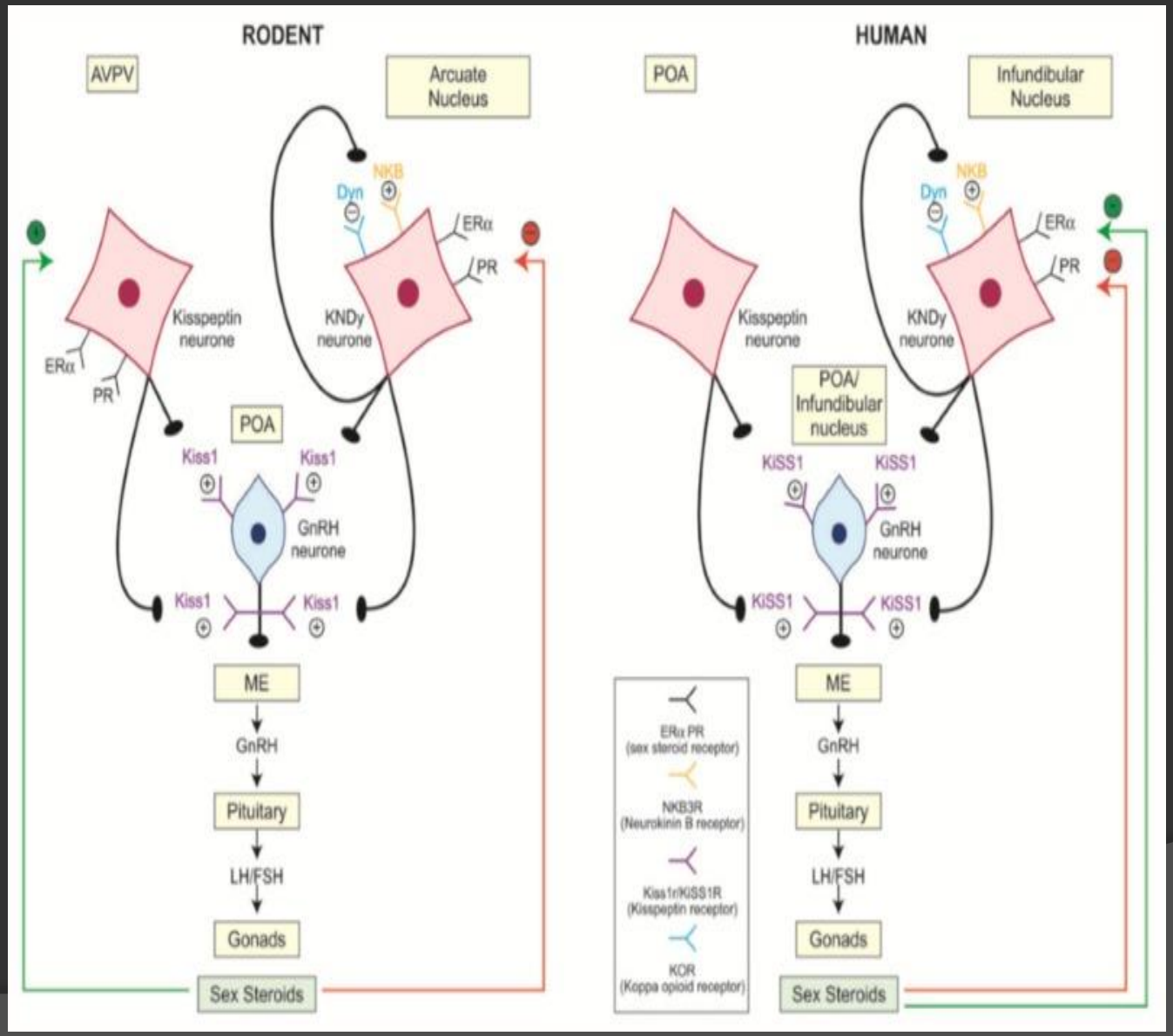

HEALTHYPLACE.COM

Types of Opioids

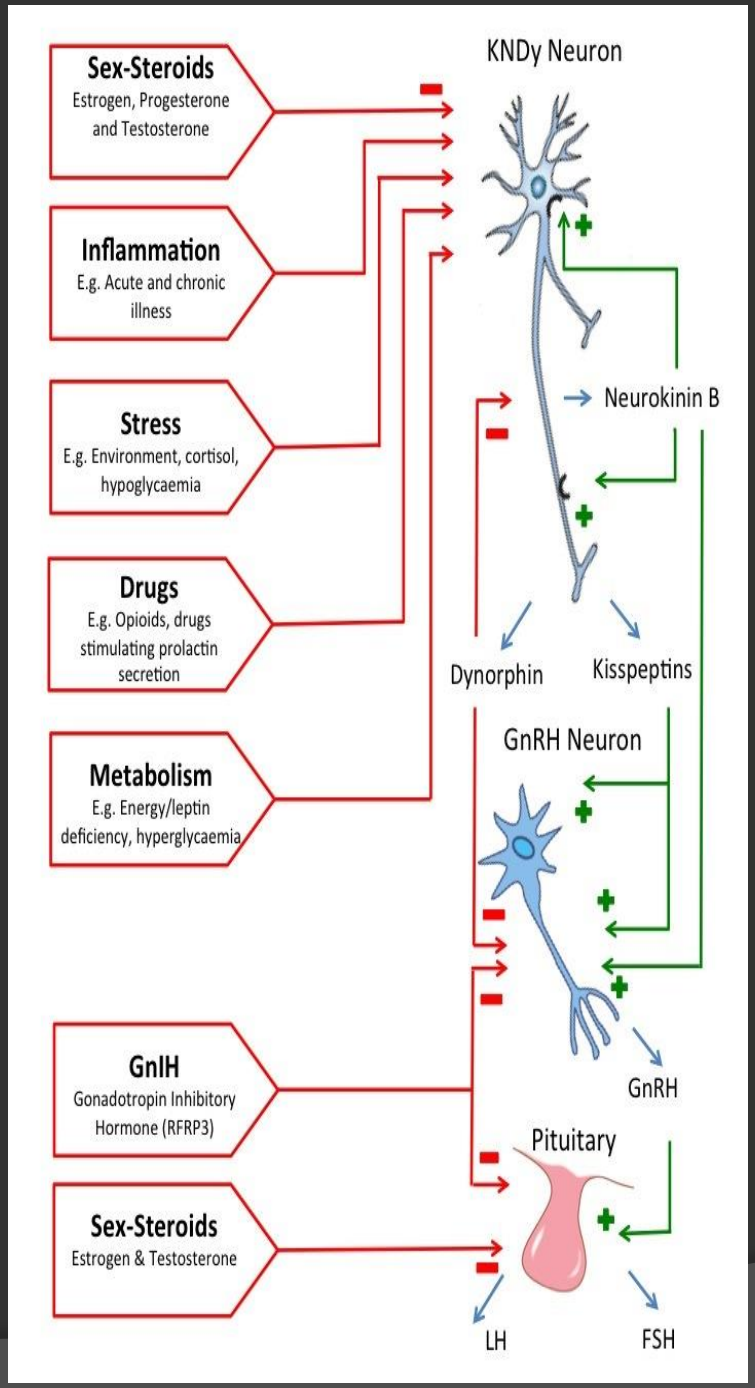


PSYCHOPHARMACOLOGY, Figure 10.4

Physiology of GNRH and Gonadotropin Secretion



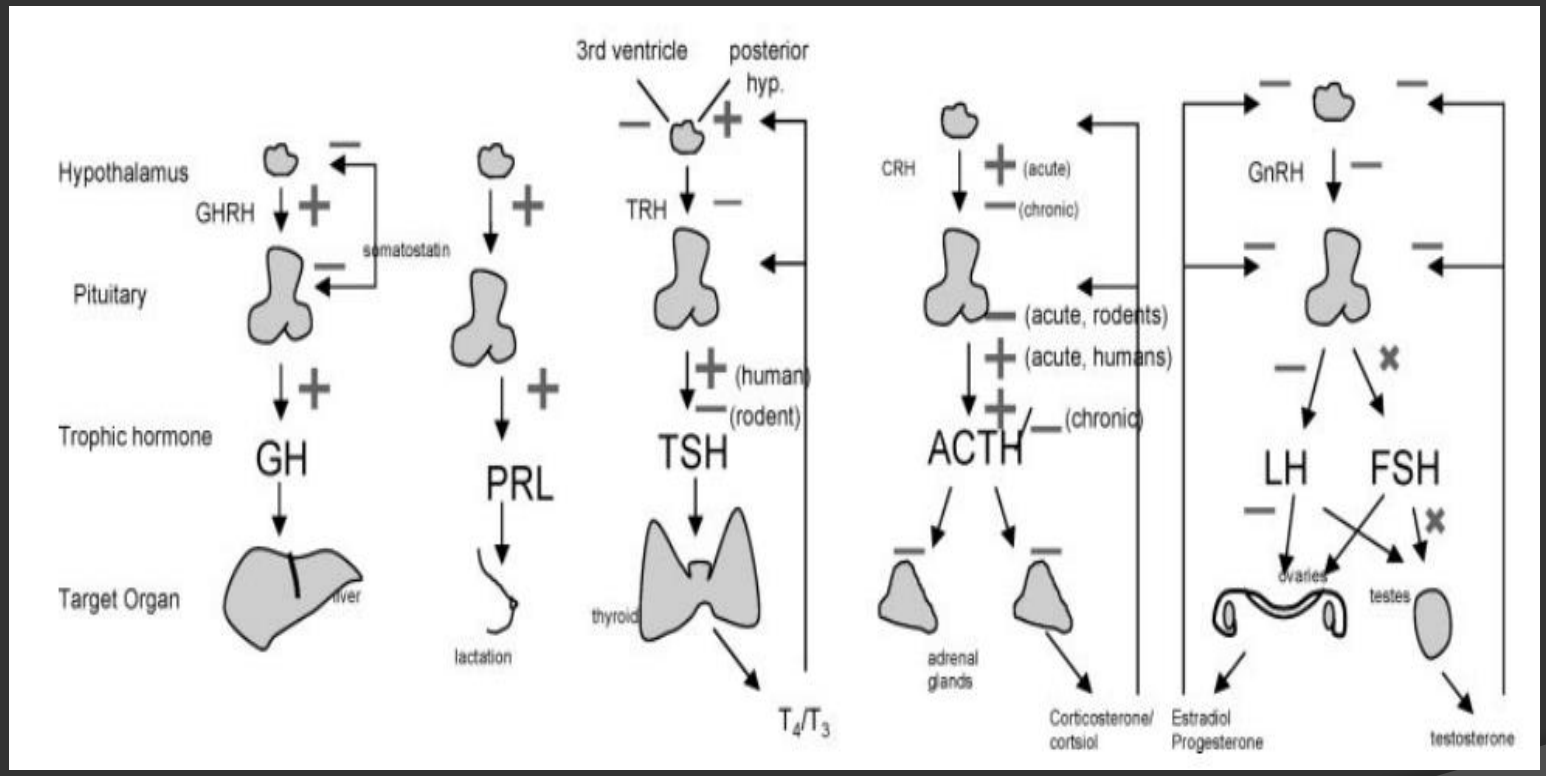
Disruption of normal physiology



Ligand	Opioid receptors		
	μ	δ	κ
β-Endorphin	++++	++	++
Leu-enkephalin	++	+++	0
Met-enkephalin	++	+++	0
Dynorphin A (1-17)	++	0	+++
Endomorphin-1	+++++	0	0
Endomorphin-2	+++++	0	0
Morphine	+++	0	+
Heroin	+++	+	0
Fentanyl	+++	0	0
Sufentanil	+++	0	0
Methadone	+++	0	0
DALA (DN-32-24)	++	+++	0
DAMME	++	++	0
U50,488H	0	0	++++
Nalorphine	−	0	+++
Naloxone	−	−	−
Naltrexone	−	−	−
CTOP	−	0	0
Buprenorphine	+/−	− (?)	−
Pentazocin	−	0	+++

