

Opioids in Chronic Pain and PTSD: Liability or Potential Therapy?

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Outline

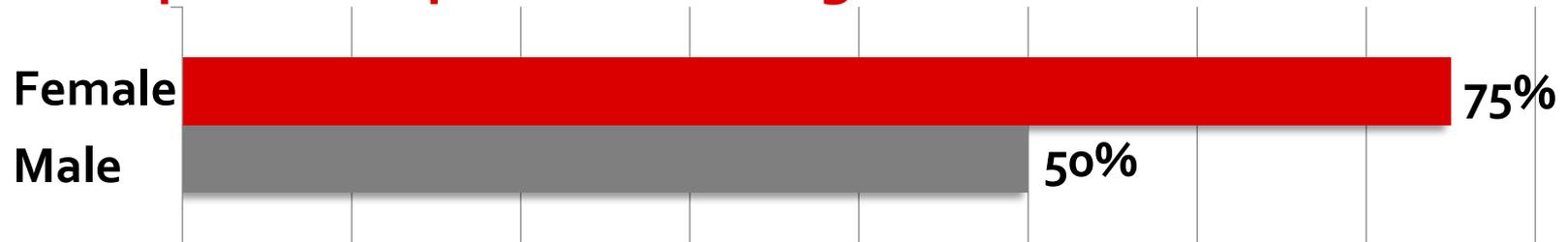
- Pain/PTSD connection
- PTSD and prescription opioid risk
- Novel therapies for patients with pain & PTSD
- Why opioids may prevent/ameliorate PTSD
- Buprenorphine for pain, PTSD, opioid use disorder

PTSD and Pain:

Why the connection?

