TONIX PTSD AWARENESS DAY FOCUS ON SLEEP AND TREATMENT POPULATIONS

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DIAGNOSIS OF POSTTRAUMATIC STRESS DISORDER (PTSD) DSM-5

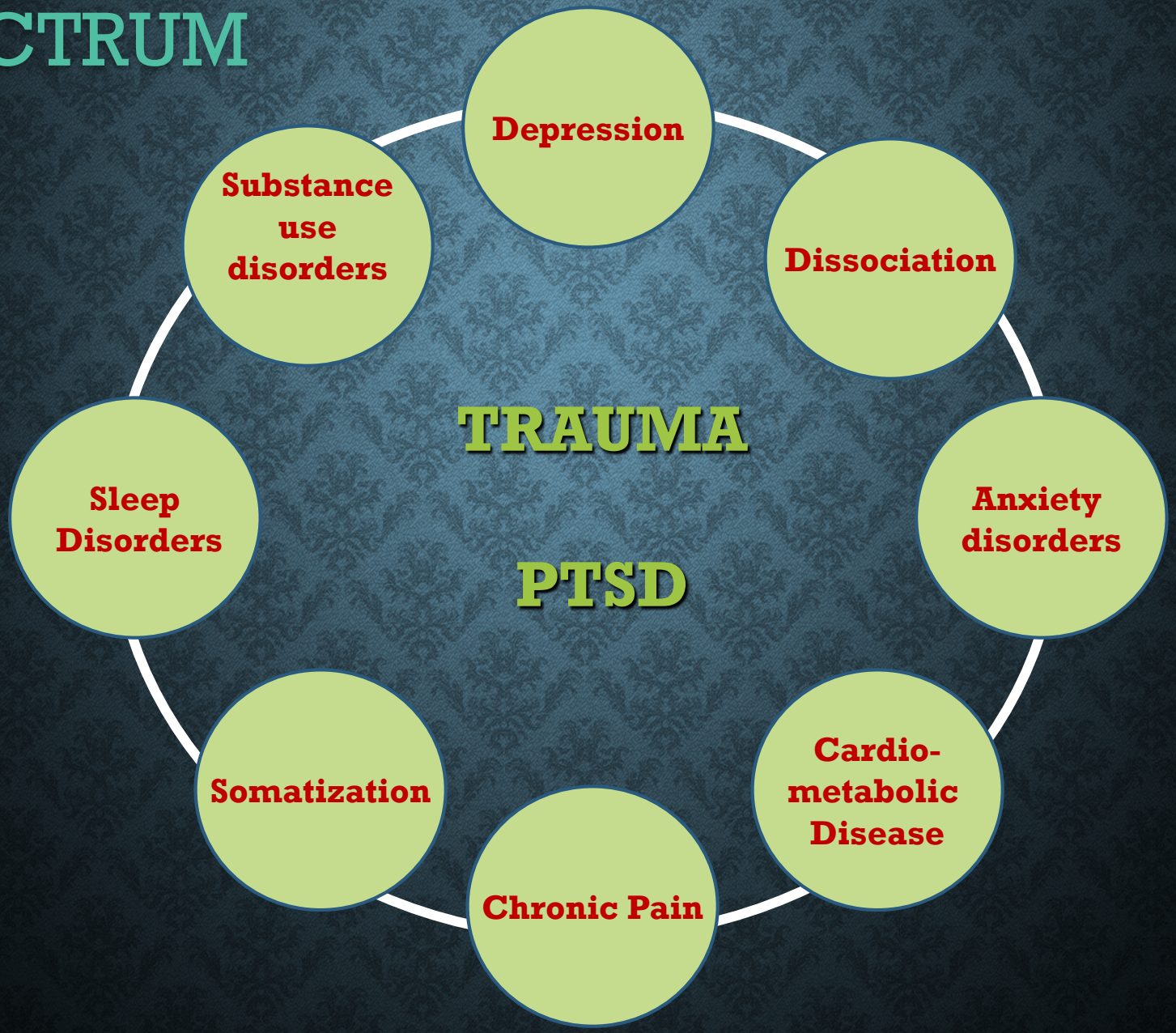
- Exposure to a trauma that is severely threatening
- Intrusive distressing memories, nightmares and/or flashbacks
- Avoiding thoughts and/or reminders
- Emotional numbing; negative effects on thoughts or mood
- Insomnia, increased startle, heightened vigilance
- Duration >1 month, distress or impairment