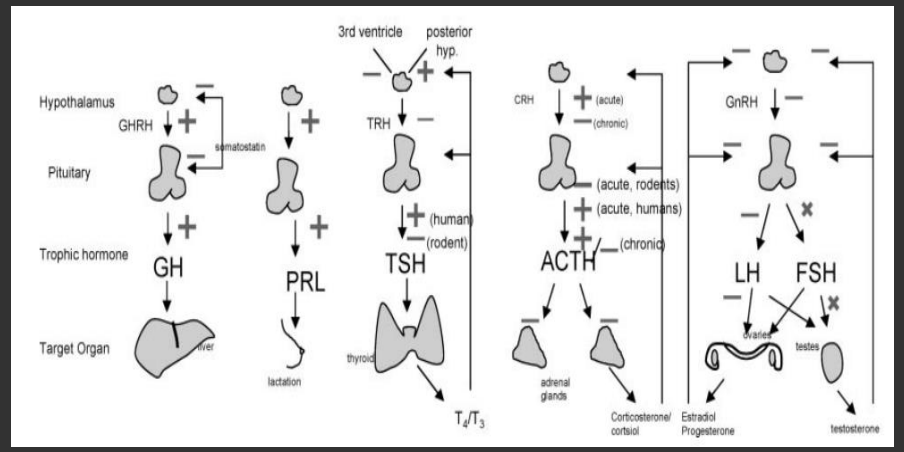
+, Agonist; −, antagonist; 0, no significant affinity; +/−, partial agonist; (?), unclear; CTOP, D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2. [Taken from Refs. 24 and 404–408.]

Effects of Opioids in Hormonal Axis
Animal and Human Models



Vuong et al. Opioids on the Endocrine System Endocrine Reviews, February 2010, 31(1):98 –132

Effects of Opioids in Hormonal Axis
Animal and Human Models

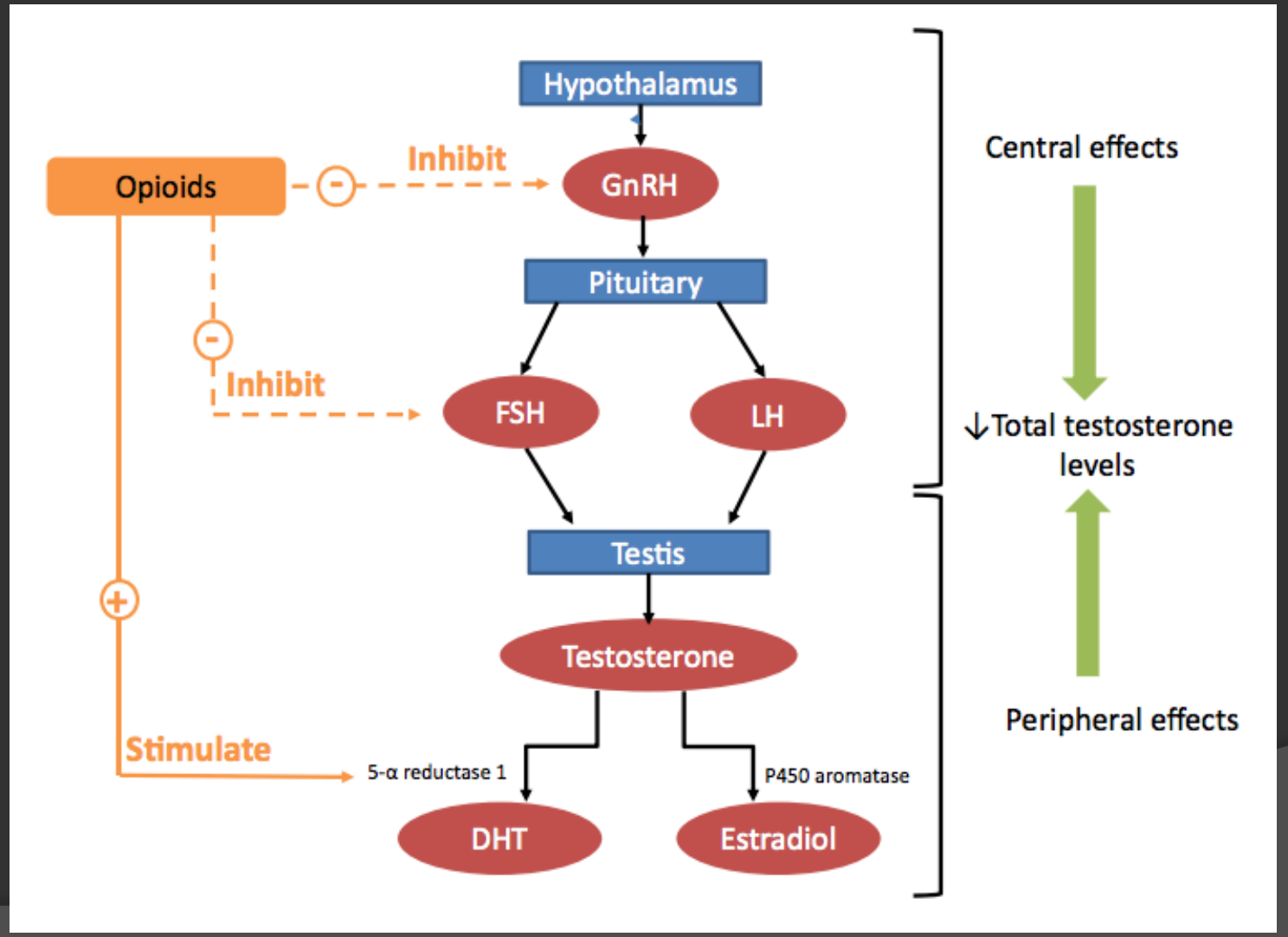


	Acute		Chronic	
Hormone	**Animals**	**Humans**	**Animals**	**Humans**
GH	↑	↑	=	?
PRL	↑	↑	↑	↑/=
TSH	↓	↑	?	?/=
ACTH	↑	↓	↓/↑	↓/=
LH	↓	↓↓	↓	↓↓
FSH	=	=	=	=
Estradiol	↓	↓↓	=	↓=
Testosterone	↓	↓↓	↓	↓↓
AVP	↑/↓	↑/↓	↑/↓	↑/↓
OT	↓	↓	↓/=	↓/=

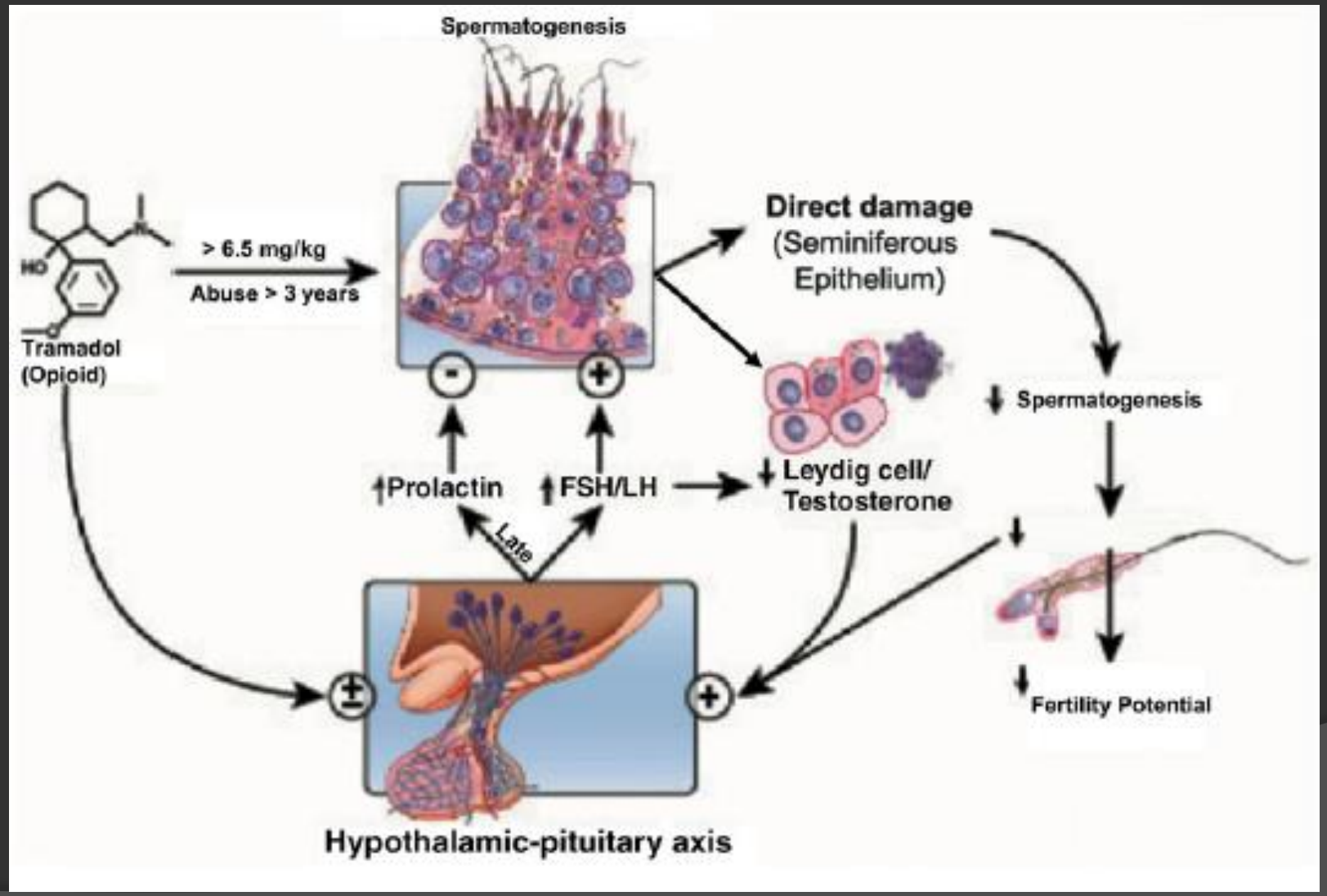
↑, Stimulation; ↓, inhibition; ↑↓, conflicting; =, no change; ?, not studied.