Chronic Pain in Veterans

Most prevalent problem among US Veterans



Vietnam

66%- 80% of veterans with PTSD reported chronic pain^{1,2}

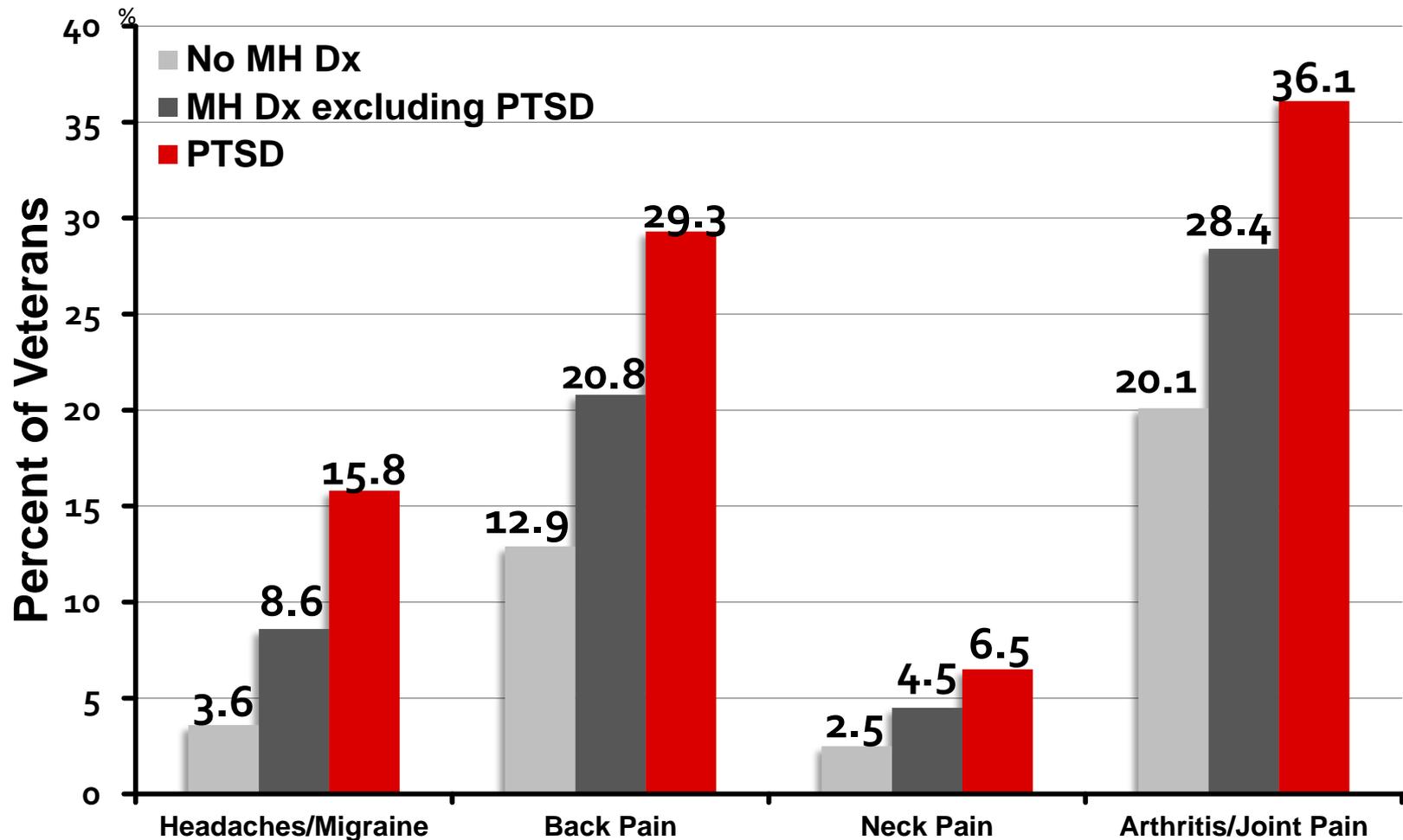
Iraq/Afghanistan

Veterans – carry heavy combat equipment/body armor and weaponry > 100 lbs

- Chronic pain more prevalent in female vets^{3,4}
- >50% with PTSD have received chronic pain diagnoses⁵

1. Beckham, 1997
2. Shipherd, 2007
3. Frayne, 2011
4. Haskell, 2010
5. Seal, 2013

Pain and Mental Health Comorbidity in 445,767 Iraq and Afghanistan Veterans



PTSD Diagnostic Criteria (DSM-V)

Criteria A: Traumatic Event (> 30 days ago)

Criteria B : Re-experiencing (intrusive traumatic memories)

Criteria C : Avoidance

Criteria D : Negative alterations in cognitions and mood-persistent negative emotional state

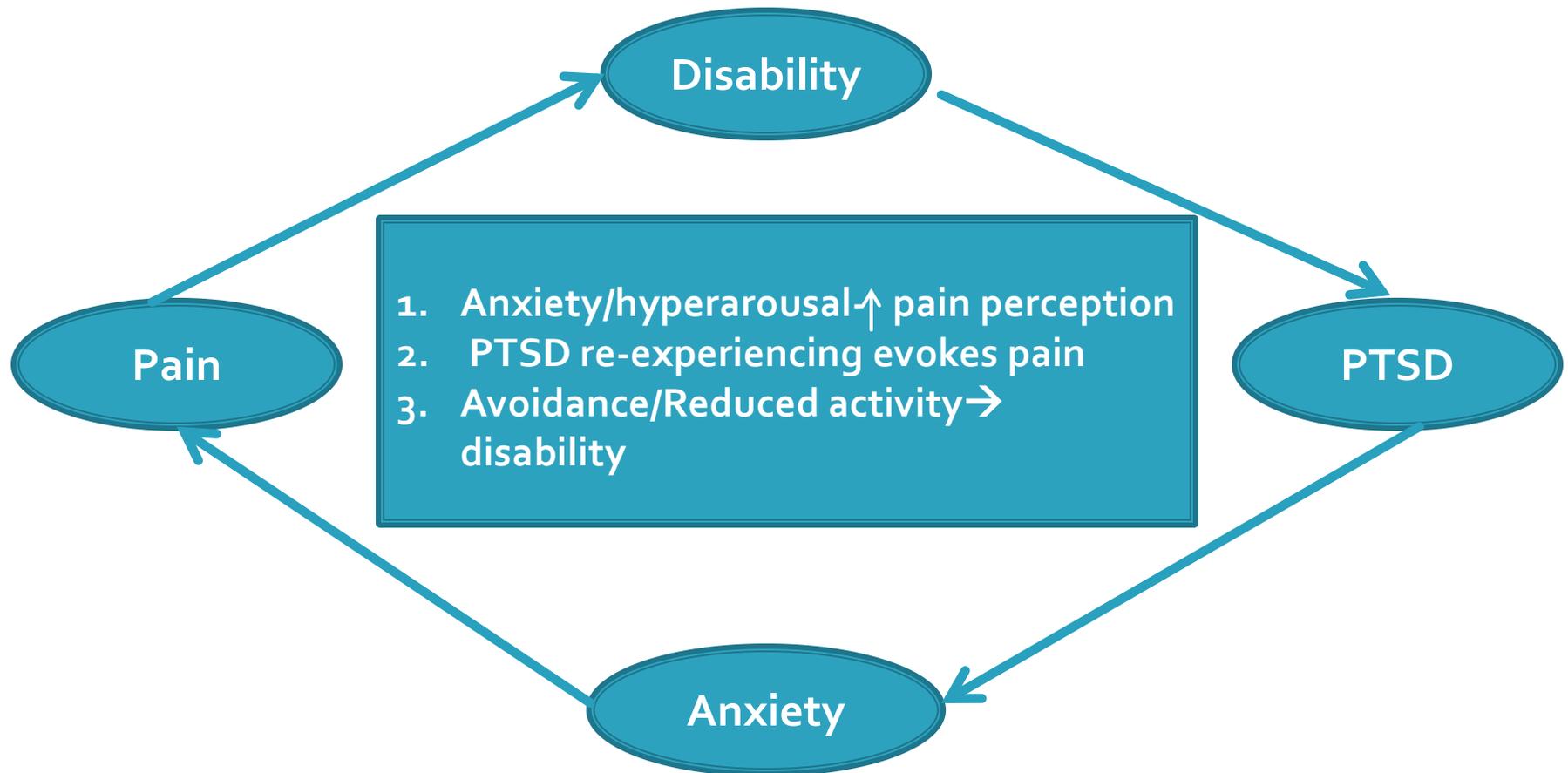
Criteria E : Alterations in arousal and reactivity-reckless or destructive behavior