PTSD PREVALENCE AND COMORBIDITY

- 8% adult U.S. population
- 13 – 19% of Veterans/military personnel deployed to war zones
- 10-40% exposed to severe trauma (e.g. assault, combat, terrorist attacks)
- 2X > in females
- Chronic in 1/3 affected, typically comorbid with other psychiatric, substance use disorders and medical conditions

Kessler et al., ’95,
Dohrenwend et al., Hoge et al. ’06

TRAUMA DISORDERS SPECTRUM



RISK FACTORS FOR PTSD FOLLOWING TRAUMA

- Traumas of human origin, prolonged duration, involving severe threat and loss
- Prior early life trauma
- Prior personal or familial depression or anxiety disorder
- Having intense physical and/or dissociative reactions to the initial trauma
- Avoidant coping
- Limited social support
- Sleep disturbance

PTSD MODELS

- Fear Conditioning/failure of extinction
  - animal models, psychophysiologic response to trauma stimuli, conditioning experiments
- Impaired fear memory processing
  - Inferred from response to exposure Tx, brain imaging
- Persisting abnormal stress response
  - ↑ Norepinephrine, ↓ cortisol
- Psychological
  - Avoidant coping, over-generalization, poor social support

ROLE OF SLEEP

- Sleep's role in physical, emotional regulation and memory
- PTSD Symptoms
  - Insomnia/nonrestorative sleep (less specific)
  - Trauma nightmares (specific)
- Laboratory
  - Shallow sleep - ↑ N1 (light sleep) ↓ N3 (deep sleep)
  - Sleep initiation and maintenance fxs inconsistent (context dependent)
  - Increased REM density; interrupted/ fragmented REM sleep (early in PTSD)
  - Blunted reduction of SNS activity

Ross et al., 1994; Mellman et al., 1997, 2002, 2014; Kobayashi 2007.

