



NEUROCRITICAL CARE WITHOUT BORDERS

16TH
Annual Meeting

SEPTEMBER 25-28, 2018
BOCA RATON RESORT & CLUB

NEUROCRITICAL
CARE SOCIETY

Held in Conjunction with



 iCSD 2018 | Florida
International Conference on
Spreading Depolarizations
September 22-24, 2018 | Boca Raton Resort & Club

Promising Pharmacologic Treatment to Prevent Post-Traumatic Stress in ICU Survivors

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Speaker Disclosures

I do not have financial relationships to disclose.



Objectives

- Identify pharmacologic treatments to prevent and treat PICS
- Summarize recommendations from Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption (PADIS) Guidelines
- Compare post concussion syndrome (PCS) and post intensive care syndrome (PICS)

PADIS

Clinical Practice guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

- Recently published updates now include immobility and sleep
- Challenges common practices
 - Antipsychotics for delirium
 - Multidisciplinary
- Four critical illness survivors included as collaborators

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

PADIS

“The effect of depth of sedation on post-ICU, patient centered outcomes such as 90 day all cause mortality and cognitive function, physical recovery, PTSD, anxiety and depressive symptoms has not been well evaluated in randomized controlled trials.”

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

Prevention of PIcs

- Cognitive Impairment
- Sleep



Cognitive Impairment

- Prevent hypotension, hypoxemia
- Manage glucose dysregulation
- **ABCDEF** bundle
 - Choice of Analgesia and Sedation
 - Delirium

Wergin R, Modrykamien A. *Cleveland Clinic Journal of Medicine*. 2012 Oct;79(10):705-712
Stollings JL et.al. AACN Advanced Critical Care. 2016;27(2):133-140

Choice of Analgesia and Sedation

- We suggest using an assessment-driven, protocol based, stepwise approach for pain and sedation management...
- Conditional recommendation
 - Moderate quality of evidence

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

Choice of Analgesia and Sedation

- We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation...
- Conditional recommendation
 - Low quality of evidence

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

Delirium

- Delirium strongly associated with long-term cognitive impairment
- Delirium NOT associated with PTSD, post ICU distress or depression
- Does prevention of delirium limit long term cognitive impairment?

Pandharipande PP et.al. *N Engl J Med.* 2013;369:1306-16



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Dexmedetomidine for Delirium

- MENDS
 - More delirium free and coma free days 7 vs 3; P=0.01
- SEDCOM
 - More delirium free days 2.5 vs 1.7; P=0.002
 - Prevalence of delirium 54% vs 76.6%; P<0.001
- MIDEX/PRODEX
 - No differences in delirium

Pandharipande PP et.al. JAMA. 2007;298(22):2644-2653

Riker RR et.al. JAMA. 2009;301(5):489-499

Jakob SM et.al. JAMA. 2012;307(11):1151-1160



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Dexmedetomidine for Delirium

- We suggest not using...dexmedetomidine...to prevent delirium..
- Conditional recommendation
 - Very low to low quality of evidence

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873



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Deliriogenic Medications

- Benzodiazepines
- Steroids
- Anticholinergics
 - Tricyclic Antidepressants
- Beta blockers
- Lithium
- Diuretics
- Digoxin
- Dopamine agonists
- Narcotics
- Non steroidal anti-inflammatory drugs
- Histamine 2 blockers
- Skeletal muscle relaxants
- Ketamine
- Theophylline
- Antibiotics

Stollings JL et.al. *Advanced Critical Care*. 2016;27(2):133-140

Cognition After Levetiracetam

- Spontaneous intracerebral hemorrhage patients
- Neuro-Quality of Life at 1, 3 and 12 months
- Similar delirium between groups
 - 8% vs 6%; $p>0.2$
- Lower adjusted cognitive scores in LEV treated at 3 months

Naidech AM et.al. *Crit Care Med.* 2018;46:1480-1485

Sleep in ICU Patients

- Now included as part of the PADIS guideline
- Sleep disruption
 - Fragmentation, abnormal circadian rhythms, increased light sleep, decreased slow wave and REM sleep
- Contributes to **delirium**, prolonged mechanical ventilation, deranged immune function and **cognition**

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873



Dexmedetomidine for Sleep

- Dexmedetomidine 0.2 mcg/kg/hr between 2130-0600
- Sleep was similar based on a questionnaire
- Delirium free
 - 80% vs 54% RR 0.44; 95% CI, 0.23-0.82
- Ventilation, ICU stay, hospital stay, and mortality was similar
- Low dose dexmedetomidine ***prevents*** ICU delirium