Criteria F: Negative impact on functioning

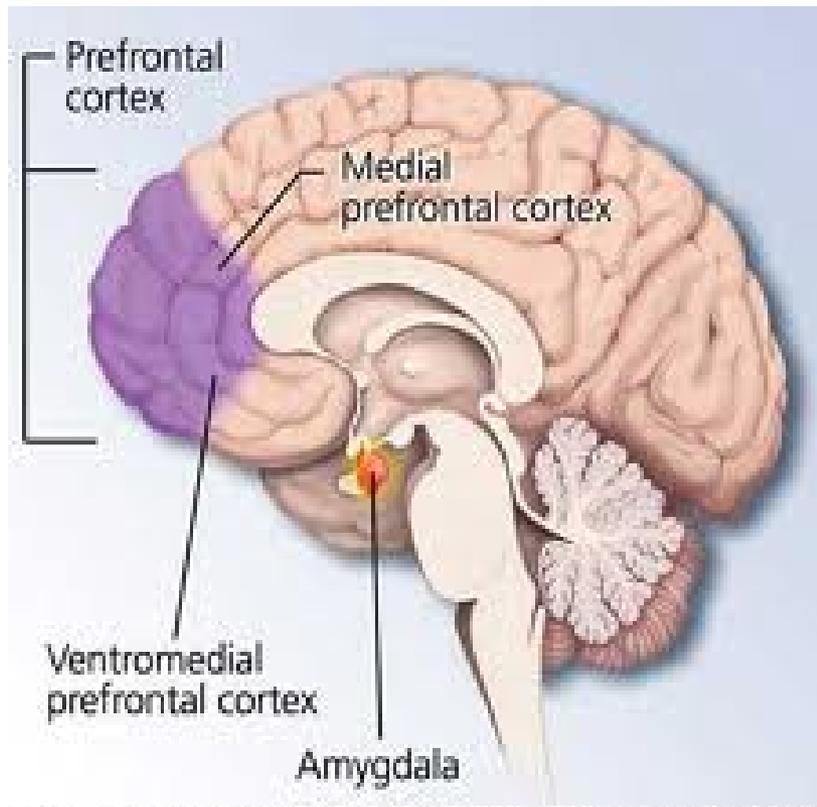
PTSD and pain link- Why?

- Shared Vulnerability- Anxiety sensitivity/Distress intolerance
- PTSD alters HPA axis- increased inflammatory conditions
- PTSD can cause dysregulation of the autonomic nervous system, endogenous opioid and serotonergic systems
- Neuropeptide Y and neuroactive hormones (allopregnanolone and pregnanolone) help with pain control; low in individuals with pain and PTSD.
- PTSD decreases frontal lobe inhibition of exaggerated responses to pain and fear triggers.
- Mutual Maintenance- pain & anxiety maintain each other.

Chronic pain and PTSD: Mutual Maintenance



Shared brain regions for pain and fear response



Brain Structures Involved in Dealing with Fear and Stress

In patients with PTSD, poor pre-frontal cortical inhibition leads to dysregulated amygdala and limbic systems, which can lead to exaggerated responses to both fear and pain stimuli.

PTSD & Prescription Opioid Use

PTSD and prescription opioid use for chronic pain

- Patients with pain and PTSD were significantly more likely to have been prescribed opioids for pain control than patients without PTSD (Phifer et al., 2011)
- Opioids were most likely to be prescribed in those with the highest PTSD symptom severity scores.