Vuong et al. Opioids on the Endocrine System Endocrine Reviews, February 2010, 31(1):98 –132

Opiate Induced Hypogonadism (OIH)

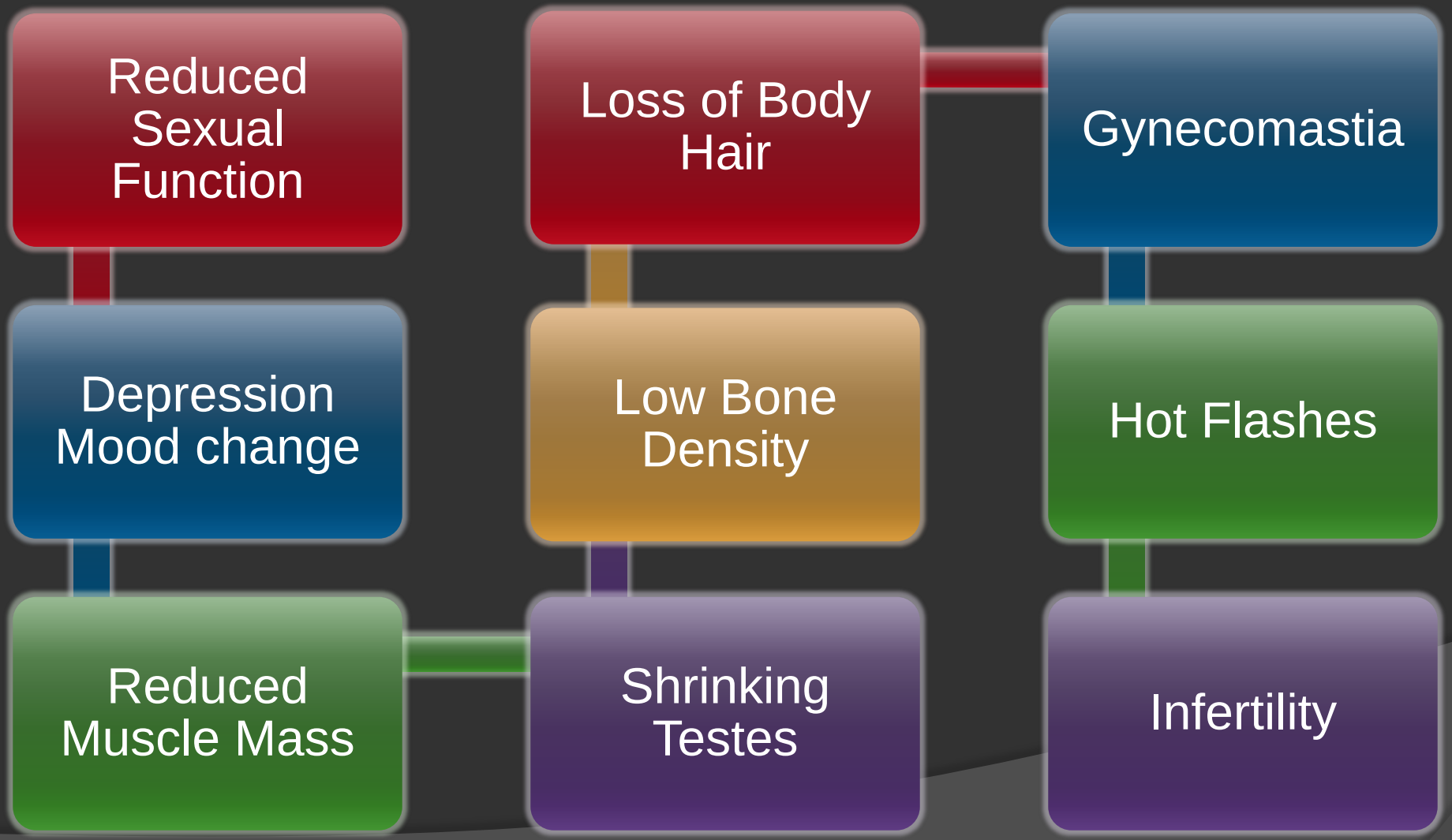


Tramadol Direct Testicular Damage



Farag et al, Andrologia 2018

OIH Symptoms
(not specific to chronic opioid use)



Gudin et al, Pain Medicine 2015

Prevalence of OIH

Author	Study Design	N	Opioids	MSE (mg)	Hypogonadism , %
Abs et al	Cohort	29	Morphine/ Intrathecal	4.8	86.2
Finch et al	Cross-sectional	11	Morphine/ Intrathecal	0.5-40	100
Daniell et al	Cross-sectional, Cohort	23	Mixed/ oral	70-120	74
Roberts et al	Cross-sectional	10	Mixed/ oral or Intrathecal	3.3	100
Rajagopal et al	Cross-sectional	20	Mixed/ oral	>200	90
Fraser et al	Cross-sectional	12	Mixed/ oral or transdermal	718	83
Duarte et al	Cross-sectional	20	Morphine/ Intrathecal	2.68	85
Rubentstein et al	Cross-sectional	81	Mixed/ oral	184	53
Kim et al	Cross-sectional	8	Intrathecal	12.3	50
Rubentstein et al	Cross-sectional	1585	Mixed/ oral	76	43.6
Cepeda et al	Cross-sectional	8146	Mixed/ oral	NR	35.1
Ajo et al	Cross-sectional	120	Mixed/ oral	77	19
Rubenstein et al	Cross-sectional	1159	Mixed/ oral	44	38.9

Coluzzi et al JCI 2018

HPG Axis Suppression and Risk Factors

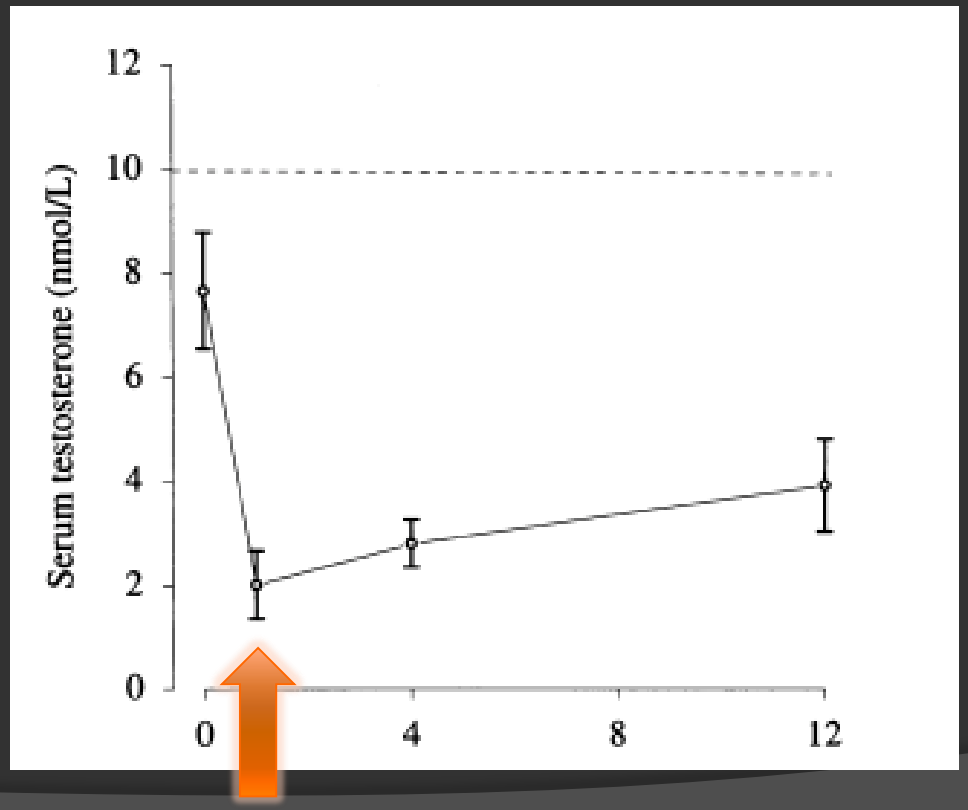
- Advanced Age
- Obesity
- DM, Hypothyroidism
- Long acting or sustain release formulations
- Chronic use > short term
- Higher potency opiates
- Higher serum concentration

Rubinstein et al Pain Medicine 2017

Sex Hormone Suppression by Intrathecal Opioids: A Prospective Study

*†Lindy J. Roberts, F.F.P.M.A.N.Z.C.A., ‡Phillip M. Finch, F.F.P.M.A.N.Z.C.A., §‖Peter T. Pullan, F.R.A.C.P., ¶Chotoo I. Bhagat, F.R.C.P.A., and ‡Leanne M. Price, R.N.

10 Men administered intrathecal opioids x 12 weeks



Symptom	Baseline	Week 1*	Week 4	Week 12
Poor libido	7	7	9	9
Not sexually active	6	7	9	10
Does not masturbate	6	8	9	8
Erectile difficulty	5	6	7	8
Unable to achieve penetration	3	4	6	5
Absence of early morning erections	8	8	9	8

Hormone	Reference range	Baseline	Week 1	Week 4	Week 12
SHBG (nmol/L)	10–50	28.7 ± 4.2	28.1 ± 5.0	24.9 ± 4.0	28.3 ± 4.2
FSH (U/L)	1–8	4.6 ± 0.5	2.5 ± 0.2	3.2 ± 0.3	3.8 ± 0.4
LH (U/L)	2–9	3.3 ± 0.5	2.3 ± 0.7	1.8 ± 0.3	3.0 ± 0.6
PRL (mU/L)	<420	256 ± 61	319 ± 43	274 ± 35	223 ± 39

Values are mean ± SEM.
SHBG, sex hormone–binding globulin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin.

Roberts et al JCP 2002

The Journal of Pain, Vol 9, No 1 (January), 2008: pp 28-36
Available online at www.sciencedirect.com

ELSEVIER

Opioid Endocrinopathy in Women Consuming Prescribed Sustained-Action Opioids for Control of Nonmalignant Pain

Harry W. Daniell, MD, FACP
Department of Family Practice, University of California Davis Medical School, Redding, California.

Table 1. Subject Use of Sustained-Action Opioids

Opioid Dosage Form	Percentage of Subjects	Mean Daily Dose (Range)
Oxycodone SR, oral	45%	141 (60–400) mg
Morphine sulfate SR, oral	16%	168 (60–330) mg
Methadone, oral	15%	97 (35–200) mg
Fentanyl, transdermal	24%	1500 (600–2400) µg

- 47 woman 30-78 y/o
- 68 control
- Significant suppression of testosterone, DHEA-S, estradiol

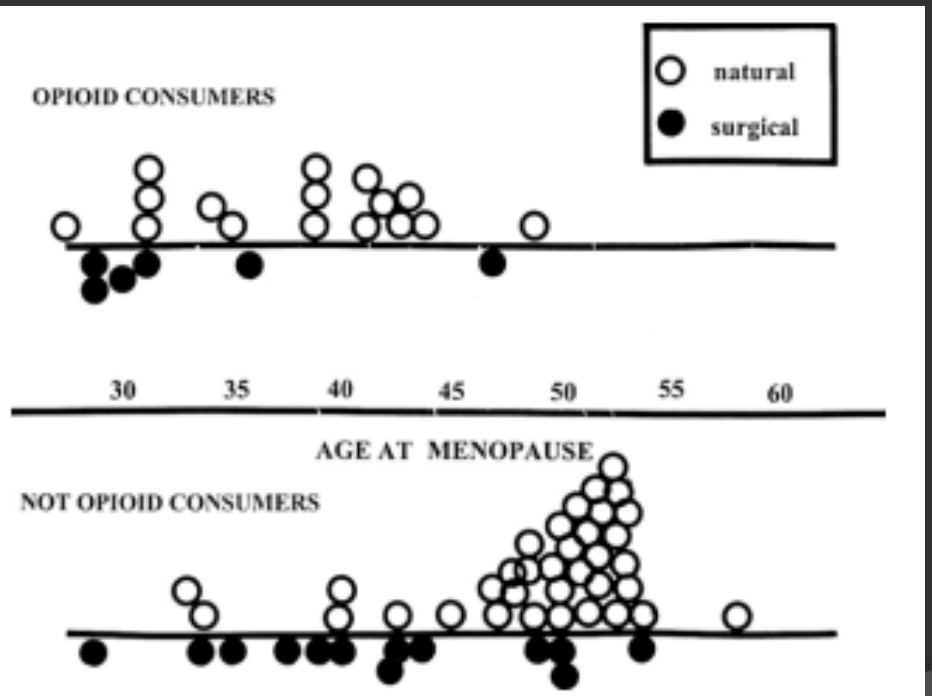


Figure 1. Age at menopause in women beginning sustained-action opioid use before 50 and in opioid nonconsumers.