EVIDENCE THAT SLEEP FACILITATES EMOTIONAL PROCESSING

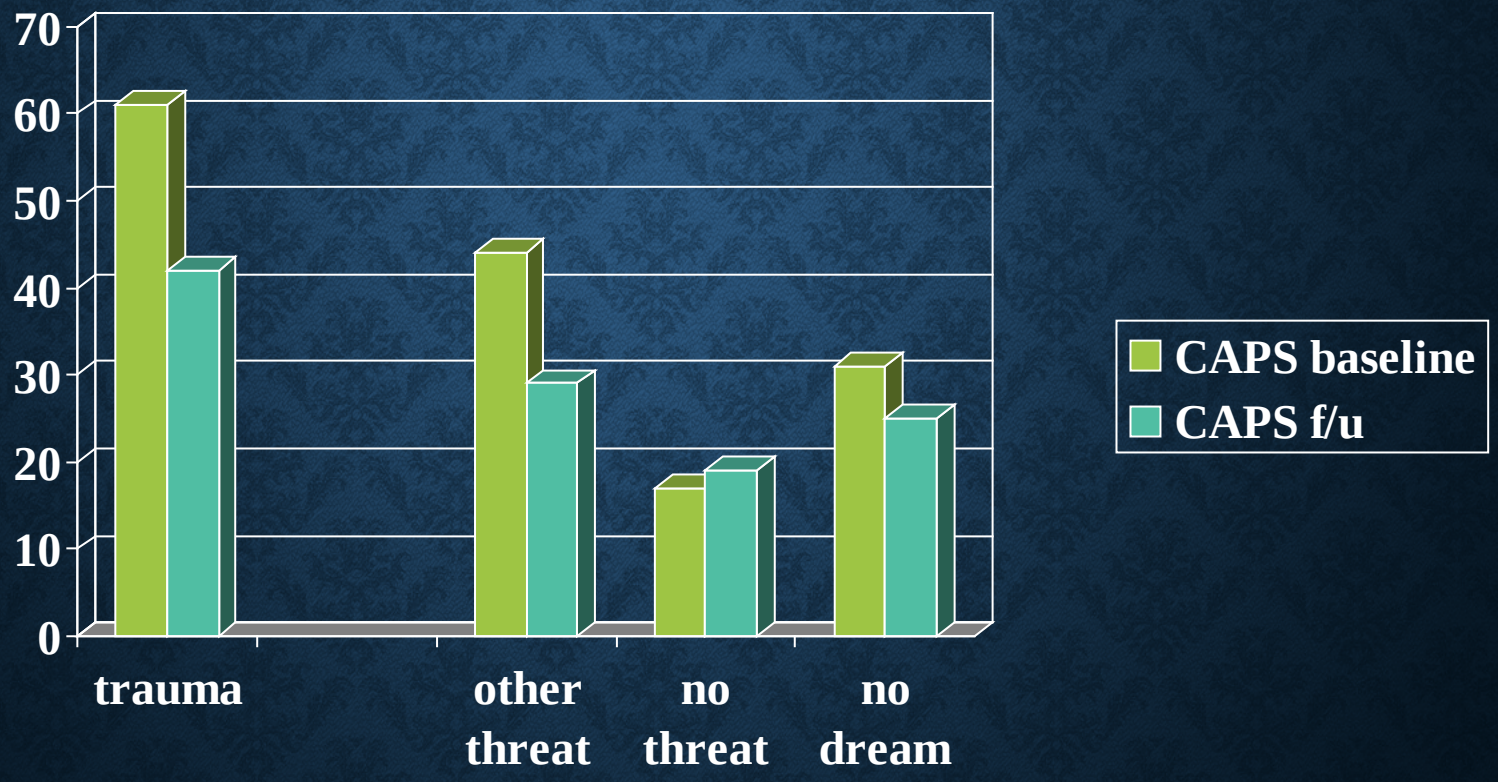
- Role of sleep in extinction recall and generalization (Pace Schott et al. 2015)
- REM sleep and associative learning (Cai et al. 2009, Stickgold et al. 1999)
- REM and dream findings in adjustment to divorce (Cartwright 1991)
- Sleep increases learning consolidation of recent emotional stimuli (Wagner et al., 2001) and during treatment of PTSD (Lommon et al., 2015)
- Maintaining depth of sleep associated with response to written exposure (Kobayashi, Mellman et al., 2016)

UNIVERSITY OF MIAMI/DARTMOUTH ACUTE TRAUMA STUDY MH54006

- Many factors are likely to influence sleep when PTSD has persisted for many years.
- The study aim was to determine how sleep, particularly REM sleep and its associated functions related to the development of PTSD (or resolution of posttraumatic distress) soon after a traumatic event.

  dream reports, overnight memory test, polysomnography, heart rate variability during sleep.