(Schwartz et al., 2006)

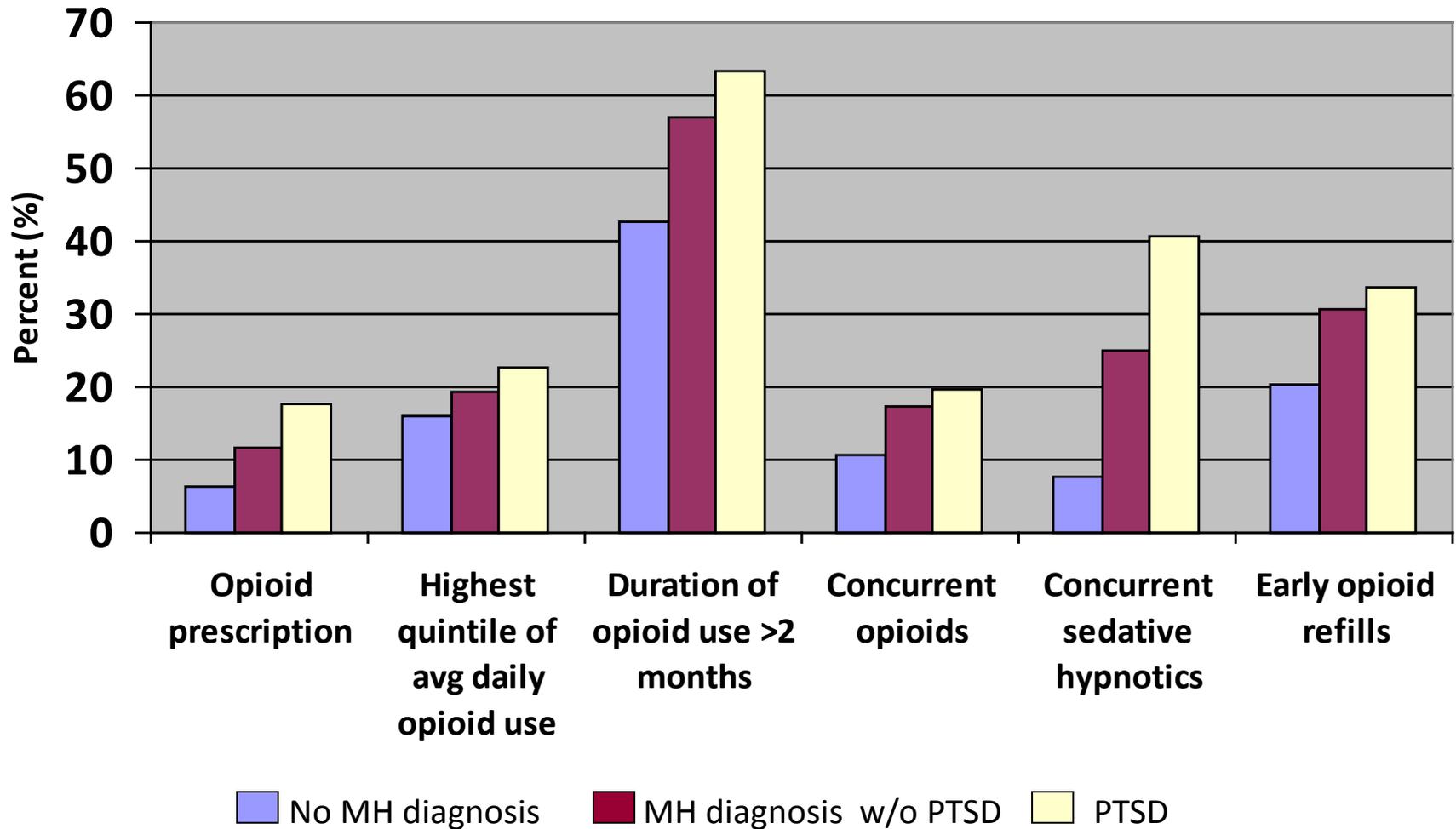
Association of MH diagnosis with prescription opioids within 1 year of pain diagnosis in 141,029 OEF/OIF veterans

Mental Health Diagnostic Category	Opioid Prescription n (%)	Relative Risk (95% CI)
No MH Diagnosis (Ref)	4488 (6.5)	1.00
MH Diagnosis (No PTSD)	3205 (11.7)	1.74 (1.67, 1.82)
PTSD	7983 (17.8)	2.58 (2.49, 2.67)

All p-values < 0.001; Relative risk adjusted for sociodemographic and military service characteristics

