Pharmacological Approaches to Targeting the Sleep-Pain Interaction

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JOHNS HOPKINS MEDICINE

PPP PERSONALIZED PAIN PROGRAM

Disclosures

Traci Speed, MD, PhD has documented that she has nothing to disclose.

This presentation does contain off-label or investigational use of drugs or products.

Learning Objectives

1) Describe potential mechanisms linking chronic pain and insomnia
2) Describe side effects of commonly used treatment approaches for comorbid pain and insomnia
3) Describe treatment approaches for comorbid chronic pain and insomnia disorder

Outline

- Sleep
- Pain
- Overlapping mechansims
- Pain medications affect on sleep
- Sleep medications affect on pain
- Psychotropic medications for insomnia and pain

Importance of Sleep

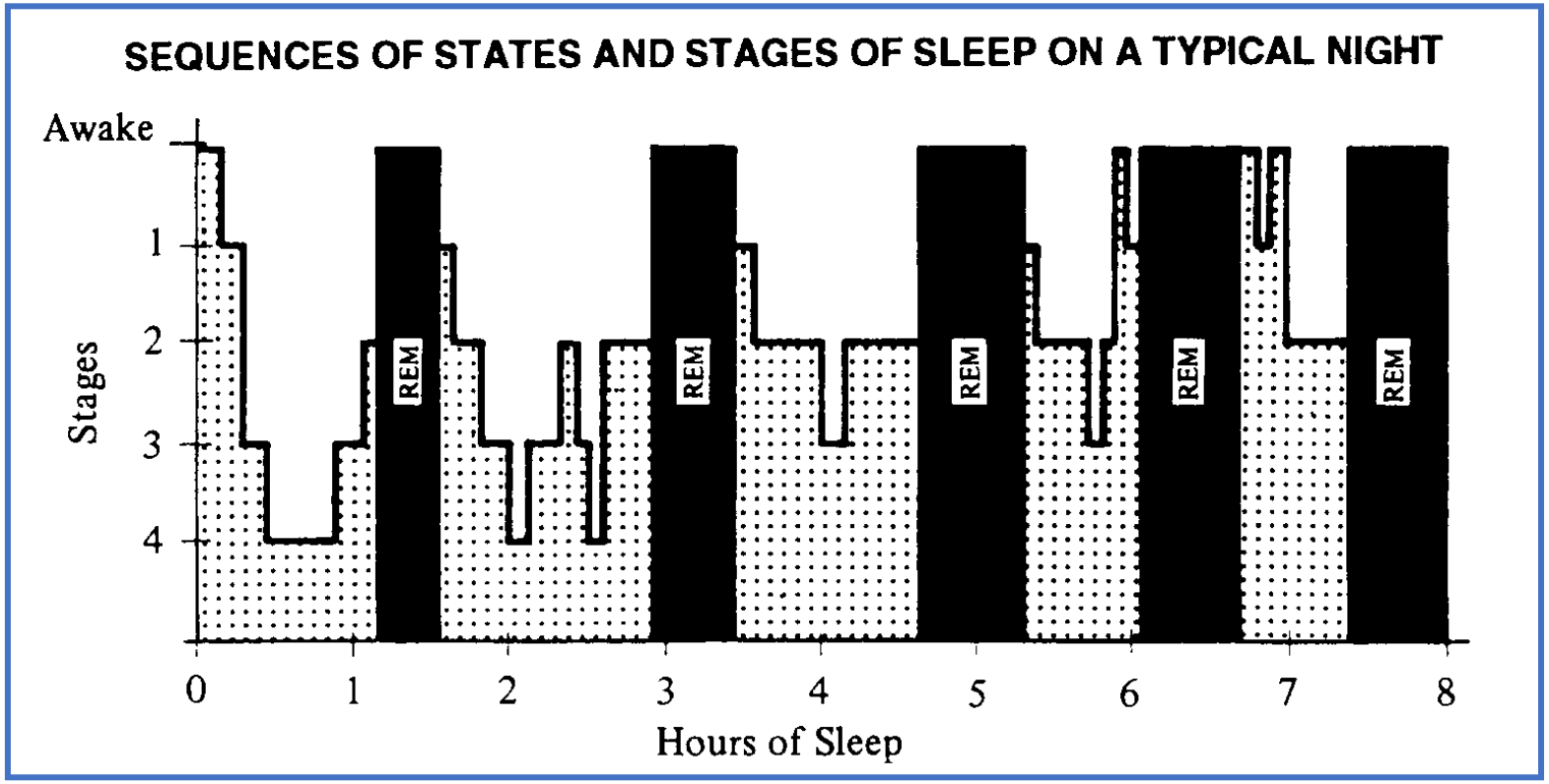
- Highly conserved behavior across animal evolution

- Although functions of sleep are not fully known, the various states of sleep perform vital mental and physical functions
  - Memory consolidation
  - Mood regulation
  - Repair, restoration, & regulation of endocrine and immune function

Sleep Is an Active Process
Complexly Orchestrated, Dynamic

7-9 hours

- More Slow Wave Sleep (deep) in first half of the night
- More REM sleep in the second half of the night
- Cycle is approximately 90 minutes