Skrobik Y et.al. *Am J Respir Crit Care Med.* 2018;197(9):1147-1156

Sleep in ICU Patients

- We make no recommendation regarding...melatonin
- We make no recommendation regarding...dexmedetomidine
- We suggest not using propofol to improve sleep
- Insufficient information for other medications
 - Tricyclic antidepressants, atypical antipsychotics, hypnotics

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

Suvorexant

- Orexin is an alerting neurochemical
- Wake promoting centers are under active control of orexin neuronal projections
- Dual antagonist of orexin receptors; OX1R, OX2R
 - Blocks actions of endogenous orexin A and B
- Indirect acting sleep promotion

Howland,RH. *J of Psychosocial Nursing.* 2014;52(10):23-26

Suvorexant

- 5 studies focused on prevention of delirium
- One case report for treatment
- All sample sizes ~100 or less
- Some studies investigated multiple agents for sleep
- Little to no delirium detected in suvorexant groups
- Large scale, methodologically sound RCTs are needed

Treatment

- No studies identified for treatment of PICS
- Uncertainty exists regarding the best approach
- Lack of basic science and translational research
- Epidemiologic studies are needed
- Further investigation is needed regarding the design of post-ICU interventions

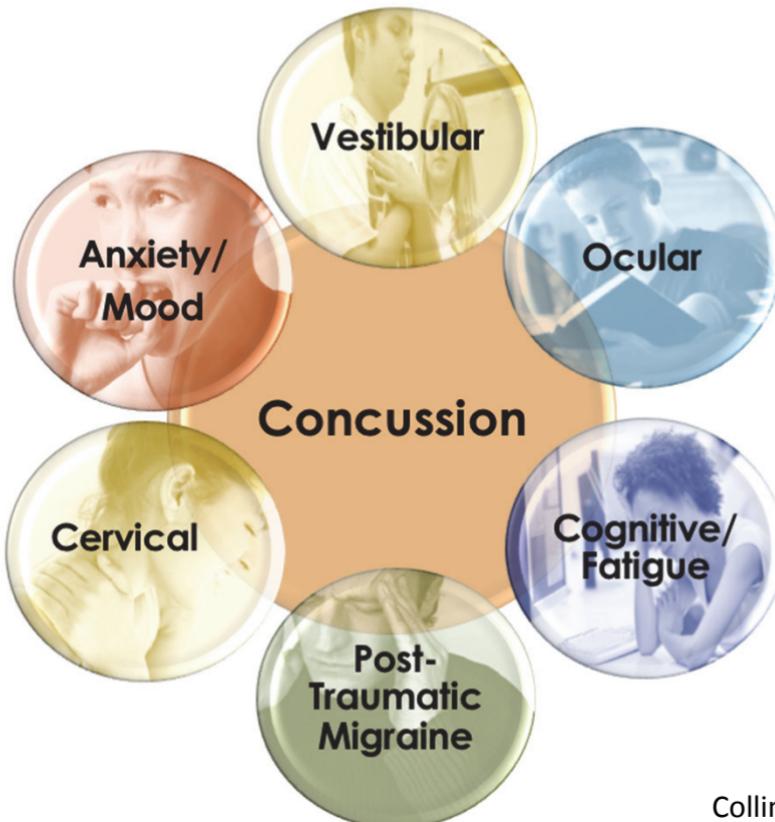
Needham et.al. *Crit Care Med.* 2012;40(2):502-509

Post-concussion Syndrome

a syndrome that occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and includes a number of disparate symptoms such as headache, dizziness, fatigue, irritability, difficulty in concentration and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol.

Graham R et.al.(2014). *Sports-related concussions in youth: Improving the science, changing the culture.*
Washington D.C. The National Academies Press.