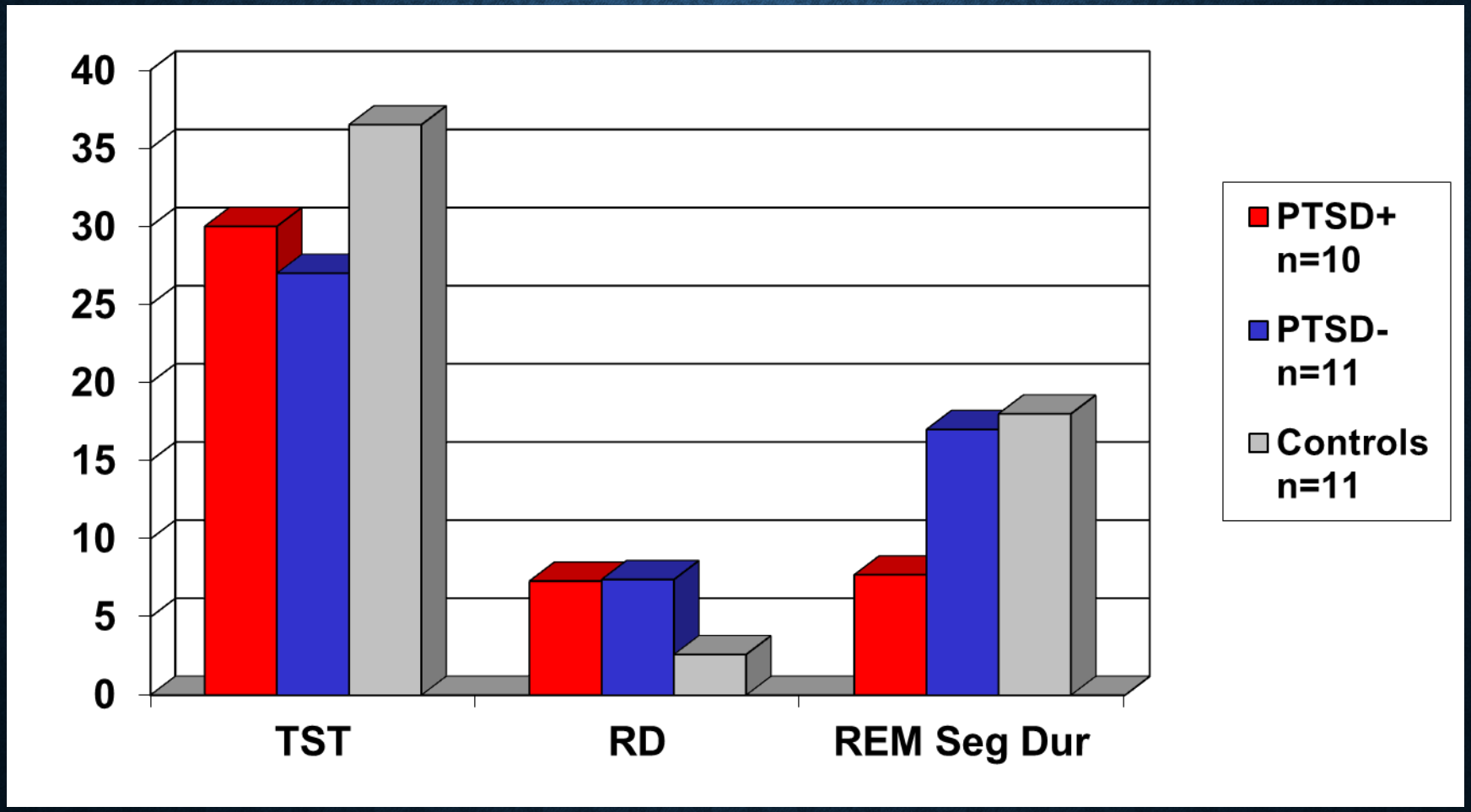
TYPES OF DREAMS AND PTSD SEVERITY



Mellman et al., JTS, ‘01

ACUTE TRAUMA STUDY: POLYSOMNOGRAPHY

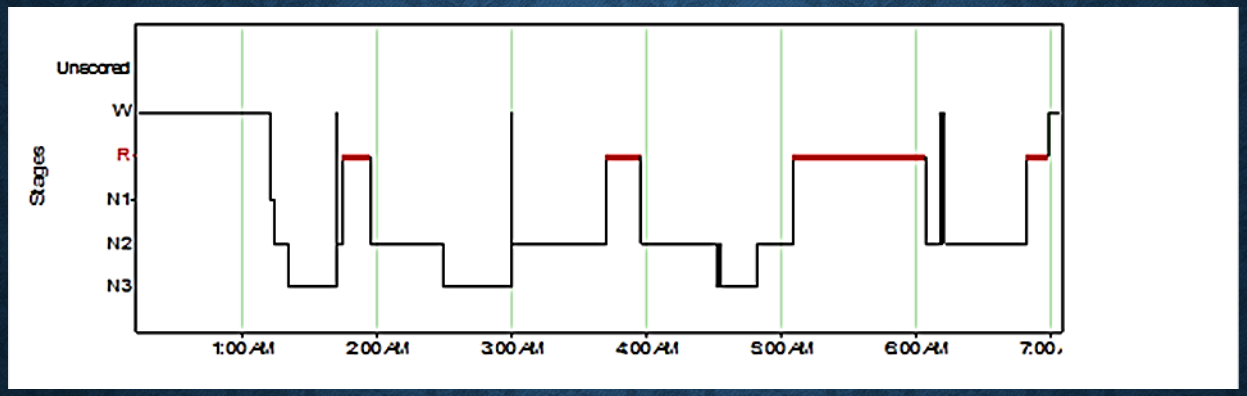
MELLMAN, T.A., BUSTAMANTE, V., FINS, A.I., PIGEON, W.R., NOLAN, B. (2002). RAPID EYE MOVEMENT SLEEP AND THE EARLY DEVELOPMENT OF POSTTRAUMATIC STRESS DISORDER. AM J PSYCHIATRY, 159: 1696-1701



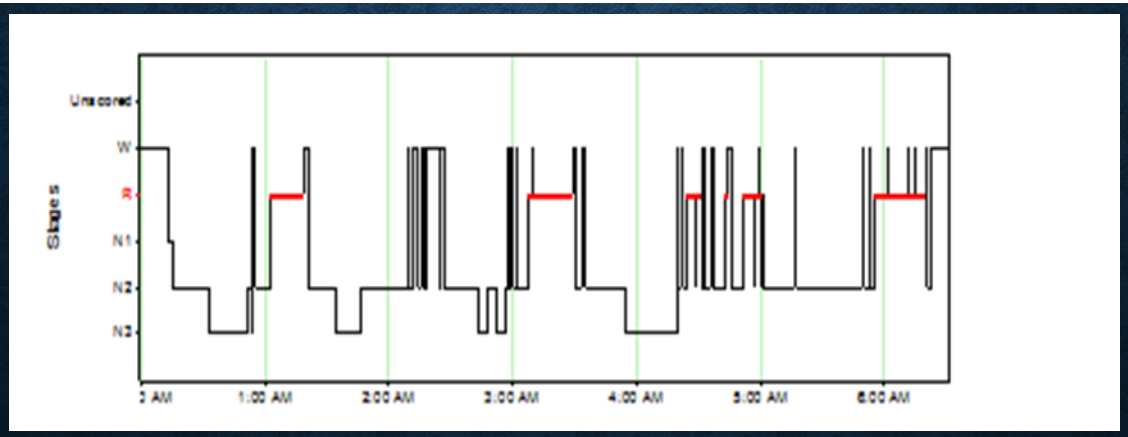
TST, total sleep time; RD, REM density; REM Seg Dur, REM segment duration

SLEEP RECORDINGS: HEALTHY CONTROL VS. PTSD

Healthy Control



PTSD



SUMMARY OF FINDINGS

The early development of PTSD is associated with:

1) dreams that replicate trauma memories

2) fragmented REM sleep

3) increased sympathetic signal during early REM sleep.

HOWARD UNIVERSITY SLEEP STRESS RESEARCH PROGRAM

- PTSD, Neighborhood Stress, Sleep, Nocturnal BP, HRV study
- Sleep Resilience
- Sleep & Emotional Processing
- Trauma-related Insomnia trials