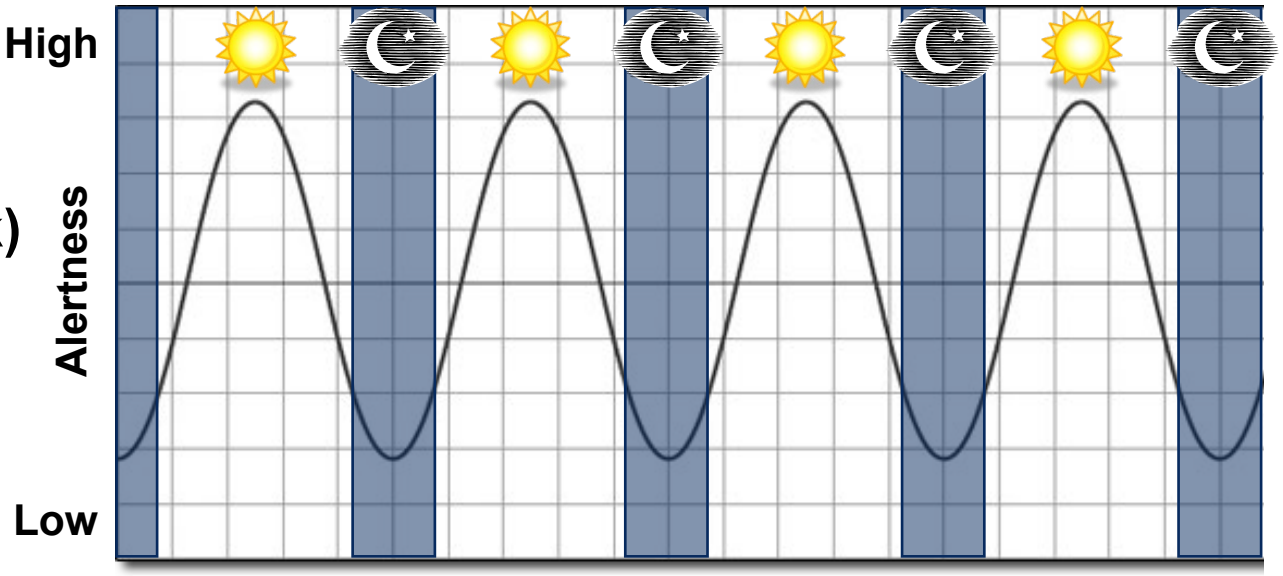


What controls sleep?

1. How long you've been awake

"I have a theory about your insomnia..."

2. Time of day (the biological clock)



Sleep Disorders

- Insomnia
- Hypersomnia
- Narcolepsy
- Sleep apnea
- Restless legs syndrome
- Circadian rhythm sleep disorders

Insomnia Disorder

Difficulty initiating and/or maintaining sleep, that <u>impacts daytime functioning</u>; “non-restorative sleep”

<u>Insomnia Disorder – DSM-5</u>

Sleep disorders coexist with other medical and psychiatric disorders

<u>Sleep parameters:</u>

Sleep latency (SL)

Light sleep

Slow wave sleep (SWS) (deep sleep)

REM sleep

Total sleep time (TST)

Sleep efficiency (SE)