Daniell et al Journal of Pain 2008

The Journal of Pain, Vol 9, No 1 (January), 2008: pp 28-36
Available online at www.sciencedirect.com

ELSEVIER

Opioid Endocrinopathy in Women Consuming Prescribed Sustained-Action Opioids for Control of Nonmalignant Pain

Harry W. Daniell, MD, FACP
Department of Family Practice, University of California Davis Medical School, Redding, California.

Table 3. Sex Hormone and SHBG Values of Opioid-Consuming Women and Control Subjects With Intact Ovarian Tissue and No Estrogen Therapy Analyzed by Age

	Opioid Consumers	Control Subjects	P Values	Normal Range
Ages 30–50				
Number	21	16		
Age (avg) ± SD (y)	39.3 ± 4.9	42.7 ± 3.5	NS	
Total testosterone ± SD (ng/dL)	30.7 ± 21.5	54.4 ± 10.3	< .001	14–76
SHBG ± SD (nmol/L)	63.2 ± 32.7	70.3 ± 27.1	NS	18–114
Free testosterone ± SD (pg/mL)	4.0 ± 3.5	7.0 ± 2.4	< .01	1–9
Estradiol ± SD (pg/mL)	63.2 ± 56.7	132.3 ± 108.1	< .05	30–230
DHEAS ± SD (μg/dL)	51.2 ± 52.1	113.3 ± 53.7	< .01	40–300
Ages 51–75				
Number	10	26		
Age (avg) ± SD (y)	59.6 ± 7.8	59.4 ± 6.5	NS	
Total testosterone ± SD (ng/dL)	24.6 ± 16.6	36.7 ± 17.7	NS	10–80
SHBG ± SD (nmol/L)	63.3 ± 41.7	62.2 ± 28.9	NS	18–114
Free testosterone ± SD (pg/mL)	3.9 ± 2.3	5.8 ± 3.9	< .04	1–9
Estradiol ± SD (pg/mL)	18.7 ± 9.3	29.7 ± 25.2	NS	11–61
DHEAS ± SD (μg/dL)	33.9 ± 24.6	66.5 ± 41.3	< .02	18–120

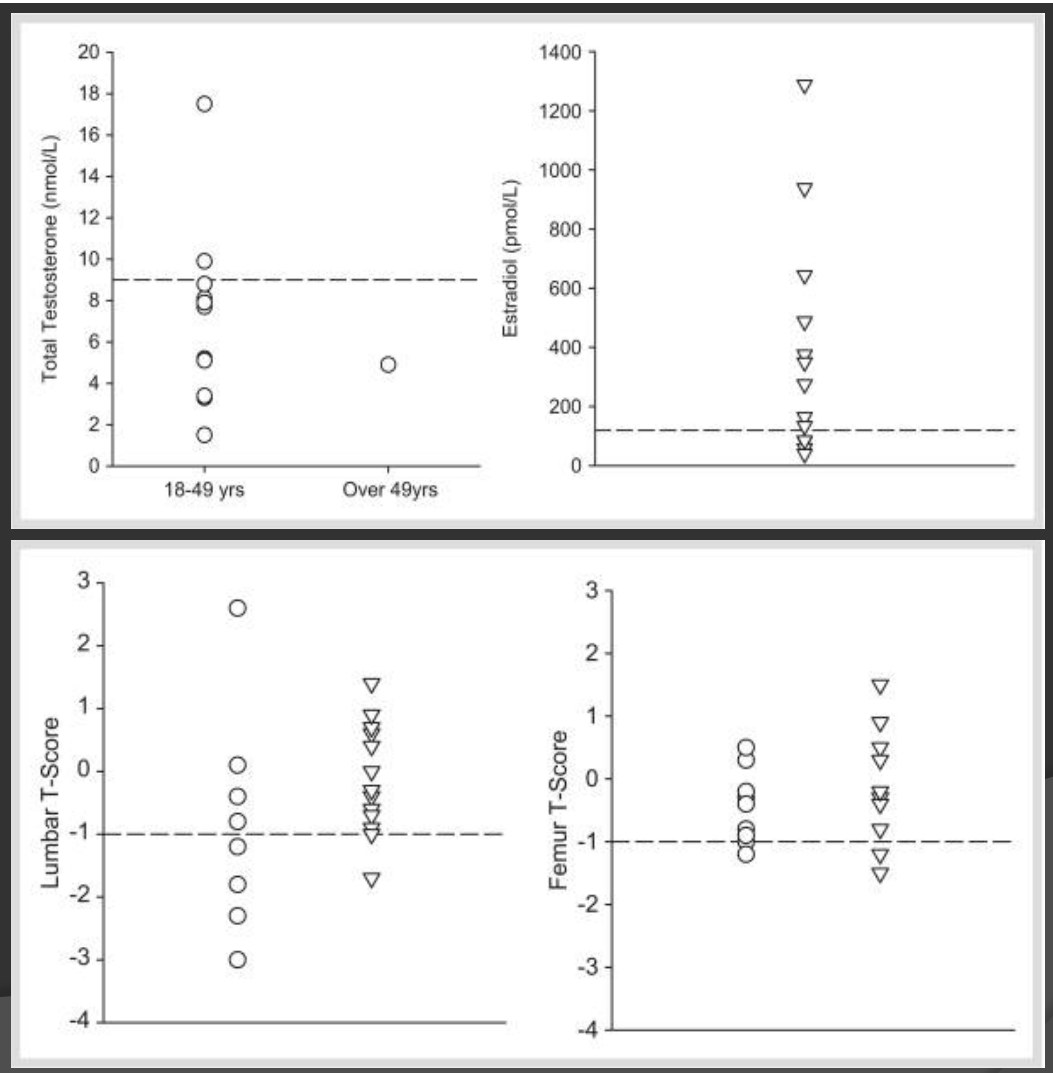
Abbreviations: SHBG, sex hormone–binding globulin; DHEAS, dehydroepiandrosterone sulfate; NS, not significant.

Daniell et al Journal of Pain 2008

Oral Opioids for Chronic Non-cancer Pain: Higher Prevalence of Hypogonadism in Men than in Women

L.-A. Fraser[1,*], D. Morrison[1,*], P. Morley-Forster[2], T. L. Paul[1], S. Tokmakejian[3], R. Larry Nicholson[4], Y. Bureau[5], T. C. Friedman[6], and S. H. M. Van Uum[1]

- 26 CNCP 18-60 y/o
- 12 men, 14 women
- Oral opioids > 1 year
- Men older than women
- Men took opioids longer time
- Equal MED and Pain Score

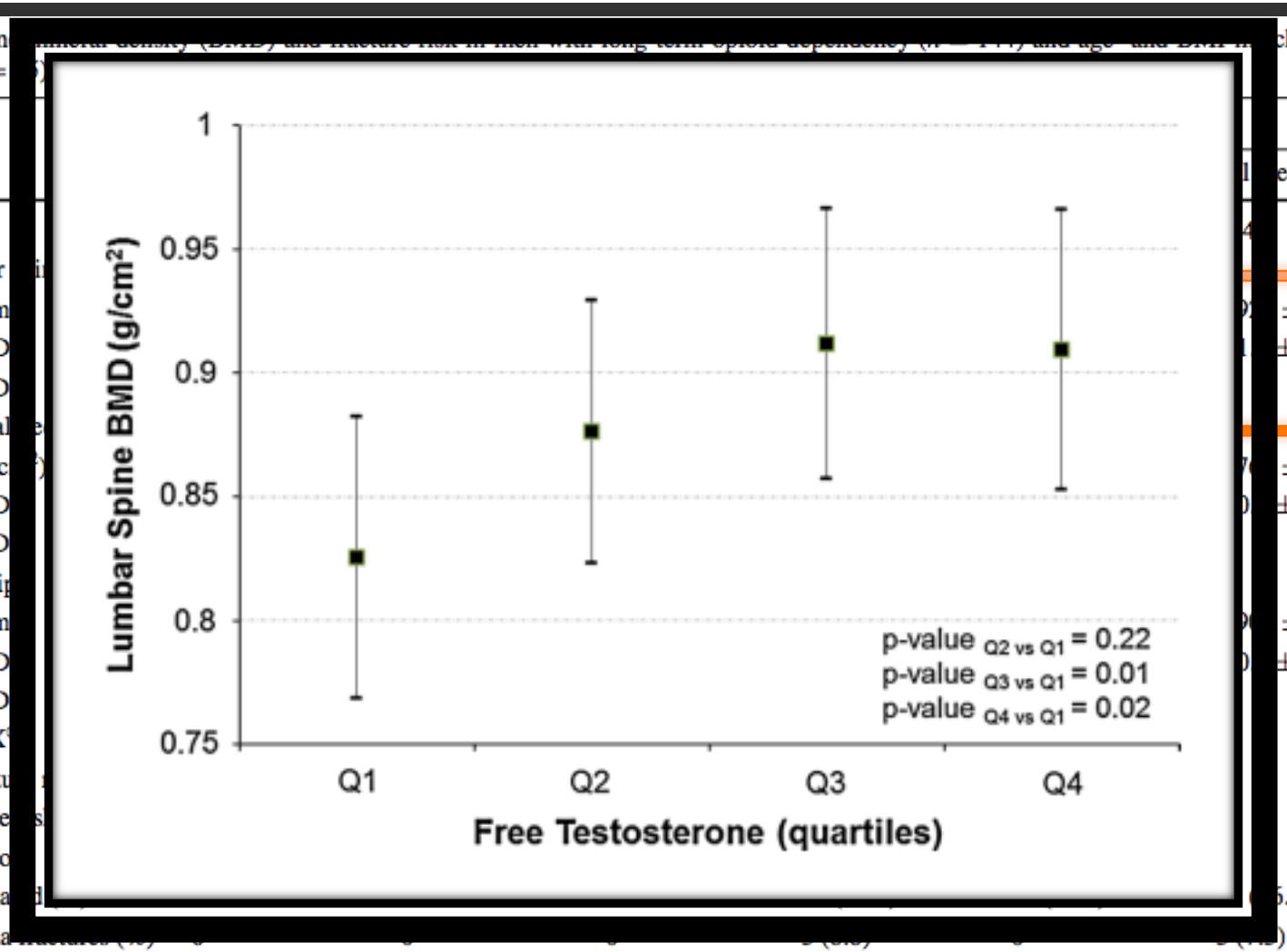


Bone mineral density and its determinants in men with opioid dependence

Frank Gotthardt[1] · Christine Huber[1] · Clara Thierfelder[1] · Leticia Grize[2,3] · Marius Kraenzlin[4] · Claude Scheidegger[1] · Christian Meier[4]