Seal et al., *JAMA*, 2012

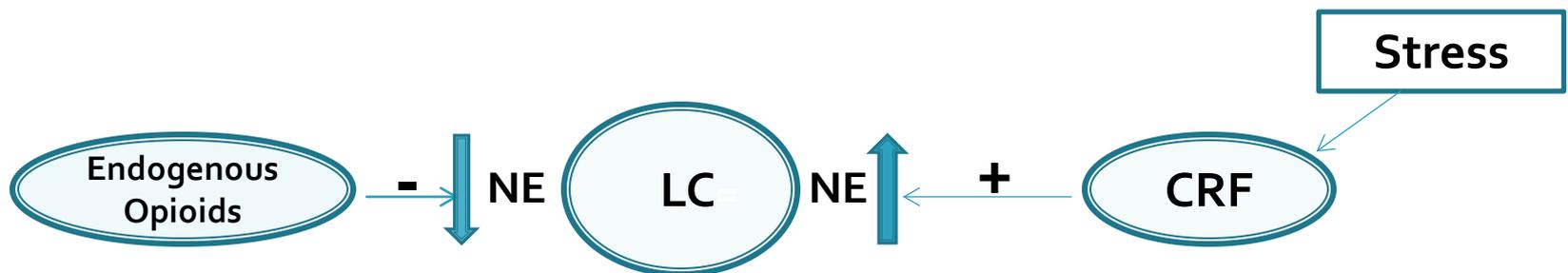
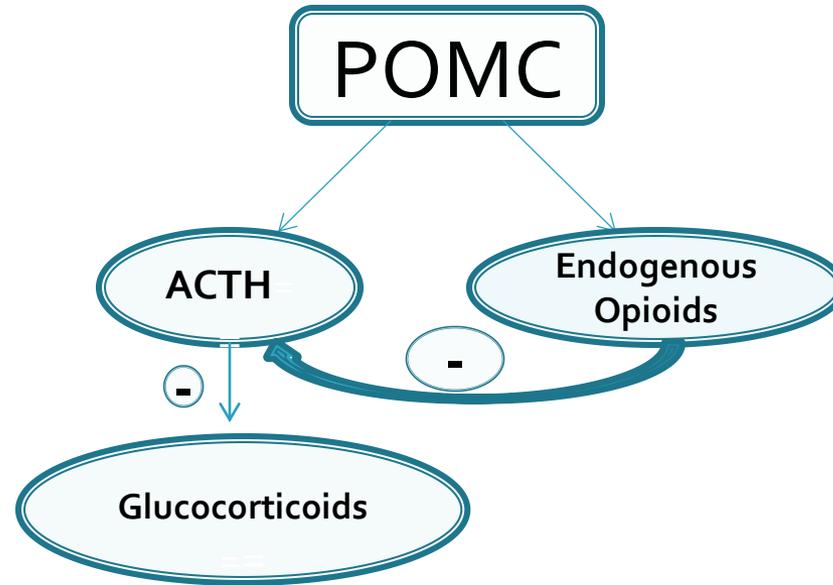
High risk opioid use in Iraq and Afghanistan Veterans with MH problems



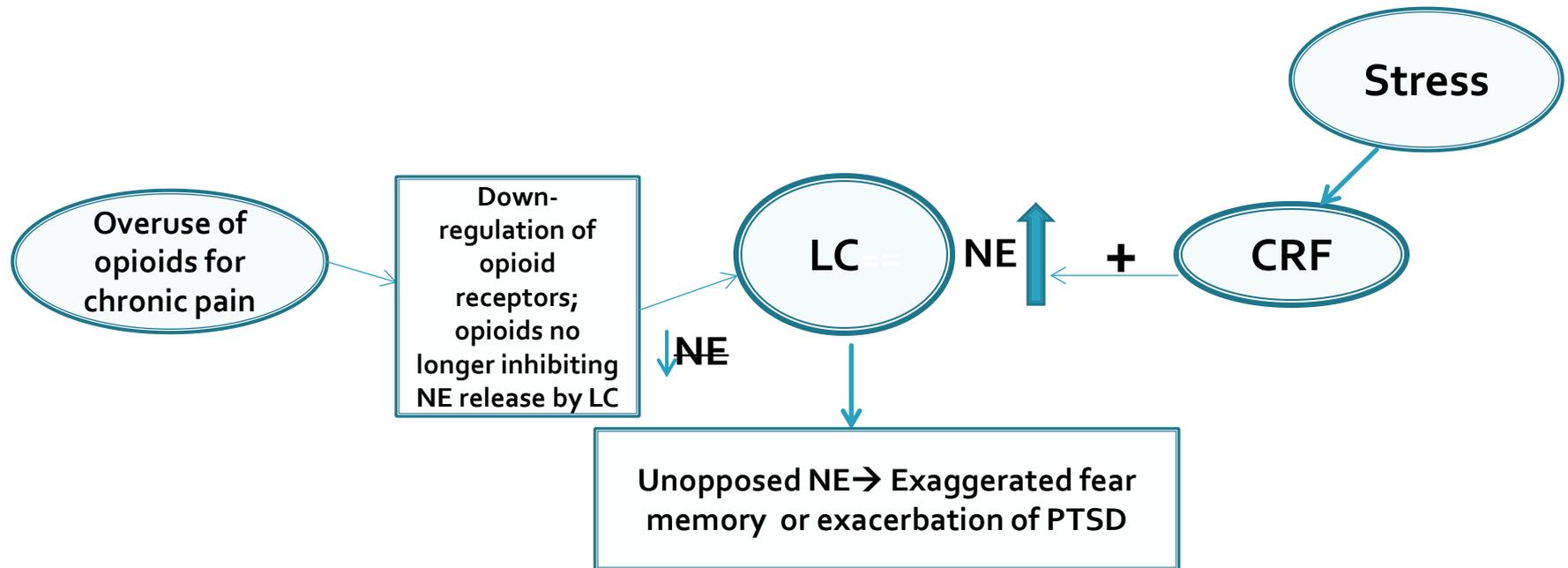
PTSD and opioid use for chronic pain- Underlying mechanisms?