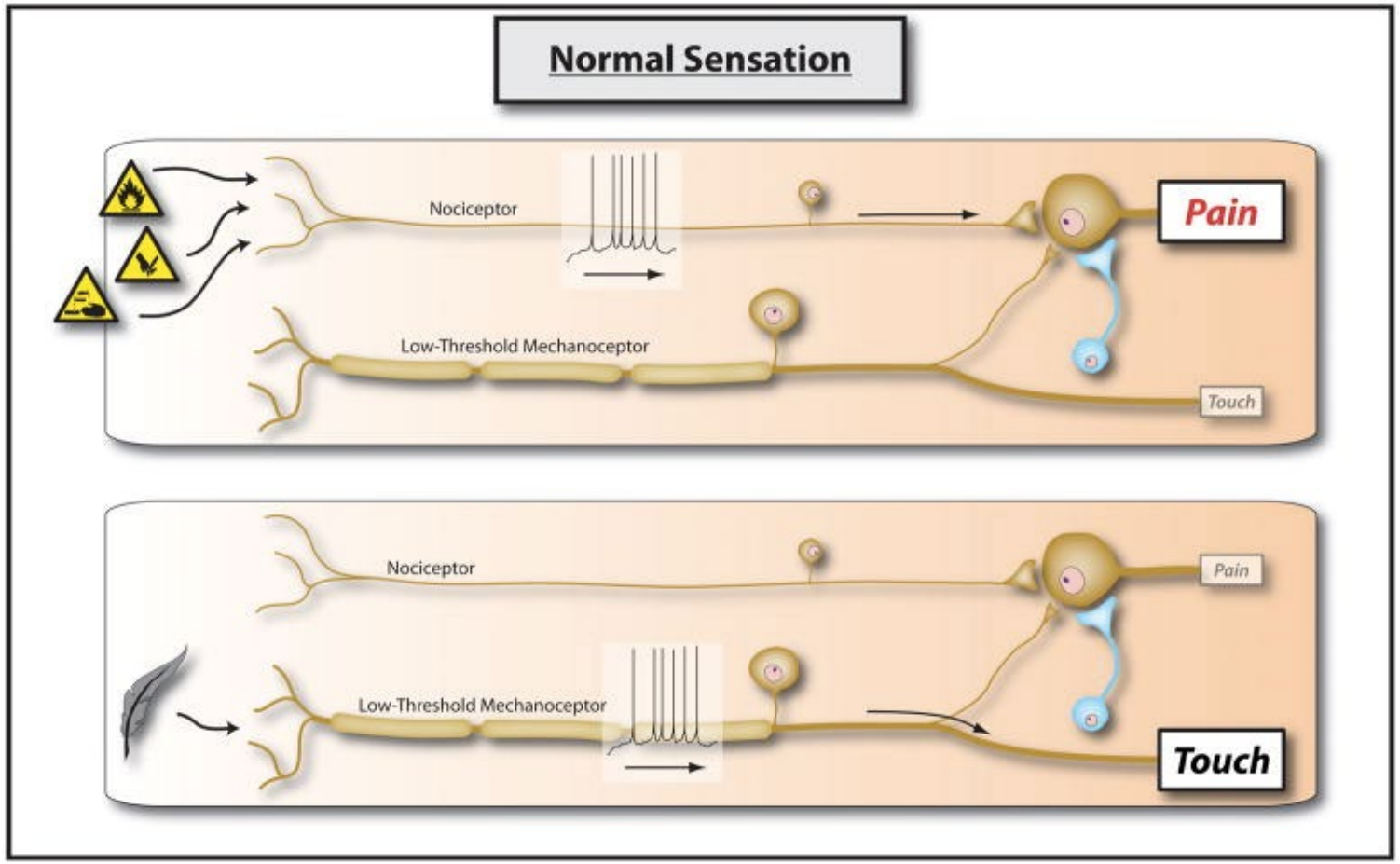
Pain is made up of two parts

- a sensory experience associated with physical manipulation
- an emotional response of distress and anxiety related to the sensory information

Patient in JH Pain Treatment Program

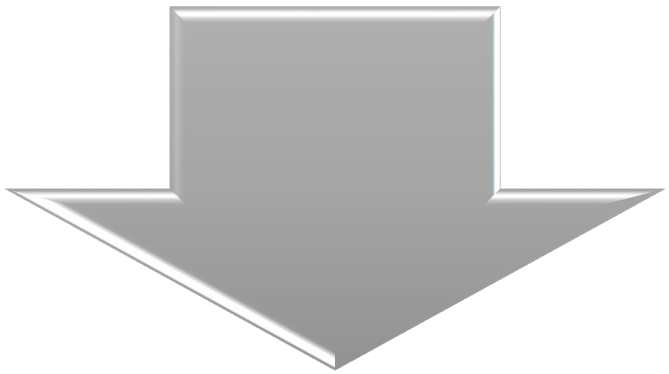
Acute Pain

- sudden onset
- often known etiology
  - surgery
  - broken bones
  - dental work
  - burns or cuts
  - labor and childbirth
- resolves when underlying cause removed