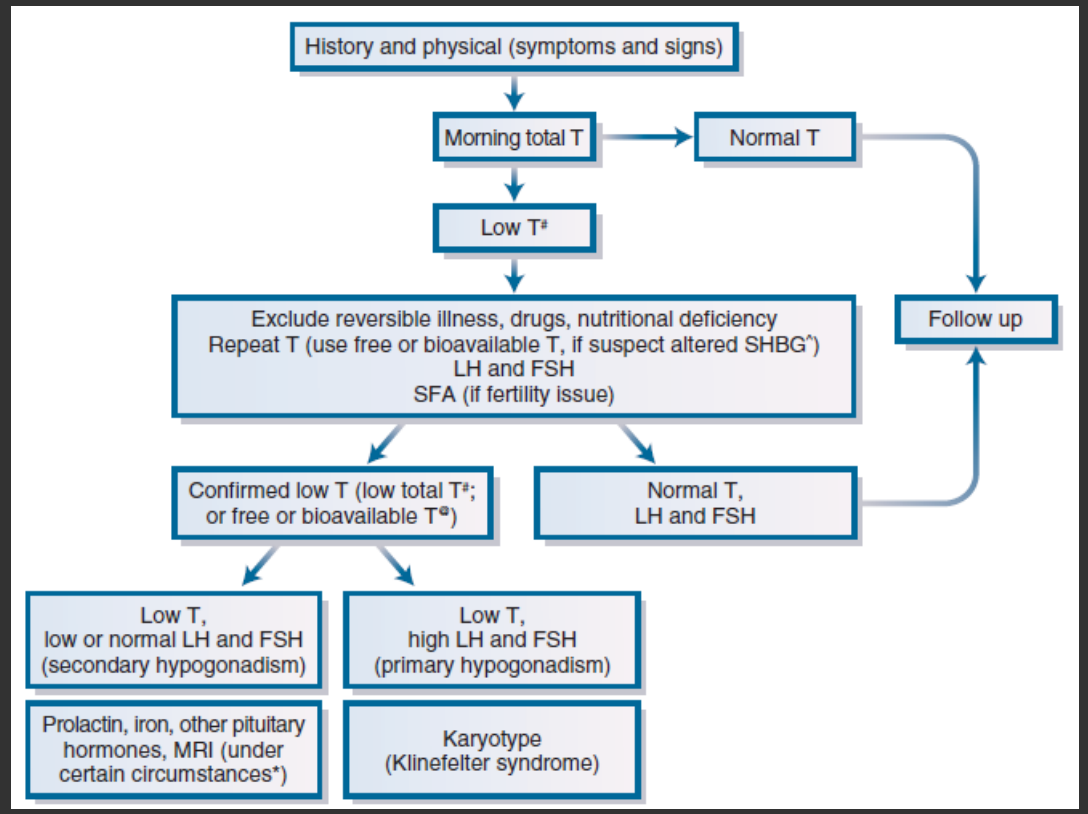
Table 2 Bon … ched male controls (n = … en

DXA lumbar …				
BMD (g/cm …				± 0.129*
Z-score (SD …				± 1.1*
T-score (SD …				
DXA femoral …				
BMD (g/c …				± 0.122*
Z-score (SD …				± 0.9*
T-score (SD …				
DXA total hip …				
BMD (g/cm …				± 0.124*
Z-score (SD …				± 0.8*
T-score (SD …				
WHO FRAX …				
Major fractu …				
Hip fracture …				
Fracture histo …				
Trauma-rela …				.4)
Low-trauma …				)



Data are given as mean ± SD or number (percentage). Comparison with age- and BMI-matched healthy men: $p < 0.01$ compared with all men*, men <40 years[§] and men ≥40 years[#]

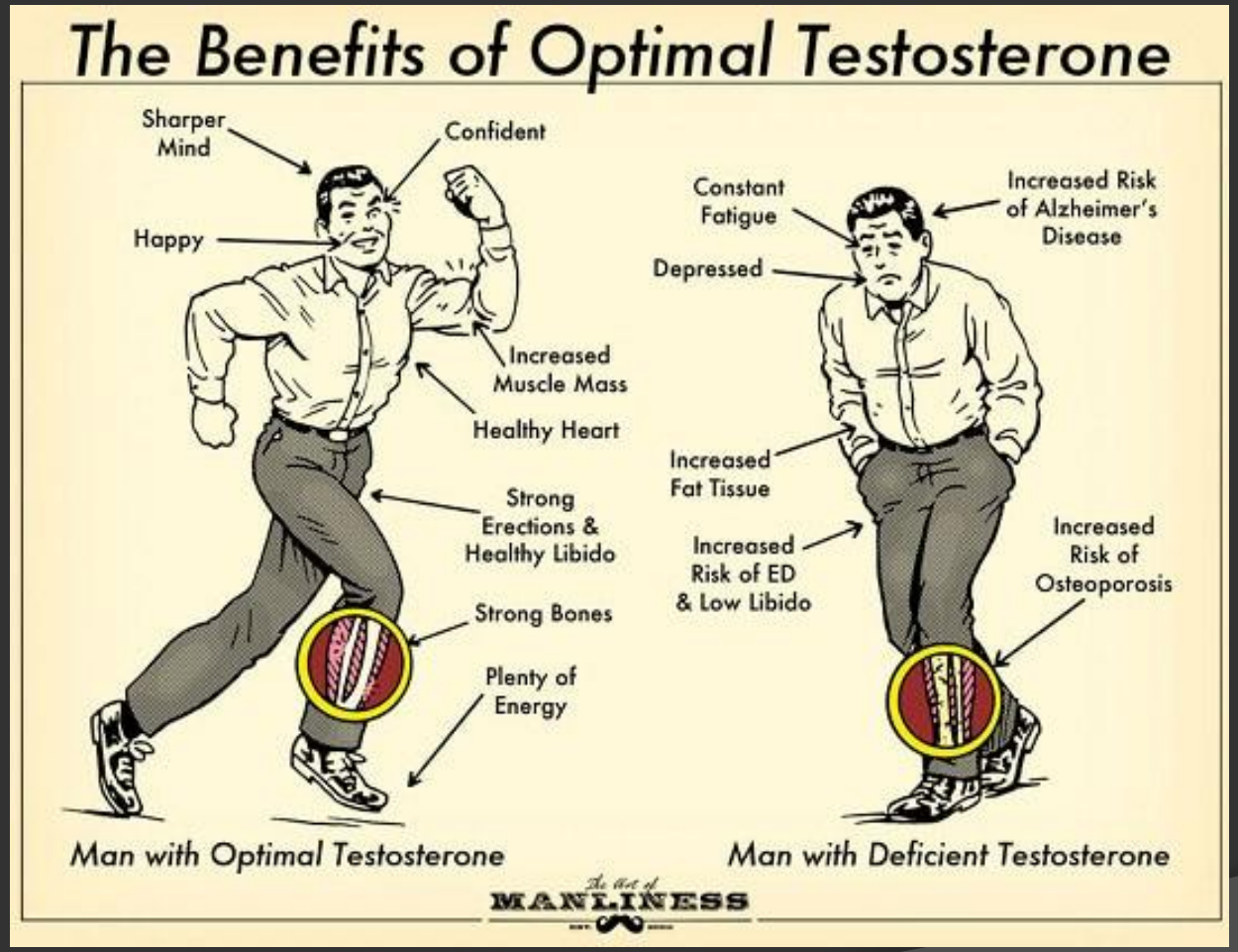
Diagnosis of OIH



- Total Testosterone am x 2
  - Free Testosterone if available
  - SHBG with TT
- Consider LH/FSH/prolactin as evaluation for other ddxs
- Pituitary MRI
- If OIH diagnosed tapper opioid as possible
- Scant data on proper recognition, diagnosis and formal treatment of OIH in women
  - DHEA-S

Does Testosterone Improves OIH Symptoms?

YES !!



YES !!

Benefit of Testosterone Tx

Study	Design	N	Sex Fx	Pain	Mood	QoL
Daniell et al.	Observational	23	↑	↓	↑	↑
Alosi et al.	Observational	17	↑	↓	↔	↑
Blick et al.	Observational	90	↑	↓	↑	NR
Basaria et al.	RCT/PC	43	↑	↓	NR	NR
Rabeen et al.	Observational	11	↑	↓	NR	NR

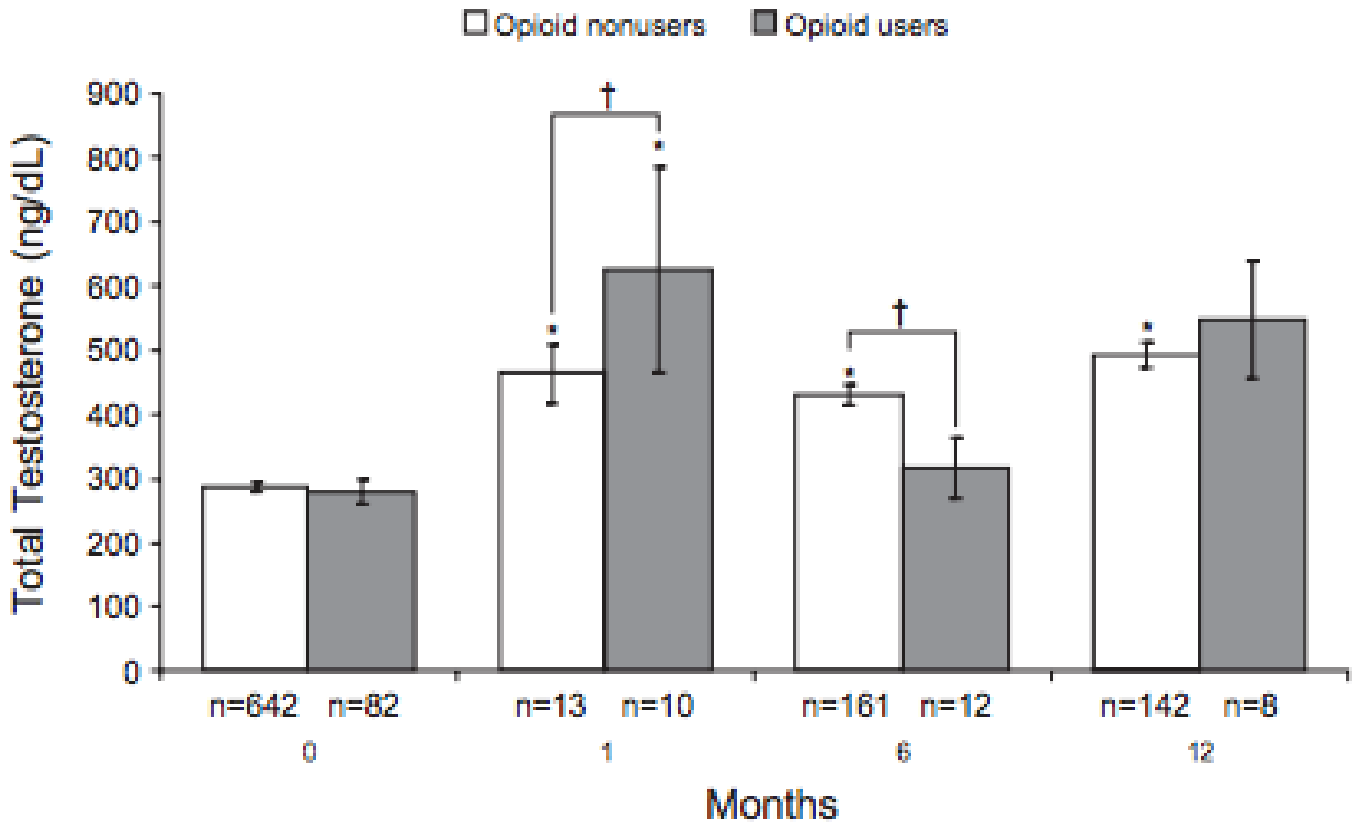
"Testosterone may have antinociceptive properties"

Adapted from Coluzzi et al JCI 2018

- Open Label
- 849 men enrolled
- 12 months observational cohort
- 1% testosterone gel 5-10 g/day
- 10% patients reported opioid use