METHODS

N = 543

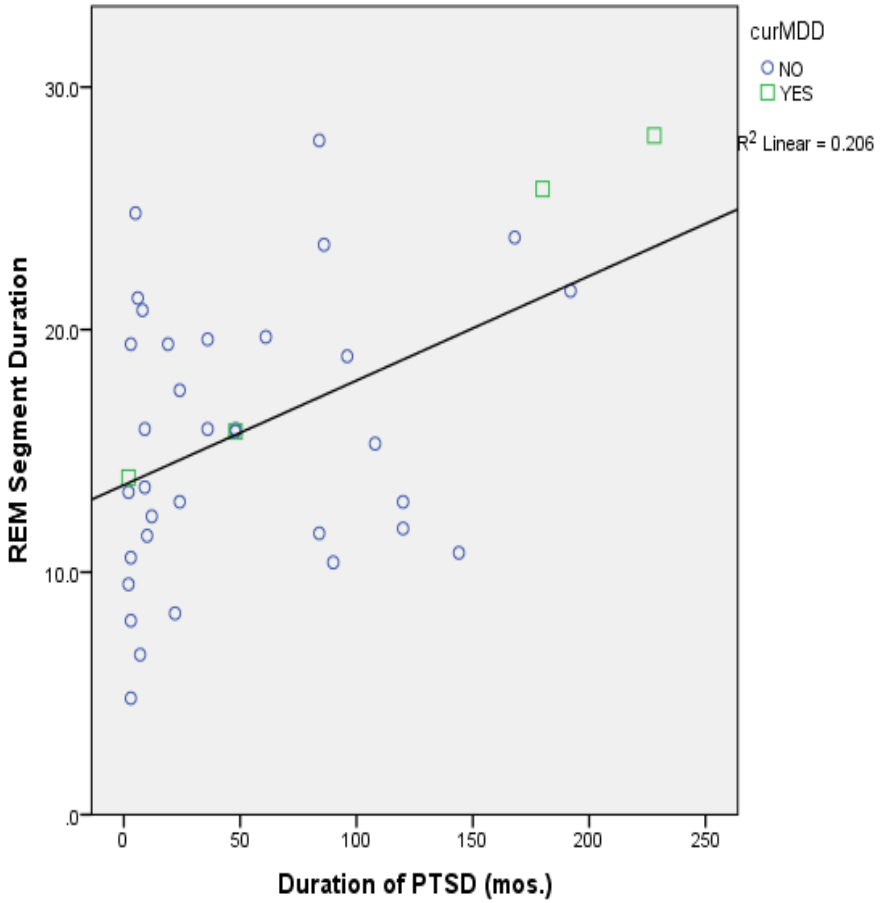
- Young adult (age 18-35) African American healthy volunteers (fliers, outreach, word of mouth)
- Self report surveys