Woolf, et al 2011

Sleep-Pain Interaction



poor sleep quality

insomnia

nonrestorative sleep

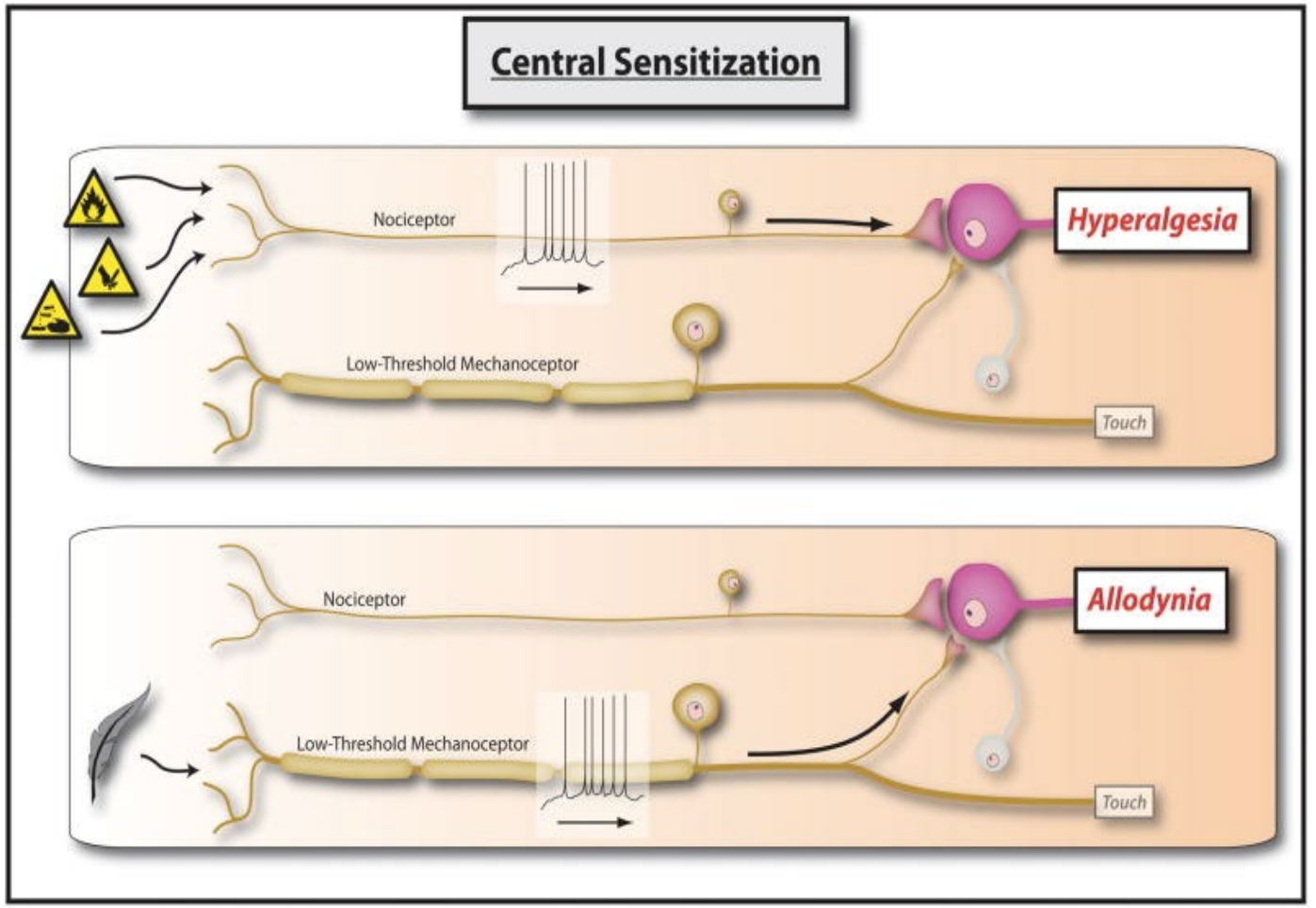
pain onset

pain intensity

pain frequency

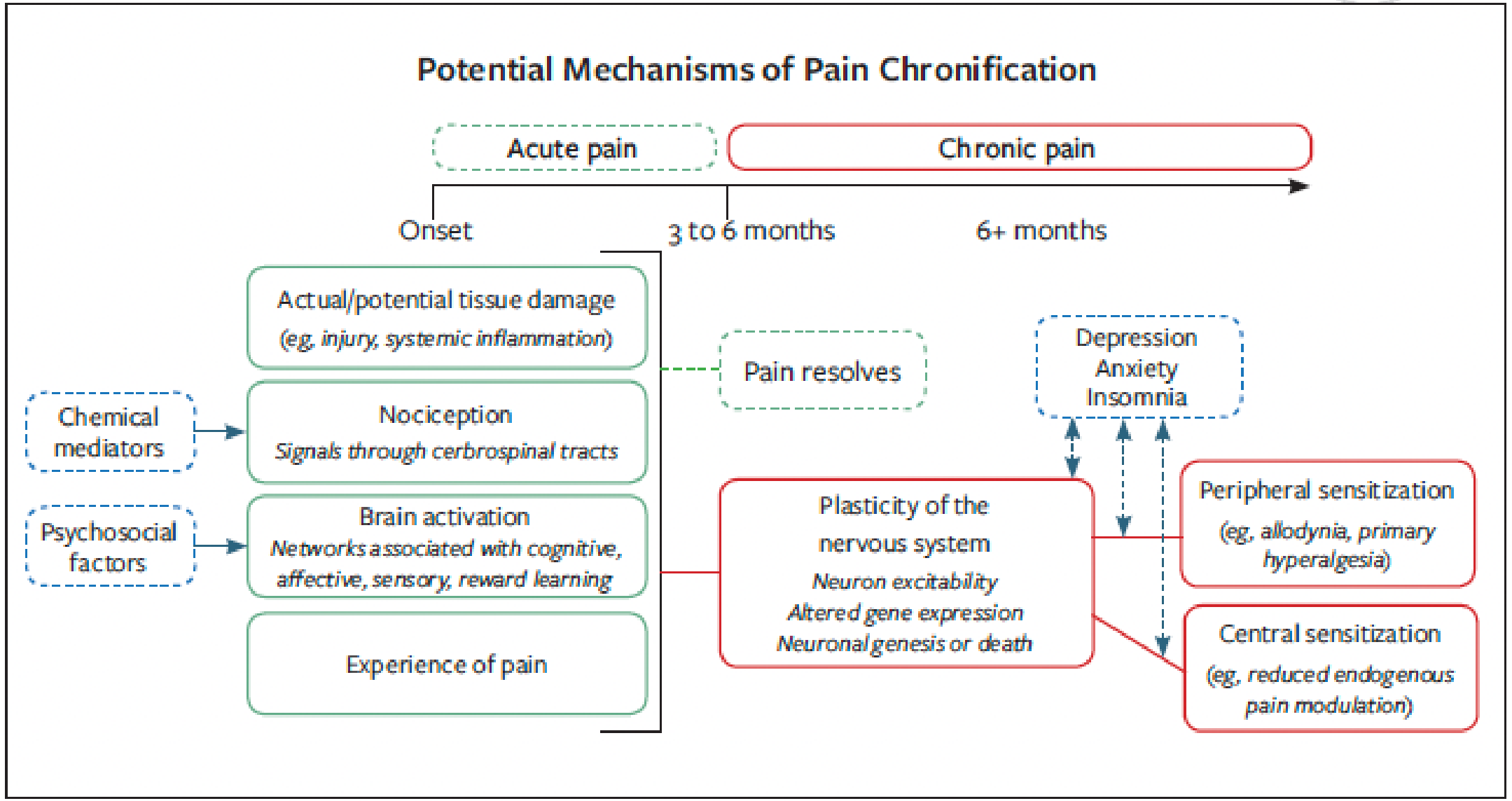
Chronic Pain

- result of ongoing acute injury
  - malignancy
  - tissue destruction
  - chronic infection
- result of an adaptation of the nervous system to injury
  - continues after initial pain provocation has resolved