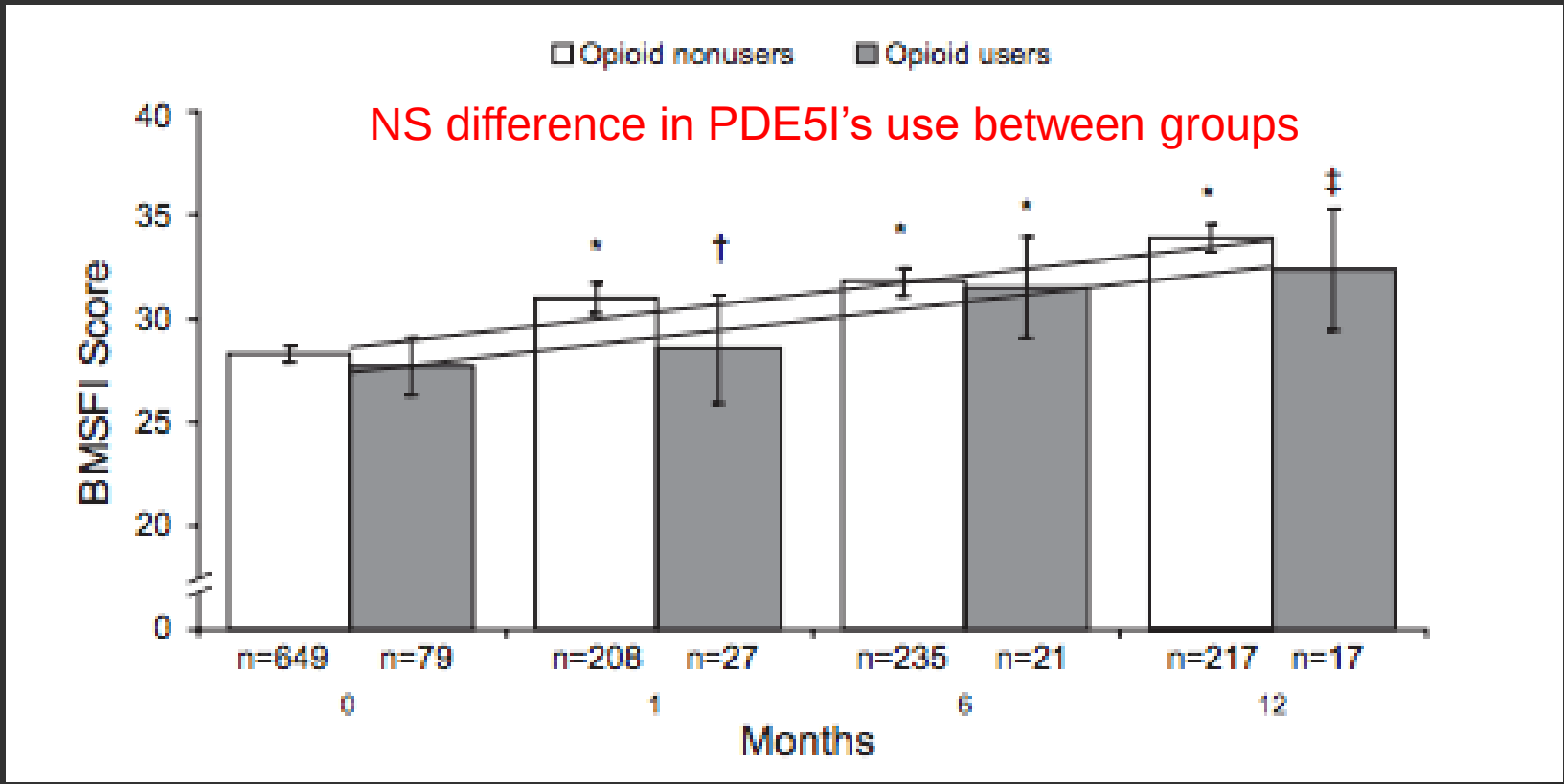
Blick et al Pain Medicine 2012

Testosterone Replacement Therapy Outcomes Among Opioid Users: The Testim Registry in the United States (TRiUS)



Blick et al Pain Medicine 2012

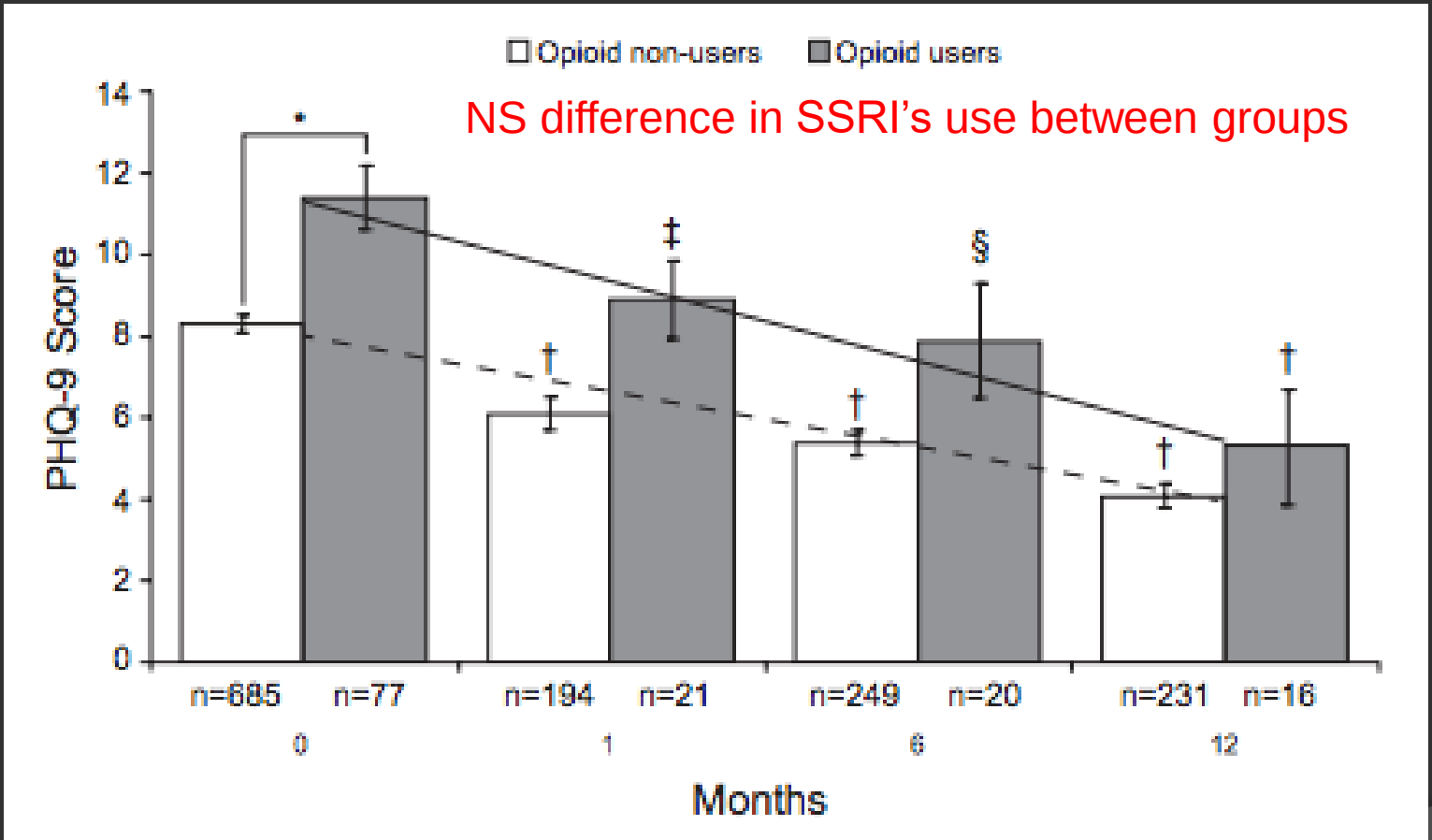
Testosterone Replacement Therapy Outcomes Among Opioid Users: The Testim Registry in the United States (TRiUS)



BMSFI: Brief Male Sexual Function Inventory

Blick et al Pain Medicine 2012

Testosterone Replacement Therapy Outcomes Among Opioid Users: The Testim Registry in the United States (TRiUS)



PHQ-9 Score: Patient Health Questionary 9 Score

Blick et al Pain Medicine 2012

The Role of Testosterone Supplemental Therapy in Opioid-Induced Hypogonadism: A Retrospective Pilot Analysis

	TST (n=11)		Non TST (n=16)	
	Baseline	Follow-up	Baseline	Follow-up
Androgen Deficiency in Aging Males	8 (7-9)	3 (2-3)	7 (-8)	7 (6-8)
International Index of Erectile Function	10	20	11	12 (11-16)
Numerical Rating Scale	2	0	2	2
Morphine Equivalent dose	67.8 (47-79)	46.8 (35-58)	69 (43-82)	71.5 (59-85)

Testosterone therapy used: Gel, Inyectables and Implants

Raheem et al American Journal Men's Heath 2017

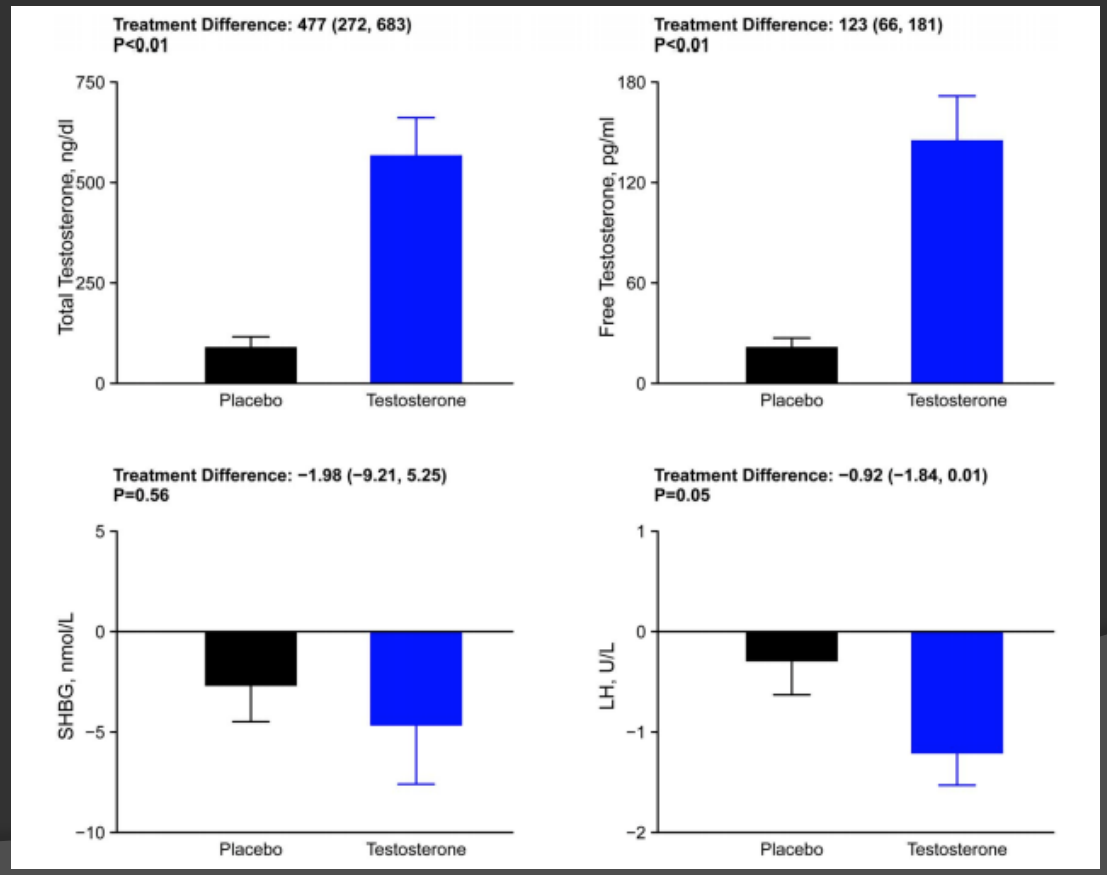
Research Paper

PAIN

Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial

Shehzad Basaria[a,*], Thomas G. Travison[a,b], Daniel Alford[c], Philip E. Knapp[c], Kjersten Teeter[a], Christine Cahalan[d], Richard Eder[a], Kishore Lakshman[a], Eric Bachman[a], George Mensing[d], Marc O. Martel[d], Dillon Le[a], Helene Stroh[a], Shalender Bhasin[a], Ajay D. Wasan[e], Robert R. Edwards[d]