- High rates of PTSD-SUD comorbidity. (Morasco et al., 2010; Seal et al. 2010)
- PTSD patients exhibit high distress about pain; PCPs with little training in managing PTSD prescribe opioids to mitigate distress.
- Self-medication hypothesis (Bremner et al., 1996; Jakupcak et al., 2010)
 - Opioids blunt trauma-related negative cognitions
 - Opioids inhibit ACTH and glucocorticoid release; decrease “stress” response
 - Opioids decrease NE release from locus coeruleus (LC); reduce exaggerated fear response

Endogenous Opioids and the Stress Response- In Balance



Overuse of opioids for chronic pain may make PTSD worse



Exogenous opioids may drive “Feed-Forward” stress enhancing circuit in PTSD

Managing Patients with the “Trifecta” of Pain, PTSD, and Opioid Use Disorder

Opioid Efficacy for Chronic Pain

- Mostly surveys and uncontrolled case series
- RCTs of short duration with small sample sizes
- Most studies are pharma sponsored

Outcomes:

- **Better analgesia with opioids vs. placebo**
- **No difference with opioids vs. non-opioid**
- **Mixed reports on function**
- **Addiction not assessed**

Ballantyne JC, Mao J. N Engl J Med. 2003 Nov 13;349(20):1943-53.

Kelso E, et al. Pain. 2004 Dec;112(3):372-80.

Eisenberg E, McNicol ED, Carr DB. JAMA. 2005 Jun 22;293(24):3043-52.

Furlan AD, et al. CMAJ. 2006 May 23;174(11):1589-94.

Noble M, et al. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006605.

Martel B, et al. Ann Intern Med. 2007 Jan 16;146(2):116-27.

Opioids and quality of life?

- Among patients with chronic pain...
 - Those who received opioids had lower quality of life at follow-up
 - Those who received opioids were 4 times less likely to recover from chronic pain..

Erickson, Pain 2006; Dillie , J Am Board Fam Med 2008

Opioids and chronic pain-Harms

■ Uncertain Benefits:

- ? Pain relief
- ? Improved physical functioning, QOL

■ Potential known harms:

- Tolerance/physical dependence
- Addiction/abuse/diversion
- Respiratory depression, OD
- Cognitive impairment/ somnolence
- Hypogonadism- ED, fatigue, OP, muscle wasting
- Sleep disturbances; worsening of sleep apnea
- Increased pain from withdrawal and hyperalgesia



Overdose risk increases with daily opioid dose

	VA patients (fatal overdose)	HMO patients (any overdose)
Dose (mg/day)	Hazard Ratio (95% CI)	
<20	1.0	1.0
20-49	1.9 (1.3, 2.7)	1.4 (0.6, 3.6)
50-99	4.6 (3.2, 6.7)	3.7 (1.5, 9.5)
≥ 100	7.2 (4.9, 10.7)	8.9 (4.0, 19.7)

Prescription opioids and adverse outcomes in Iraq and Afghanistan veterans

- Receiving prescription opioids (vs. not) was associated with increased risk of adverse clinical outcomes; particularly elevated in veterans with PTSD.
 - Wounds or injuries
 - Opioid-related accidents and overdoses
 - Other accidents and overdoses
 - Self-inflicted injuries
 - Violence-related injuries



Case: 38 y.o. Iraq veteran with chronic lower back pain and PTSD

- Drinking about 12 beers a night to “relieve pain”; receiving benzodiazepines for “anxiety” from outside doc; not receiving evidence-based PTSD treatment.
- Nightmares of combat nearly every night, poor sleep quality-checking doors and windows; avoids leaving house; no longer goes out to gym to exercise
- LBP started in Iraq from injury. Has been on opioids in past for back pain. **Requests MS Contin and oxycodone.**
- **This is a new patient. What do you do?**

Clinical dilemma

- *On the one hand*, desire to establish therapeutic alliance, relieve pain and distress
- *On the other hand*, desire to do no harm

Getting unstuck-general principles

Patient-Centered Education/Universal Precautions

- Non-confrontational style; contextualize
- Assess patient's prior experience with opioids
- Educate about risks/ questionable benefits of opioids
- Educate re: non-opioid/non-pharm alternatives/adjuncts
- If opioids used, frame as a ***trial*** with clear *functional* goals; use shared decision-making to form *multi-modal* "Pain Care Plan"
- Monitor and re-assess risk/benefit ratio (UDS, PEG, COMM)
- Have clear functional benchmarks; up-front agreements if goals not met or evidence of aberrant opioid behavior.