Woolf, et al 2011

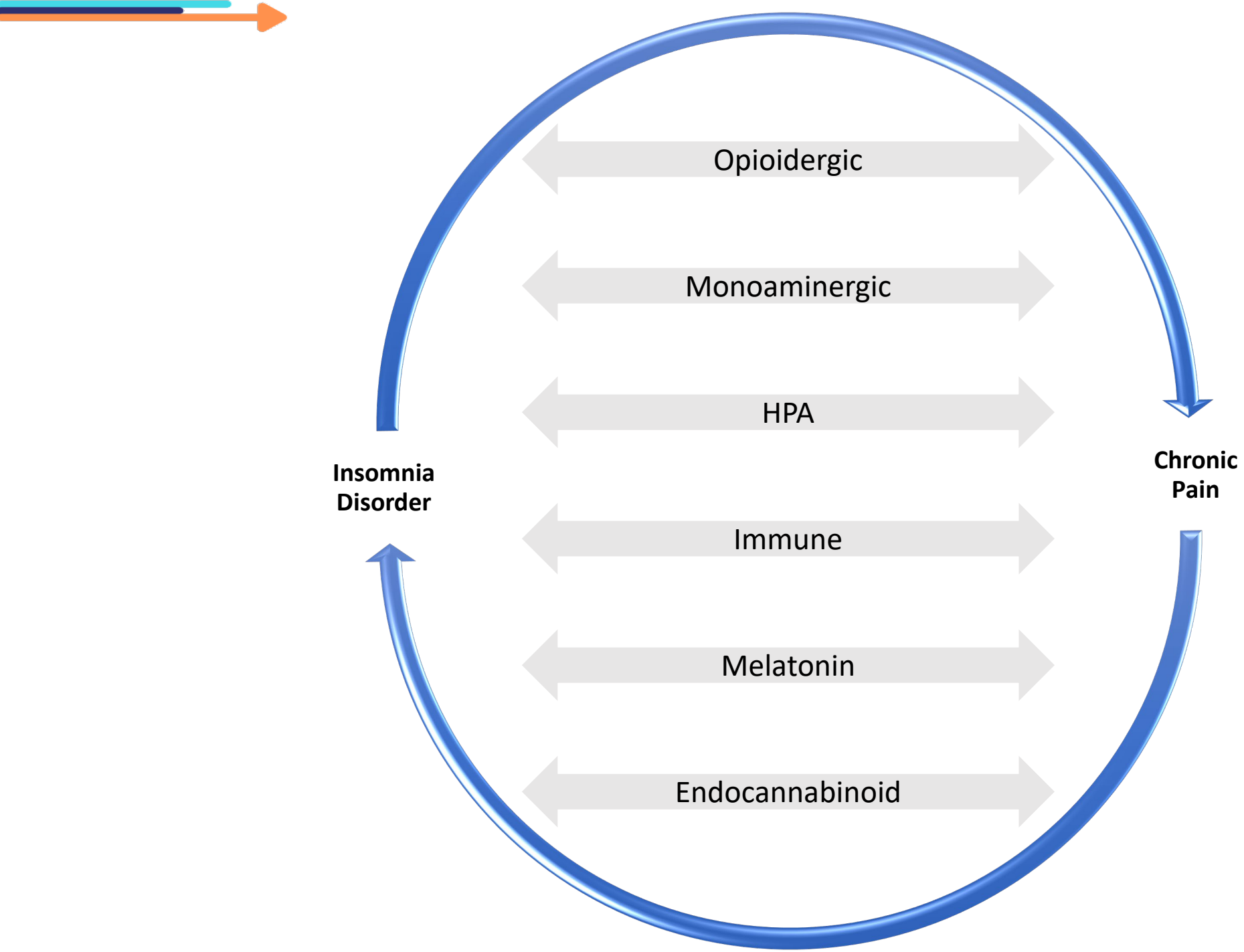
Pain-Sleep Interaction



Campbell CM et al. Sleep Medicine for Dentists, 2020

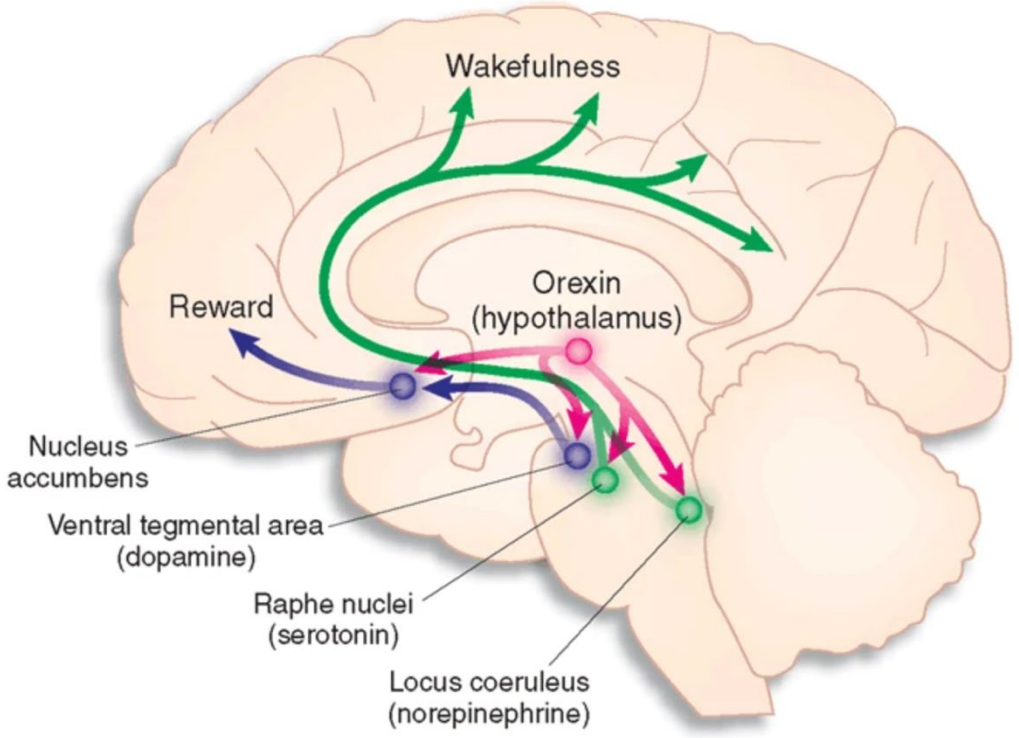
Nociceptive pain	Neuropathic pain	Nociplastic pain
- Tissue damage	- Injury to nervous system	- Maladaptive changes to pain processing/modulation; unknown pathology
- Degenerative changes (DDD) - Aging (arthritis) - Trauma (burns) - Visceral (renal stones)	- Nerve compression (radiculopathy) - Metabolic (diabetes) - Trauma (postsurgical) - Infection (HIV) - Inflammatory (MS)	- Diffuse pain (fibromyalgia) - Visceral pain (IBS, cystitis) - Peripheral sensitization (TMD) - Sensory amplification (headaches) - (Functional)
- Throbbing, aching, pressure - Pain localized - Hypersensitivity at injury site	- Shooting, stabbing, electric - Pain radiates along nerve distribution - Hypersensitivity and allodynia	- Shooting, stabbing + aching - Diffuse (not along nerve distribution) - Diffuse hypersensitivity
- Infrequent sensory deficits - Pain-induced motor weakness	- Numbness/tingling - Motor nerve weakness, spasticity	- Non-focal sensory deficits - Fatigue - Deconditioning
- Dysautonomia rare - **Comorbid insomnia**, cognitive impairment, depression, anxiety	- Localized autonomic signs (CRPS) - Dysautonomia possible - **Comorbid insomnia**, cognitive impairment, depression, anxiety	- Comorbid nociceptive conditions - Dysautonomia common - **Comorbid insomnia**, cognitive impairment, depression, anxiety

Modified from Cohen et al. 2021 Lancet


Opioidergic
Monoaminergic
HPA
Immune
Melatonin
Endocannabinoid
Insomnia Disorder
Chronic Pain


OPEN
24
HOURS

Neurobiology of the Orexin System



- Orexin neurons promote and sustain wakefulness
  - < 100K orexin secreting neurons in the lateral hypothalamus