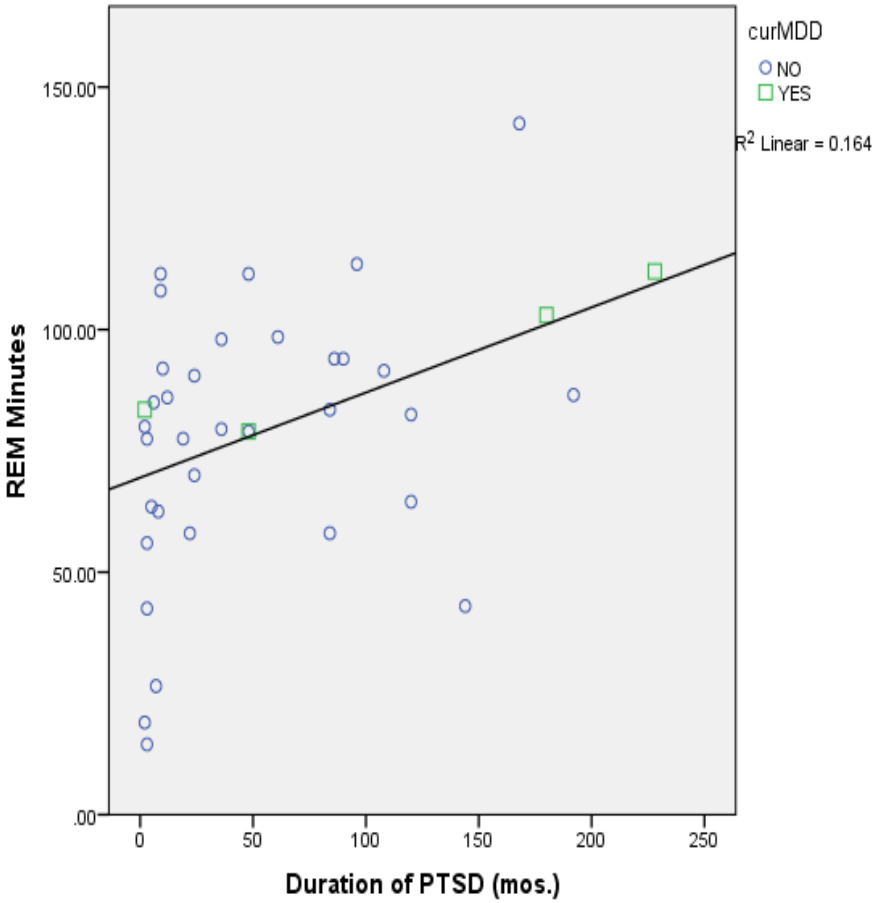
N = 136

- Clinical Interviews
- Overnight sleep recordings
- Morning blood drawing
- Two, 24-hour ambulatory blood pressure monitoring with ECG and actigraphy