Validate, Educate, Motivate, Activate (*VEMA*)

1. Validate

- “Real” pain
- Patient’s experience and efforts

3. Motivate

- Assist patient toward readiness for change

2. Educate

- Realistic expectations
- From “I will fix it” to “I will assist you in improving your functioning & QOL”

4. Activate

- Collaborative goal-setting

Management of Chronic Pain in the context of PTSD

Non-opioid, non-pharmacological interventions should be first-line:

- Non-opioid pain medications/ procedures
- Target sleep
- Treat PTSD comorbidities (e.g., dep, AUD)
- PT and gentle exercise
- CAM for pain & PTSD
- CBT for pain & PTSD



CAM therapies—Pain

Scientific evidence on CAM for low back pain	Promising evidence of potential benefit	Limited, mixed, or no evidence to support use
Acupuncture	√	
Massage	√	
Spinal Manipulation	√	
Progressive Relaxation	√	
Yoga	√	
Herbal Remedies		√

From National Center for Complimentary and Alternative Medicine-NCCAM

CAM therapies—PTSD

From VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress:

- There is insufficient evidence to recommend CAM approaches as first line treatments for PTSD. [I]
- CAM approaches (e.g. mindfulness, yoga, acupuncture, massage, and others) may be considered for adjunctive treatment of hyperarousal symptoms
- CAM approaches may be considered as adjunctive approaches to address some co-morbid conditions (e.g. acupuncture for pain). [C]

Non-pharmacological treatment of PTSD and chronic pain in VA

- Strong evidence for collaborative care models that use a Care Manager and combine pain and mental health treatment (Dobscha et al., 2009; Kronke et al., 2010)
- Interdisciplinary approach used in VA PACT
- Combined CBT for pain and PTSD- promising preliminary results in a limited number of subjects; second study ongoing (Otis, 2009)
- Ongoing exercise trial examining changes in pain and PTSD symptoms and stress hormone levels (allopregnanalone and pregnanalone and NPY) (Scioli)
- Shared decision-making and Care Manager telephone motivational coaching to promote non-opioid pain management strategies and decrease high-risk opioid use in complex chronic pain patients (Seal, NCCAM)

Selective opioid receptor agonists: Possible therapy for PTSD?

Opioids for acute pain Prevent PTSD?

After trauma, patients (pediatric burn victims, adult trauma victims, Iraq soldiers) administered morphine within 48 hours were significantly less likely to develop PTSD and/or had less severe PTSD symptoms.

(Holbrook et al., 2010; Saxe, 2001; Bryant, 2009)

Nocioceptin opioid (NOP) receptor agonist

- After acute (mouse) trauma, infusion of a selective (NOP) agonist blocked fear memory consolidation in the amygdala.
- Mice given NOP agonist displayed no or fewer sx of PTSD after trauma.
- Selective NOP agonist spared μ opioid receptor; did not produce undesirable reward effects of opioids leading to addiction and dependence.
- Clinical implications; PEP for first responders?