- Orexin receptors (ORX1 and ORX2) are expressed in areas of the brain that regulate:
  - appetite, metabolism, reward, stress, and autonomic function

Scammell TE, et al. *Nat Med*. 2007;13(2):126-128. Alexandre C, et al. *Curr Opin Neurobiol*. 2013;23(5):752-759. Li J, et al. *Br J Pharmacol*. 2014;171(2):332-350. Herculano-Houzel S. *Front Hum Neurosci*. 2009;3:31. Dubey AK, et al. *J Pharmacol Pharmacother*. 2015;6(2):118-121.

Potential Pathways Linking Pain and Sleep

	Insomnia	Pain
Inflammatory modulators	↑ prostaglandins, cytokines	↑ prostaglandins, cytokines
HPA	↑ HPA reactivity	↑ HPA reactivity
Opioidergic	↓ endogenous opioids ↓ opioid receptors	Impaired descending pain inhibitory system
Serotonin	↑ 5-HT (acute) ↓ 5-HT 1A receptor activity (chronic)	Impaired descending pain inhibitory system ↓ pain threshold
Norepinephrine	↑ NE	mixed
Dopamine	↓ DA	↓ DA
Adenosine	↑ Adenosine	↑ Adenosine associated with hyperalgesia
Orexin	↑orexinergic system	Pain modulation

Modified from Andreucci A et al. Children 2021

Can pain medications target sleep?

Can sleep medications target pain?

Treatment Considerations								
	NSAIDS	**Neuro-modulation**	**Exercise**	**Behavioral Therapies**	**Injections**	**Opioids**	**Anti-depressants**	**Antiseizure meds**
Nociceptive Pain	X	X	X	X	X	X	X	
Neuropathic Pain		X		X	X	X	X	X
Nociplastic Pain			X	X			X	X
Insomnia Disorder	?	?	X	X		X	X	X

Modified from Cohen et al. 2021 Lancet

CLINICAL GUIDELINES | 19 JULY 2016

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians FREE

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians (*)

Recommendation 1: *ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*

Edinger JD, et al. *J Clin Sleep Med*. 2021;17(2):263-298. Wu JQ, et al. *JAMA Intern Med*. 2015;175(9):1461-1472.