Concussion Clinical Profiles

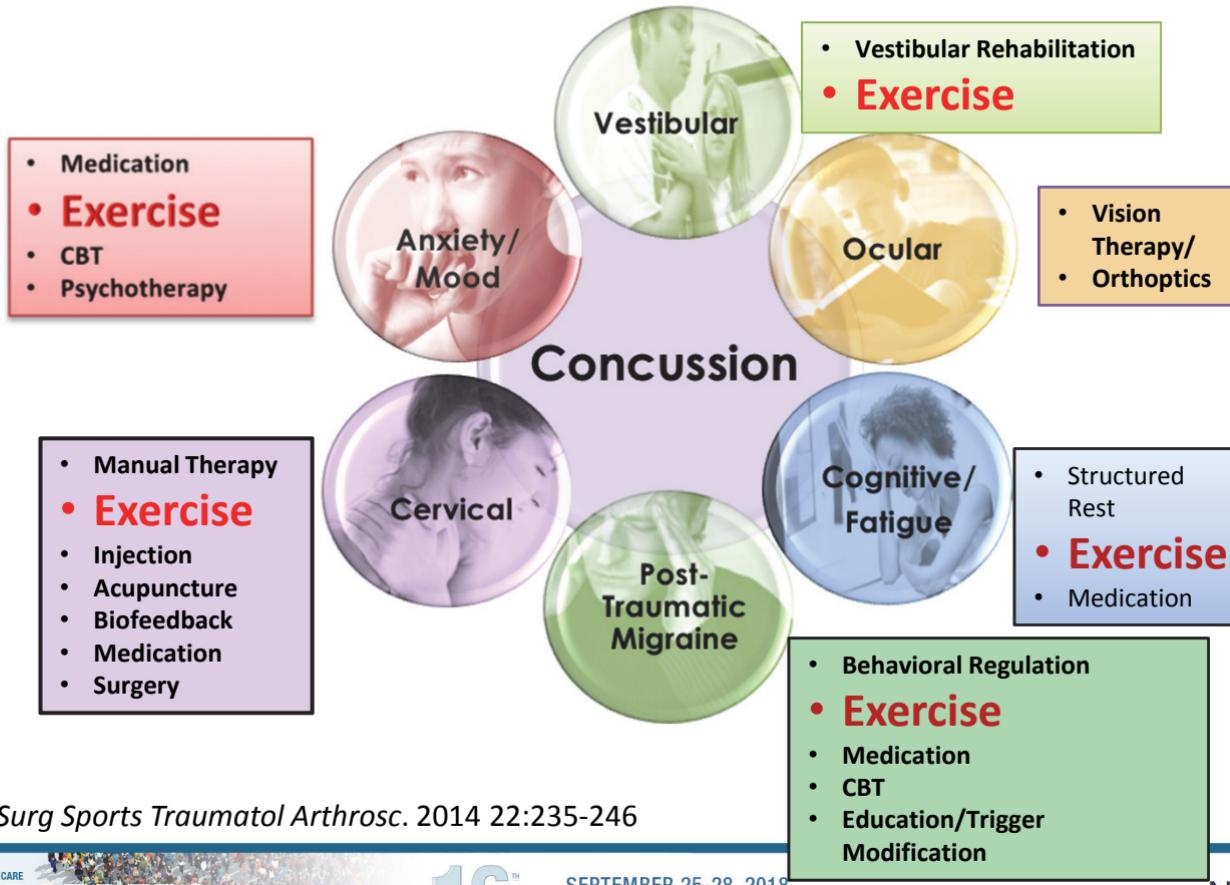


*A Model for Understanding
Assessment, Treatment and
Rehabilitation*

Clinical Profiles Determined by:
Clinical Interview and
Symptoms
Vestibular-Ocular Testing
Neurocognitive Testing
Exertional Testing