Civilian and Military Trauma

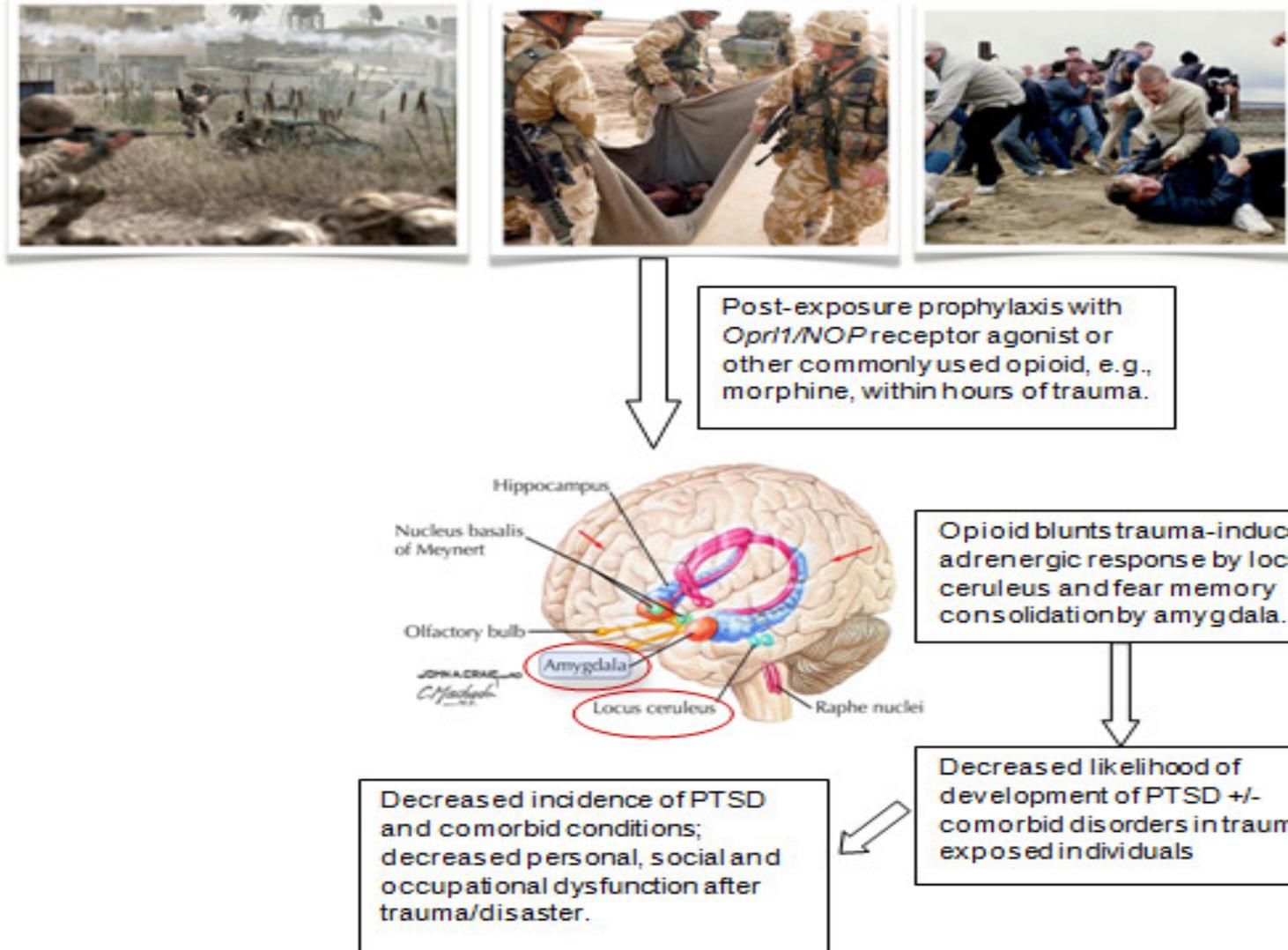


Figure 1. A model of post-exposure prophylaxis against PTSD in the aftermath of trauma

Buprenorphine-Possible therapy for chronic pain/PTSD/opioid use disorder?

Buprenorphine-Promising Features

- Buprenorphine is a partial NOP receptor agonist
- FDA-approved for opioid use disorder (SL) and chronic pain (transdermal patch)
- Partial μ opioid receptor agonist, high affinity, and long half-life produce analgesic effect and ability to block opioid craving
- Less stimulation of reward pathways; lower risk for abuse/addiction
- Kappa opioid receptor antagonist-explains observed anti-depressant/anxiolytic effects; benefits in PTSD?

Buprenorphine vs. other opioids for pain control

	Other Opioids	Buprenorphine
Pain control	Moderate to severe	Mod to severe; neuropathic pain
Tolerance, physical dependence, withdrawal	Yes	Less
Respiratory depression/OD	Yes	Rare
Cognitive impairment	Yes	Less
HPA axis dysregulation	Yes	No
Immunosuppression	Yes	No
QTc prolongation/sudden cardiac death	Yes	No
Safe in renal failure, elderly, hepatic dysfunction	No	Yes
Drug-drug interactions	Yes	Few

Buprenorphine and PTSD: Limited data

- Published case report of incidental improvement in PTSD symptoms when buprenorphine was used for ORT

Danovitch, 2009

- In a retrospective cohort of 717 Iraq and Afghanistan veterans with PTSD, chronic pain and SUD, those who switched from opioid to buprenorphine therapy (N=257) had significantly improved PTSD and pain symptom severity scores compared to controls who remained on moderately high-dose opioid therapy (N=460) (p-values for PTSD and pain < 0.01)

Seal et al., prelim data

Wrap-Up!

- High pain-PTSD comorbidity observed in veterans and other populations.
- Those with pain and PTSD more likely to be prescribed opioids, have higher-risk opioid behavior & adverse outcomes.
- Evidence is accumulating for collaborative care and combined PTSD and chronic pain therapies (including CAM) as effective non-opioid pain management strategies.
- Buprenorphine (as an NOP-R agonist) may have efficacy (and greater safety) for refractory opioid use disorder, chronic pain and PTSD; more research is needed.

QUESTIONS ?

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