FDA-approved pain medications

	Level of evidence (pain)	Target pain population	Mechanism of action	CNS depressant	Addiction potential	Withdrawal symptoms
NSAIDs	High	Acute pain Inflammatory pain	Inhibit COX-2 to relieve inflammation	–	Low	–
Acetaminophen	High	Acute and chronic pain	May inhibit COX pathway; analgesic and antipyretic	–	Low	–
Opioids	High	Acute, chronic, cancer, and palliative pain	Activate μ-opioid receptors; inhibit neural pain pathways	↑	High	↑
Corticosteroids	High	Inflammatory pain	Inhibit cytokine production	↑	High	–
Cyclobenzaprine	Moderate	Acute and chronic MSK pain	Antispasmodic, inhibits 5-HT2 receptors in brainstem	↑	Mod	–
Baclofen	Moderate	Trigeminal neuralgia, CLBP, CRPS	Antispasmodic, targets $GABA_B$ to inhibit descending motor nerves	↑	Low	↑ (CV)
Clonidine	Low	Neuropathic pain, CRPS	α2-adrenergic receptor agonist with antihypertensive effect	↑	Low	↑ (CV)
Propranolol	Moderate	Headache	β-blocker that reduces sympathetic activity	–	Low	↑ (CV)

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Side effects of FDA-approved pain medications

	GI	Sedation	Dizziness or headache	Weight gain	Dry mouth	Mood changes	Fall risk
NSAIDs	+	+	+	=	=	=	–
Acetaminophen	=	=	=	=	=	=	–
Opioids	++	++	++	=	++	++	↑
Corticosteroids	#	=	#	#	=	#	–
Cyclobenzaprine	+	++	++	=	++	+	↑
Baclofen	++	++	++	=	+	+	↑
Clonidine	++	++	++	=	++	+	↑
Propranolol	+	+	+	=	=	=	↑

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Sleep outcomes of FDA-approved pain medications

	Sleep latency	Light sleep	Slow wave (deep) sleep	REM sleep	Total sleep time	Subjective sleep quality	Sleep efficiency	Evidence
NSAIDs	↓	↓	=	↑	_	↑	↑	Low
Acetaminophen	=	-	-	-	-	↑	=	Low
Opioids	=	=	↓	↓	↓	↑	↓	High
Corticosteroids	=	=	=	=	=	↓	=	Mod
Cyclobenzaprine	=	=	=	=	↑	↑	↑	Mod
Baclofen	=	↓	=	=	↑	=	↑	Mod
Clonidine	=	↑	=	↓	=	-	=	Low
Propranolol	=	=	=	↓	=	↓	↓	Mod

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

FDA-approved sleep medications

	Level of evidence (pain)	Target pain population	Mechanism of action	CNS depressant	Addiction potential	Withdrawal symptoms
Benzodiazepines (extazolam, flurazepam, quazepam, temazepam, triazolam)	Low	Burning Mouth Syndrome	Bind $GABA_A$ receptors and potentiate GABA inhibitory effects; neuronal inhibition in sleep-related areas	↑	High	↑
Doxepin	Low	Chronic pain	Increase CNS 5-HT and NE; H_1 antagonist causes sedation	↑	Low	↑
Z-drugs (e.g., zolpidem)	Low	Acute pain	Bind $\alpha 1$ $GABA_A$ subunit and potentiates GABA inhibitor effects; neuronal inhibition in sleep-related areas	↑	Mod	↑
DORAs (e.g., suvorexant)	Low	Fibromyalgia	Blocks orexin-1 and -2 receptors and promotes sleep	↑	?	–

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Side effects of FDA-approved sleep medications

	GI	Sedation	Dizziness or headache	Weight gain	Dry mouth	Mood changes	Fall risk
Benzodiazepines (extazolam, flurazepam, quazepam, temazepam, triazolam)	+	++	+	=	=	+	↑
Doxepin	+	+	+	+	+	=	↑
Z-drugs (e.g., zolpidem)	+	++	++	=	+	+	↑
DORAs (e.g., suvorexant)	+	++	+	=	+	#	–

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Outcomes of FDA-approved sleep medications

	Sleep latency	Light sleep	Slow wave (deep) sleep	REM sleep	Total sleep time	Subjective sleep quality	Sleep efficiency	Evidence
Benzodiazepines (extazolam, flurazepam, quazepam, temazepam, triazolam)	↓	↓/↑	↓	↓	=	↑	↑	High
Doxepin	↓	↑	=	=	↑	↑	↑	High
Z-drugs (e.g., zolpidem)	↓	↑	↓	=	=	↑	↑	High
DORAs (e.g., suvorexant)	↓	↑	=	↑	↑	↑	↑	Mod

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Potential analgesics targeting sleep and pain

✓ NSAIDs and Acetaminophen

- strong evidence of analgesia
- minimal CNS risks
- fewer side effects
- no deleterious effects on sleep architecture; possibly improve objective sleep parameters

✗ Opioids

- strong evidence of analgesia
- greater CNS risks
- greater side effects
- deleterious effects on sleep architecture contrary to subjective report

Potential sleep medications targeting sleep and pain

✓ Doxepin and DORAs

- improve objective and subjective sleep parameters
- less addiction risk
- relatively fewer side effects
- low evidence of analgesia

✗ Benzodiazepines and z-drugs

- does not benefit deep sleep
- greater CNS risks
- relatively greater side effects
- low evidence of analgesia

Psychotropics for pain and sleep

Antidepressant effects on sleep parameters

- Most ADs suppress REM sleep
  - which occurs within hours of initiating therapy
  - SSRI, SNRI, nonselective MOAIs, and $\alpha 2$ receptor antagonists
    - may be due to either noradrenergic or serotonergic modulation
- Non-REM suppression
  - Trazodone, bupropion, nefazodone
    - No direct effects on NE or 5-HT
- H1 and 5HT-2 receptor antagonism can improve sleep initiation and/or maintenance
- ADs do not reliably increase SWS (deep sleep)