Collins MW et.al. *Knee Surg Sports Traumatol Arthrosc.* 2014 22:235-246

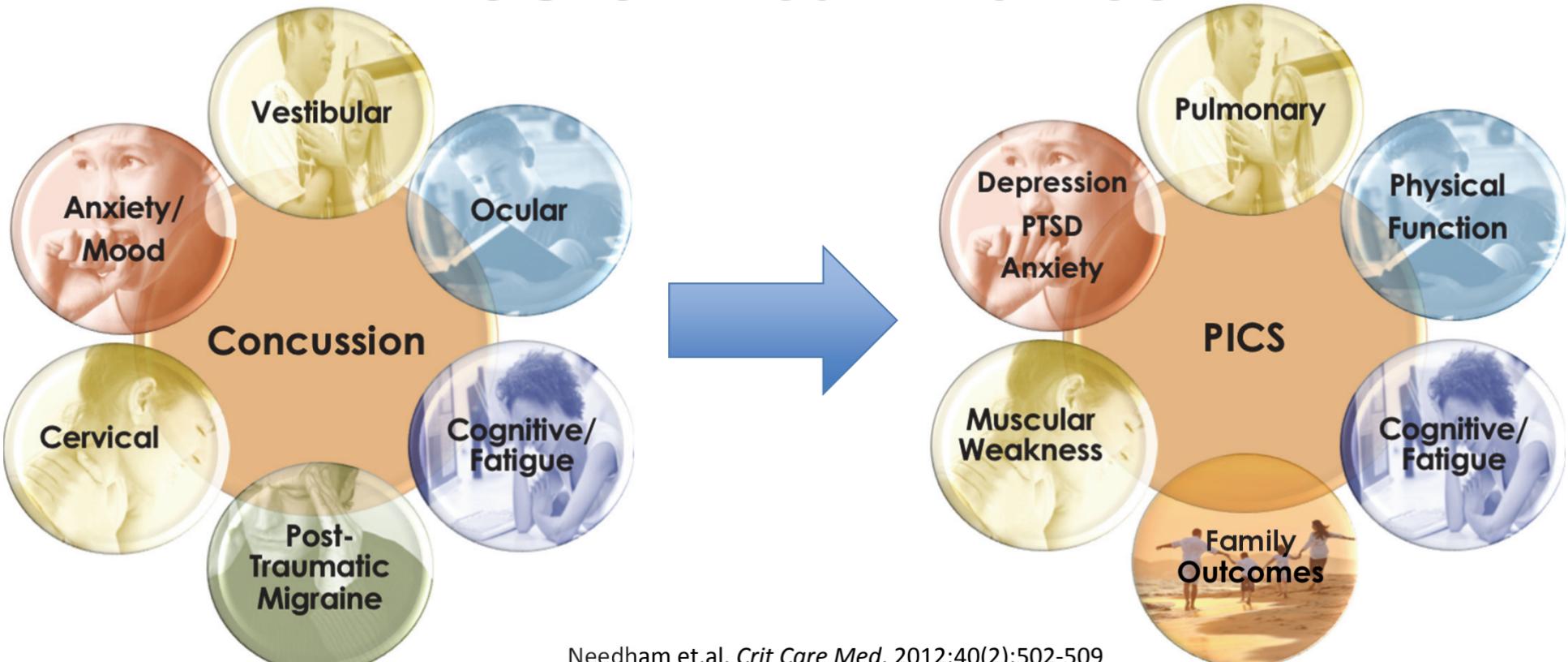
Targeted and Active Treatments for Concussion



Collins MW et.al. *Knee Surg Sports Traumatol Arthrosc.* 2014 22:235-246



PICS Clinical Profiles



Needham et.al. *Crit Care Med.* 2012;40(2):502-509

Treatment

- Amantadine
- Suvorexant

Amantadine

- Evaluated in **PCS**
- 100 mg twice daily at 3-4 weeks post injury
- Compared with matched historical controls
- Decreased subjective symptoms, increase in verbal and visual memory, visual processing speed and reaction time

Reddy CC. *J Head Trauma Rehabil.* 2013;28(4):507-17

Sleep Regulation

- Suvorexant investigation in on-going clinical trials
- Can blocking the Orexin System Enhance Sleep's Benefits to Therapeutic Exposure for PTSD?
- Suvorexant and Trauma Related Insomnia

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 July 29. Identifier NCT002849548 [cited 2018 August 31]

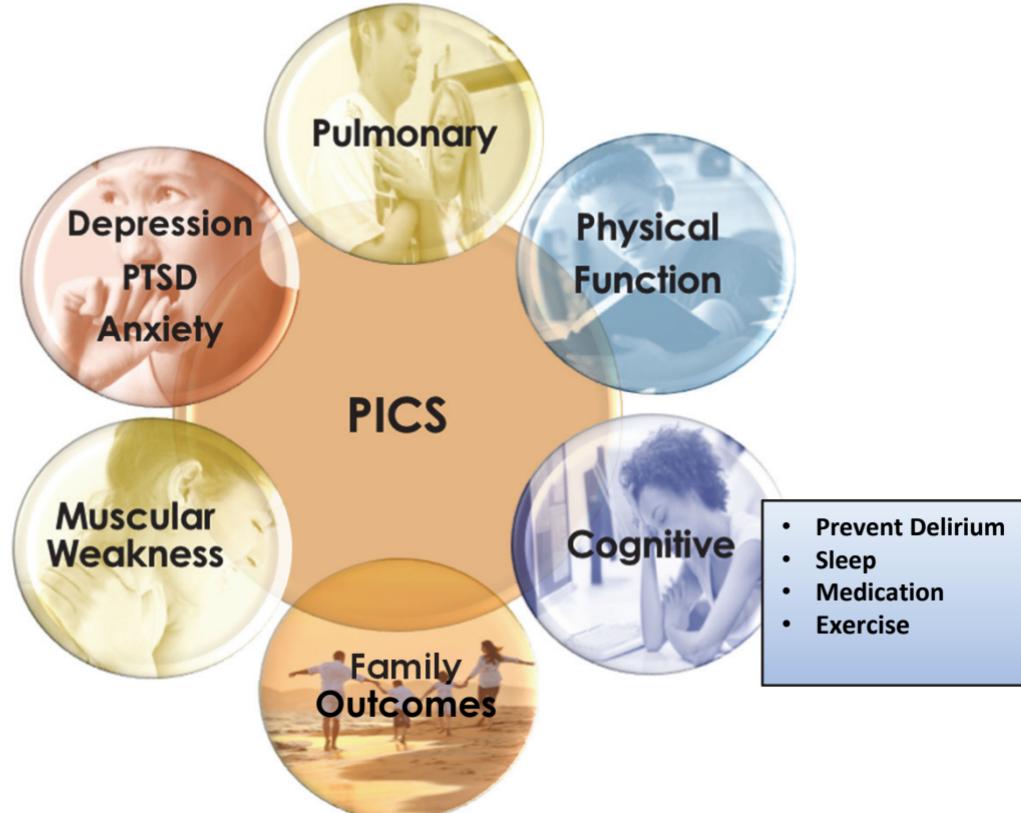
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 March 10. Identifier NCT002704754 [cited 2018 August 31]