- 84 randomized patients
- Testosterone < 350 ng/dl
- Opioids > 4 weeks
- PSA > 4 ng/ml, severe LUTS, CHF, malignancy, prior hypogonadism, CVD, oxygen dependent
  - Testosterone therapy contraindications
- Testosterone gel 5g daily vs placebo



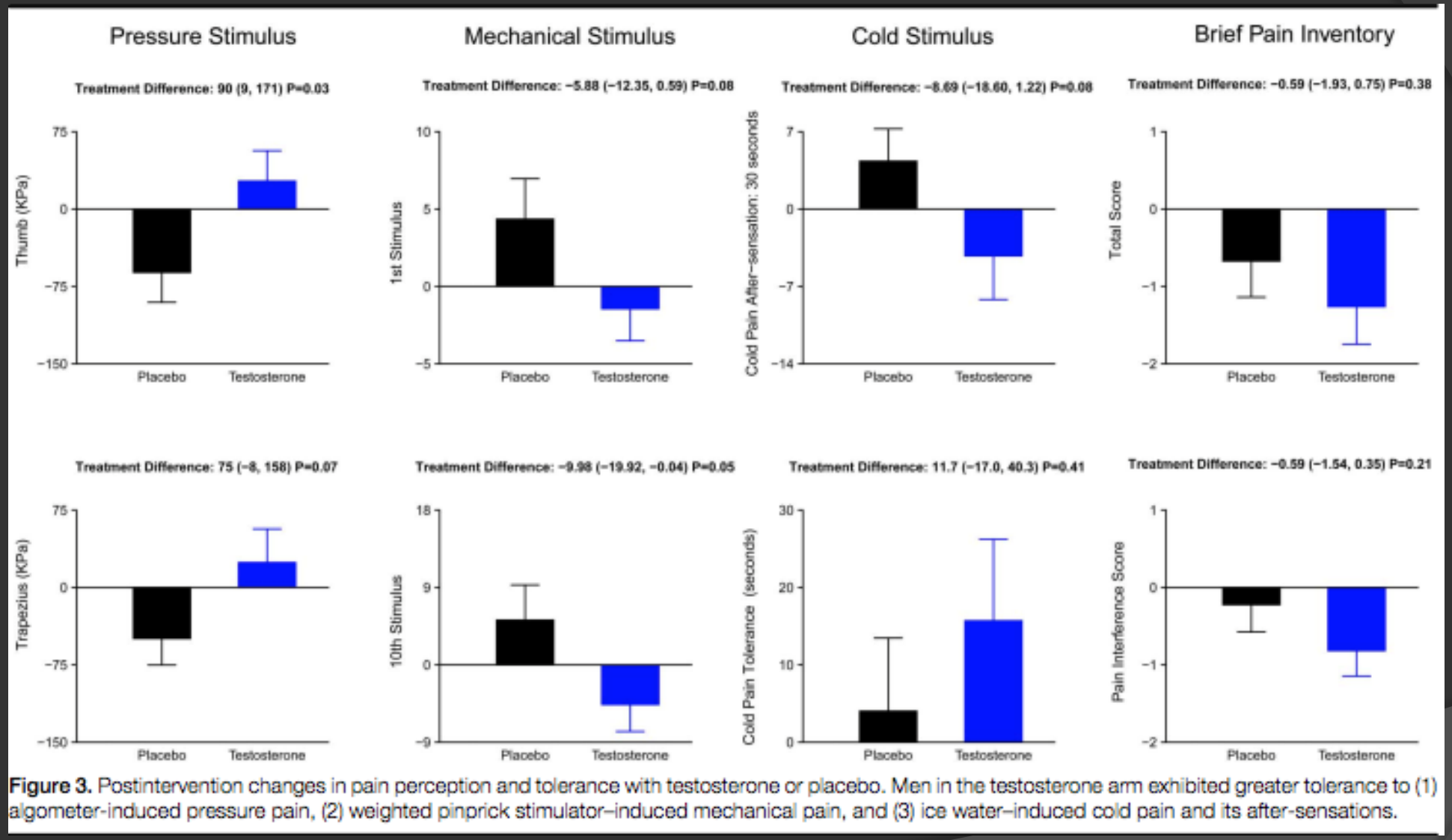
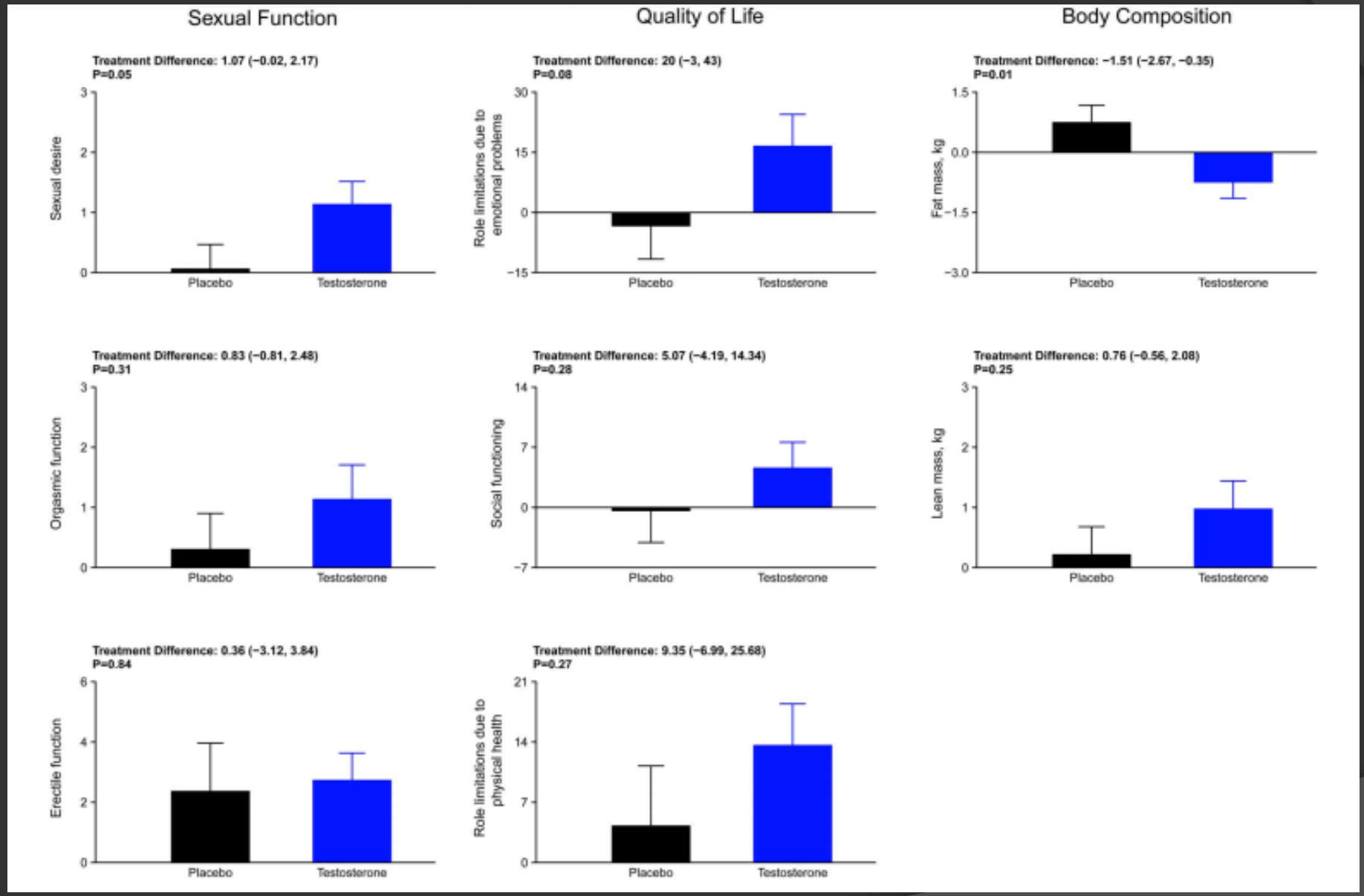


Figure 3. Postintervention changes in pain perception and tolerance with testosterone or placebo. Men in the testosterone arm exhibited greater tolerance to (1) algometer-induced pressure pain, (2) weighted pinprick stimulator–induced mechanical pain, and (3) ice water–induced cold pain and its after-sensations.

Basaria et al Pain Journal 2015



Basaria et al Pain Journal 2015

Opioid Induced Hypogonadism

- It is real and it happens early in treatment course
- It causes significant decrease in sexual function, QOL among all known hypogonadism metabolic complications
- More research is needed in women
- Once suspected based on symptoms, test for testosterone
- Wean opioids
- Testosterone Replacement
- DHEA Replacement in women*

Opioid Induced Adrenal Insufficiency (OIAI)

OPANA ER

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5, 5.6)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of OPANA ER in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OPANA ER in patients with impaired consciousness or coma. (5.10)
- Difficulty in Swallowing: Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction. (5.11)

ADVERSE REACTIONS

Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OPANA ER if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OPANA ER because they may reduce analgesic effect of OPANA ER or precipitate withdrawal symptoms. (7)

Opioid-Induced HPA Suppresion

- Chronic opioid use → ACTH, cortisol, DHEA-S suppression
- Symptoms:
  - Non specific, nausea, vomits, abdominal pain, low blood pressure, anorexia, fatigue
- High index of suspicion is needed
- May occur with any opioid after chronic use (> 1 month), long acting and higher doses
- Once suspected:
  - Treat ←→ Test → Wean off Opioids → Wean Steroids
- Mortality associated to Opioid-Induced HPA suppression → UNKNOWN