Thase M. Dialogues in Clinical Neuroscience 2022

Antidepressant effects on pain

- SSRIs less effective at targeting both pain and sleep
  - 5-HT only
    - perceived benefits of pain may be secondary to depression
      - citalopram in fibromyalgia
      - sertraline in non-cardiac chest pain
- TCAs
  - amitriptyline had been most widely prescribed AD for analgesia
- SNRIs
  - Duloxetine increasingly used due to safety profile (60-120mg)
    - neuropathic pain >> fibromyalgia

Bravo et al. Frontiers in Neuroscience 2019; Lunn et al. Cochrane Database Syst Rev 2014

FDA-approved antidepressants for pain

	Sleep latency	Light sleep	Slow wave (deep) sleep	REM sleep	Total sleep time	Subjective sleep quality	Sleep efficiency	Evidence
Duloxetine	↓	↑	↓	↓	↓	↑	↓	Low
Milnacipran	↓	↑	=	=	↑	_	↑	Low
Venlafaxine	NA	↓/↑	↓	↓	NA	NA	↓	Low

	GI	Drowsy	Dizzy	Weight	Dry mouth	Mood	Fall	Evidence
Duloxetine	++	++	++	↓	++	+	_	Mod
Milnacipran	++	=	++	=	+	=	_	Low
Venlafaxine	++	=	=	=	=	+	_	Mod

Modified from Herrero Babiloni A et al. Sleep Medicine Reviews 2021; Goodman and Gilman, 14th edition, 2022

TCAs

- SR/MA comparing ADs to placebo found NO studies with amitriptyline or nortriptyline
- Clinically used to treat neuropathic, nociceptive, and nociplastic pain
- Primary care and pain medicine
  - Dosing limited by dry mouth, constipation, weight changes, orthostasis, tachycardia, sedation, somnolence
- Improved TST, SWS (deep sleep), and decrease SL
- Suppress REM sleep
- Improved subjective sleep quality

Liu Y et al. Sleep Medicine 2017; Everitt H et al. Cochrane Database Syst Rev 2018

Other Antidepressants

	Sleep latency	Light sleep	Slow wave (deep) sleep	REM sleep	Total sleep time	Subjective sleep quality	Sleep efficiency	Evidence
Mirtazapine	↓	↓/↑	↑	↑	↑	↑	↑	High
Bupropion	=	=	=	(↑ Latency)	=	=	=	Low

	GI	Drowsy	Dizzy	Weight	Dry mouth	Mood	Fall	Evidence
Mirtazapine	++	++	+	↑	++	+	↑	Low
Bupropion	++	+	++	↓	++	+	_	Low

Semenchuk M. Neurology 2001;

Summary of Antidepressants

- TCAs and SNRIs >>> SSRIs for pain and sleep
- Mirtazapine and TCAs can improve SWS (deep sleep)
- Duloxetine is most studied / used SNRI
  - If 60-120mg daily ineffective for pain, switch to another AD

Antiepileptics

FDA-approved antiepileptics for pain

- Gabapentin
  - Inhibits a2-d subunit of VgCa Ch and modulates GABA and glutamate
  - ↑SWS (deep sleep), ↑SE, ↑sleep quality
  - Can improve RLS
  - Cautious with other CNS depressants
  - Risk of dependence
- Topiramate
  - CLBP, phantom limb, migraine
  - Appetite suppressant (OSA)
- Pregabalin
  - Linear PK (dose-response does not plateau)
  - ↑ SWS (deep sleep), ↑SE, ↑sleep quality
  - Cautious with other CNS depressants
  - Risk of dependence
- Carbamazepine, Oxcarbazepine commonly used for neuropathic pain, but effects on sleep understudied

Herrero Babiloni A et al. Sleep Medicine Reviews 2021

Antipsychotics

- Quetiapine
  - D_2 and $5HT_2$ receptors
  - H_1 and $5HT_{2A}$ antagonism
    - Improved subjective sleep quality and fibromyalgia symptoms in open label study
    - Less efficacious and worse tolerability than amitriptyline
- Olanzapine
  - $5\text{-}HT_{2A} > D_2$
  - As augmentation in non-insomnia, ↑SWS (deep sleep), ↑SE, ↑sleep quality

Calandre E et al. Psychopharmacology 2014; Shapley A et al. J Clin Psychiatr 2005; Lazowski L et al. BMC Psychiatr 2014; Jimenez X et al. Clin J Pain 2018

Additional medications with low quality evidence

- Trazodone
  - ↑ TST, SE, sleep quality
  - Benefits c/w CBT-I
  - Improved pain in fibromyalgia, neuropathy
  - Fall risk
- Melatonin
  - Reduce sleep latency in insomnia, delayed sleep phase, regulate sleep-wake in those who are blind
  - Improve pain threshold and endogenous pain inhibitory threshold
- Orexin antagonists
  - Women with fibromyalgia and insomnia, ↑ TST and reduced next-day pain

Roehrs T et al. J Clin Sleep Med 2020

Summary

- Insomnia and chronic pain have a bidirectional relationship
- SNRIs, TCAs, antiepileptics, and antipsychotics are among medications with multitarget properties that can modulate sleep, pain, and mood
- Treatment strategies targeting sleep and pain are appealing, but understudied
- Psychotropics and sleep medications have been used across different chronic pain phenotypes (e.g., nociceptive, neuropathic, nociplastic)

Npr.org

Thanks to MPS!

Questions???

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