RELATIONSHIPS BETWEEN REM SLEEP MEASURES AND DURATION OF PTSD

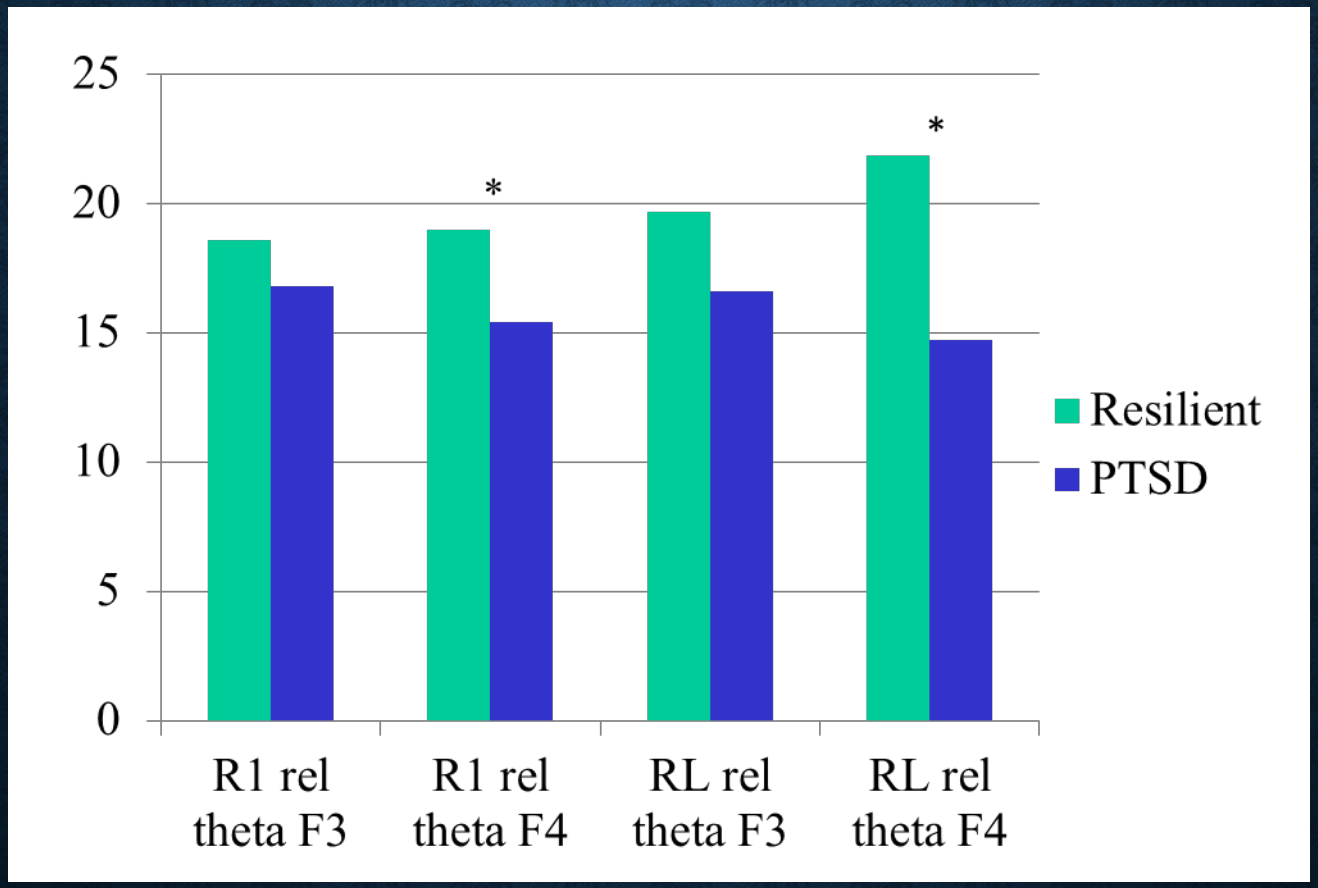
MELLMAN ET AL., SLEEP 20014





RELATIVE FRONTAL THETA DURING REM SLEEP

COWDIN ET AL. EXPER. BRAIN RESEARCH 2014



* $p < .05$

COGNITIVE BEHAVIORAL THERAPY FOR PTSD: SYNTHESIS OF THE EVIDENCE

- Trauma focused psychotherapies have significant and enduring benefits. Evidence for superiority over non-trauma-focused therapies[1]
- Most of the supportive evidence is from studies of civilians, predominantly female survivors of sexual assault
- Evidence is less clear for survivors of child abuse[2] and combat veterans[3,4]

1. IOM 2008. 3. Schnurr 2003.
2. McDonagh 2005. 4. Monson et al., 2006.

SSRIs AND PTSD: MIXED EVIDENCE

Positive studies

- 11 published RCTs
- Mean N = 195
- Predominantly female civilian populations, 1 Iranian war veterans, 1 World Trade Center survivors also receiving psychotherapy
- 6 Industry sponsored

Negative Studies

- 6 Published RCTs
- Mean N = 110
- 4 veteran, predominantly male populations
- Negative prevention study

IOM report 2008, Shalev et al. 2008, Schneier et al. 2012, Panahi et al. 2011

THE BENZODIAZEPINE DISCONNECT

- Widely Utilized!
- Not Recommended! (VA PTSD Rx Guidelines)
- Small study not showing therapeutic effects (Braun 1990)
- Reports of disinhibition and withdrawal problems (Risse, 1990)
- 2 small negative prevention studies (Gelpin 1996; Mellman 2002)

MEDICATION TREATMENT FOR PTSD NIGHTMARES AND INSOMNIA

- Most common residual symptoms following treatments (Davidson 2002, Zayfert 2004)
- Prazosin blocks adrenergic activity, preserves REM sleep. Efficacy supported by 2 controlled trials in veterans, 1 study in active duty military personnel, VA CSP study results preliminarily negative (Raskind 2002, 2007, 2014)
- Preliminary evidence for benefits from trazodone and nefazodone (both bock 5HT2) (Hertzberg et al. '96; Gillin et al. 2001)

OTHER AGENTS WITH LIMITED EVIDENCE

- Modest benefit for amitriptyline and imipramine in veterans (Davidson et al., 1990, Kosten 1988)

(benefits were reported in Veterans with chronic PTSD; while sleep specific outcomes not reported these agents are generally beneficial to sleep; 5HT2 mechanisms)

CONCLUSIONS

- PTSD is common, recent Veteran cohorts
- Significant treatment gaps, especially for targeting sleep and for Veterans
- Adrenergic and serotonergic (5HT2) antagonism promising for improving sleep