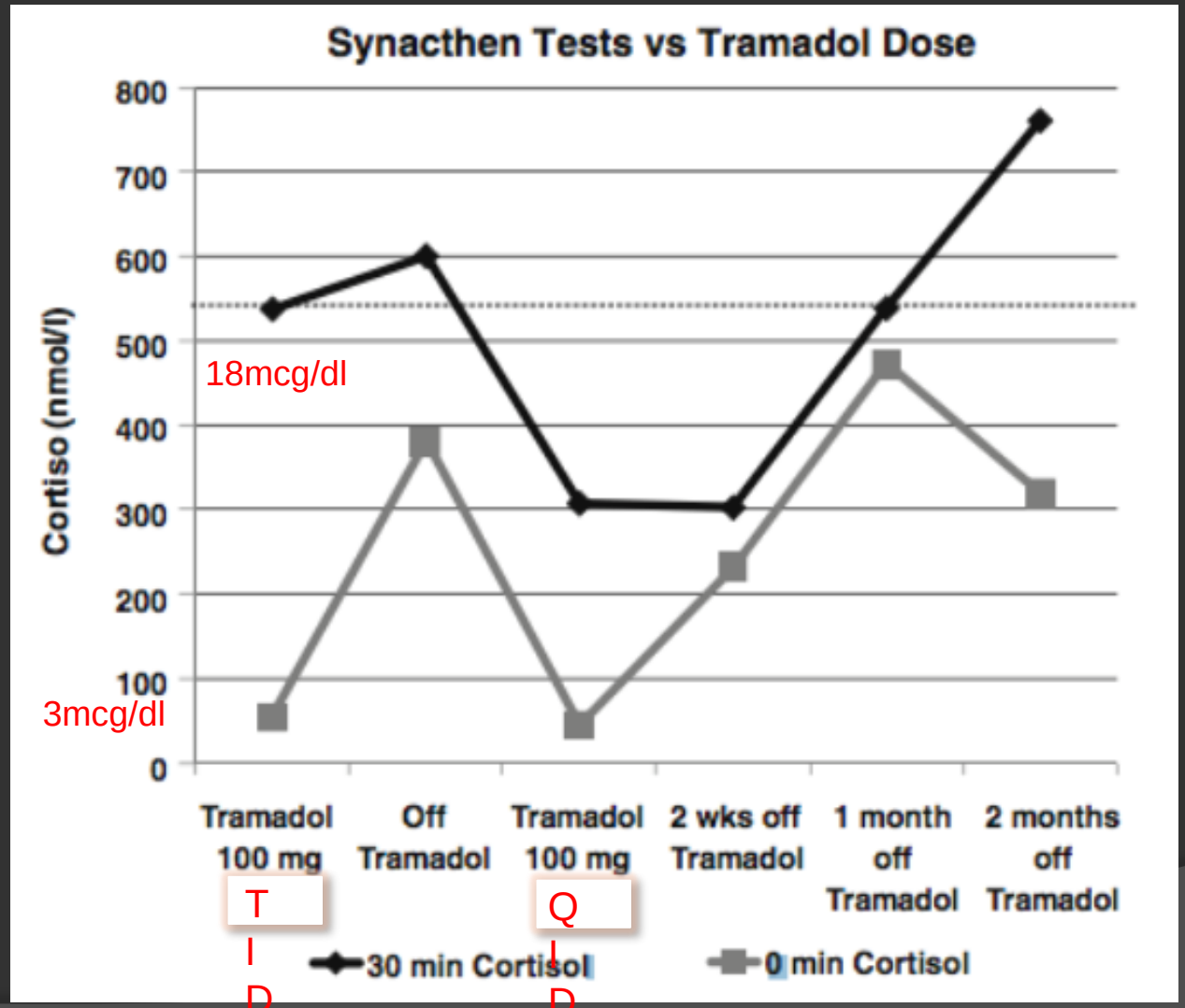
Prevalence of OI-HPA Suppression

Author (references)	Year	Study method	Number of participants	Inclusion criteria	Average MEDD in mg	Method of assessment	Prevalence
Lamprecht *et al.* [5▪]	2018	Cross-sectional	$n=40$; Control $n=25$	Opioid duration >6 months >25 mg MEDD	74 (25–265)	Baseline cortisol, ACTH, and DHEAS; 250 μg CST; overnight metyrapone test	22.5% failed CST or overnight metyrapone test
Gibb *et al.* [4]	2016	Cross-sectional	$n=48$; No control	opioid duration >6 months	68 (40–153)	8 a.m. cortisol; 30 min CST	8.3% baseline cortisol <100 nmol/l (1.8 μg/dl), three patients failed initial CST
Merdin *et al.* [6]	2016	Retrospective	Cancer-associated pain on chronic opioid $n=20$	≥25 mg for >1 month	180 (10–420)	Basaline cortisol and ACTH	15% had baseline cortisol <4.3 μg/dl (119 nmol/L)
Rhodin *et al.* [13]	2010	Cross-sectional	$n=39$; Control $n=20$	Oral opioid duration >1 year	Men: 133 (40–320); Women: 111 (30–230)	Corticotrophin releasing hormone test	33% in LTOT and 70% of controls failed to achieve cortisol >550 nmol/l (20 μg/dl)
Abs *et al.* [12]	2000	Retrospective	$n=73$; No Control	Intrathecal opioid therapy	4.8 ± 3.2	24 h UFC; ITT	19.7% had 24 h UFC <20 μg/l (550 nmol/l); 14.8% had a cortisol <18 μg/l (550 nmol/l) using ITT

ACTH, corticotrophin; 24 h UFC, 24 h urine free cortisol; CST, cosyntropin stimulation test; DHEAS, dehydroepiandrosterone sulfate; ITT, insulin tolerance test; LTOT, longterm opioid therapy; MEDD, morphine equivalent daily dose.

Donegan, Curr Opin Endocrinol Diabetes Obes, 2019

OIAH due to Tramadol



Debono et al, European Journal of Pharmacology, 2010

OIAI Suggested Algorithm

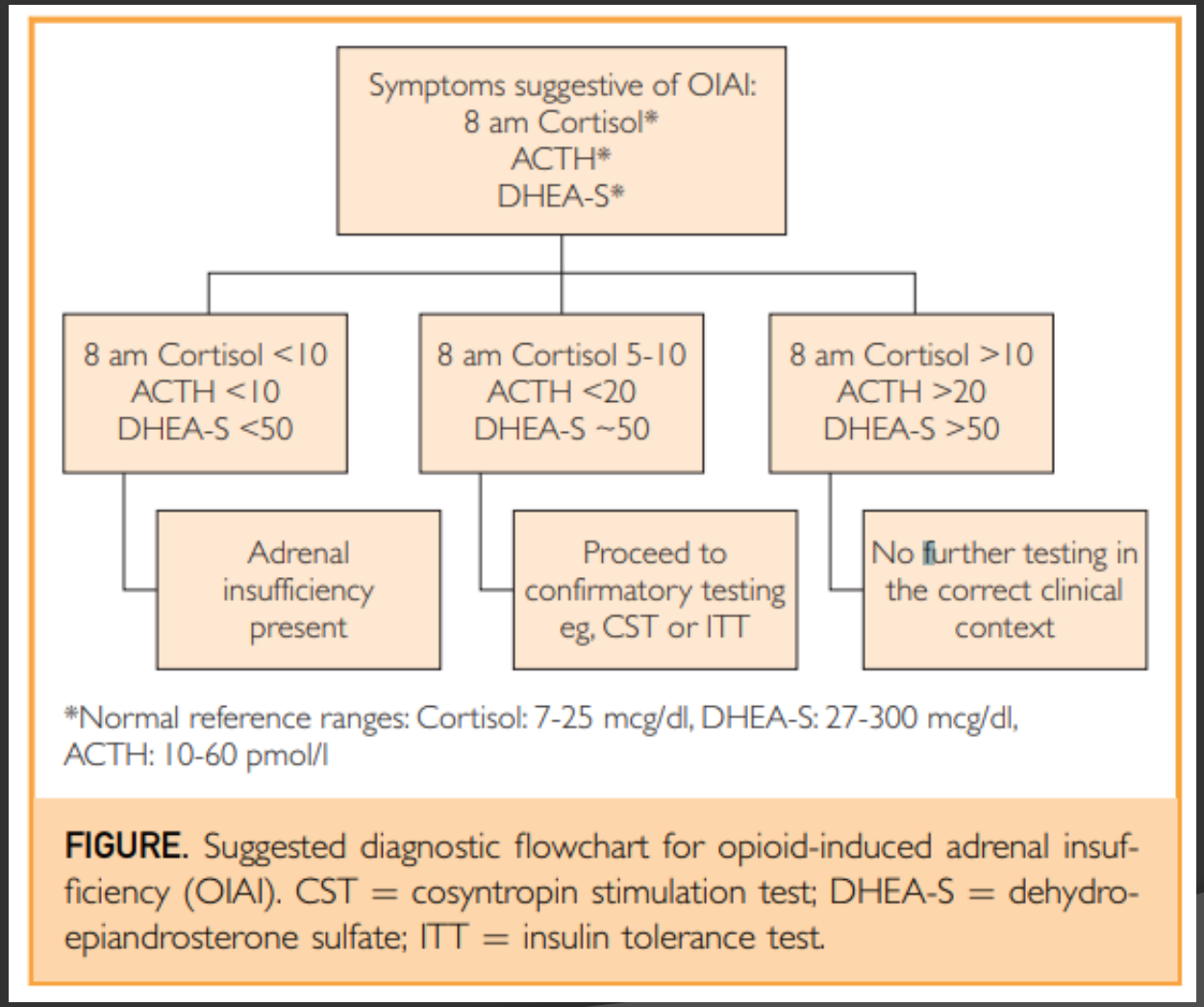


FIGURE. Suggested diagnostic flowchart for opioid-induced adrenal insufficiency (OIAI). CST = cosyntropin stimulation test; DHEA-S = dehydroepiandrosterone sulfate; ITT = insulin tolerance test.

Donegan, Mayo Clin Proc. July 2018

OIAI Suggested Treatment

TABLE 2. Management of Opioid-Induced Adrenal Insufficiency

Management	Instruction	Consideration	Alternative
Medication	Hydrocortisone 15-25 mg/d in divided doses, eg, 10 mg on waking, 5 mg 6-8 h later	DHEA supplementation in women (25 mg/d)	Dose-equivalent prednisone/ prednisolone
Education	*Sick day rule 1:* Double your daily glucocorticoid replacement therapy in times of sickness *Sick day rule 2:* Administer IM corticosteroid in times of sickness and inability to take orally (if family or patient can administer IM corticosteroids) Corticosteroid card or written adrenal insufficiency action plan stating sick day rules Medic alert bracelet or necklace indicating the presence of adrenal insufficiency	Annual check of IM corticosteroid expiration date	Dexamethasone 4 mg, methylprednisolone 40 mg
Emergency/adrenal crisis	Administer 100 mg hydrocortisone IV/IM, IV hydration	Optimize education regarding sick day rules to prevent adrenal crisis	Dexamethasone 4 mg, methylprednisolone 40 mg
Procedure/operation	Administer 100 mg hydrocortisone IV/IM before procedure followed by 200 mg/d IV until able to eat and drink	None	Dexamethasone 4 mg, methylprednisolone 40 mg

DHEA = dehydroepiandrosterone; IM = intramuscular; IV = intravenous.

Donegan, Mayo Clin Proc. July 2018

Other Opioid Endocrinopathies

Opioids and Prolactin

- Acute and Chronic
  - Net effect INCREASE
- Secondary Hypogonadism
- Negative MRI
- Cabergoline/bromocriptine not studied
- Some studies NS change
- **Tx: Tapper Opioids**

Opiods and GH

- Chronic use → Decrease GH
- Decrease LBM, increase BMI
- **Tx: Tapper Opioids**

Opiods and TSH

- Chronic use → No change

My Personal Reflexión

What if opioid overdose and death may have been induced by a profound depression caused by hypogonadism, significant decrease in QOL, ect?

What if some of those death were secondary to unrecognized Opioid Induced Adrenal Failure?

What if by having Opioid Induced Endocrinopathies undiagnosed, our patients develop more pain and enroll in a vicious cycle that leads towards higher opiod doses?

What if, if the real problem is that we may don’t want to deal with this? (cost, time consuming, diagnosis approach, tx options)


PRESCRIPTION
DATE
NAME
ADRESS
opioids