Conclusions

- Little to no data to guide prevention and treatment of PICS
- PADIS guidelines provide some framework for prevention of cognitive dysfunction
- Similarities exist between PCS and PICS
- We have a lot of work to do

Treatments for PICS?



PTSD

- SSRIs and SNRIs
 - Sertraline, paroxetine, fluoxetine
 - Venlafaxine ER
 - Appears patients need to continue medication to maintain recovery
- Treatment resistant
 - Time since trauma may affect outcomes
- Prazosin
- No benzodiazepines!
- Little support for antipsychotics unless psychosis is present
 - Recent change to VA/DoD guidelines

Bernady NC, Friedman MJ. *Curr Psychiatry Rep* 2015;17(4):564

Zohar J et al. *Dialogues Clin Neurosci* 2011;13:301-309

PTSD Guidelines

American Psychiatric Association

- Pharmacotherapy
 - SSRIs
 - Non-combat related PTSD
 - Combat related PTSD
 - Other antidepressants
 - Positive data: Venlafaxine, mirtazapine, nefazodone
 - No difference from placebo: bupropion
 - Adrenergic agents
 - Propranolol: mixed results
 - Prazosin: 3-15mg
 - Atypical antipsychotics
 - Adjunctive treatment
 - Anticonvulsants: limited data with mixed results

Benedek DM et al. *Focus* 2009;7(2):204-213

Prazosin

- Recently evaluated in combat trauma PTSD with frequent nightmares
- 271 participants completed 10 weeks of treatment
- Mean maintenance dose reached was 14.8 ± 6.1 mg
- No differences in three primary outcomes

Raskind MA. *N Engl J Med.* 2018;378:507-17

PTSD New Treatment Directions

- Shifting from serotonergic agents
 - Beta-adrenergic antagonist: propranolol
 - Glutamate modulators: memantine, d-cycloserine, ketamine
 - Endocannabinoids
 - Oxytocin
 - Morphine

Bernady NC, Friedman MJ. *Curr Psychiatry Rep* 2015;17(20)

Battista MA et al. *Psychiatry* 2007;70(2):167-174

Frijling JL et al. *BMC Psychiatry* 2014;14(92)

Shad MU et al. *Hum Psychopharmacol Clin Exp* 2011;26:4-11

Holbrook TL et al. *N Engl J Med* 2010;362(2):110-117

Dexmedetomidine for Sleep

- Two additional randomized trials
- Both demonstrated increased Stage 2 sleep
- Neither study increased deep or REM sleep
- May preserve day/night cycling
- No data on long term outcomes

Devlin JW et.al. *Crit Care Med.* 2018 Sep;46(9):e825-e873

Sleep Regulation

- Dark room
 - blackout curtains, eye mask
- Quiet
 - Ear plugs
- No artificial light exposure at least 2 hours prior
 - TV, iPad, phone
 - Consider blue light reduction (eyeglasses, apps, 'nighttime mode')
- Cool temperature
 - 60-67 degrees is ideal
- No vigorous exercise at least 2 hours prior

PICS and PCS

- PICS and PCS share similar domains
 - **Cognitive**, anxiety/mood, physical function
- Treatment of cognitive impairment post ICU is similar
- Similarities may be helpful in learning new and different treatment strategies

Wergin R, Modrykamien A. *Cleveland Clinic Journal of Medicine*. 2012 Oct;79(10):705-712



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