Snooze to Lose the Pain

Headaches and their Relationship with Sleep

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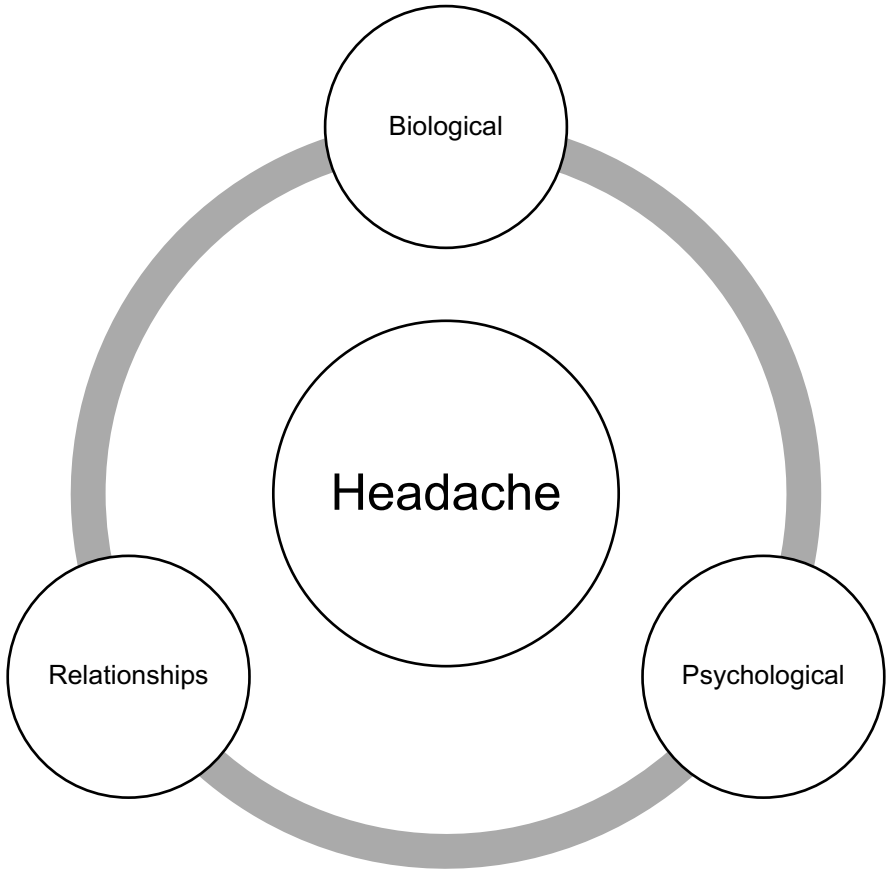
Learning Objectives

- Identify several contextual and headache and pain factors influencing sleep disturbance
- Describe headache management techniques that may influence sleep in clinical practice

Disclosures

- Executive Committee Member of AAP SOIM

Headaches = A Bio-Psycho-Social Phenomenon



Most Common Pediatric Primary Headache Disorders

- Determine diagnosis via International Classification of Headache Disorders-3rd edition (ICHD-3): https://www.ichd-3.org/
  - Migraine
  - Tension-type headache
  - Medication overuse headache
  - Chronic headache disorder: Chronic migraine, chronic tension-type headache
  - Posttraumatic headache, post-concussion syndrome

Headaches In Children

(Lewis 2002)

- Migraine Prevalence:
  - 1.2% to 3.2% in 3 to 7-year-olds
  - 4% to 11% in 7 to 11-year-olds
  - 8% to 23% in 11 to 15-year-olds

- Prevalence of any type of headache:
  - 37% to 51% in 7 year-olds
  - 57 to 82% by age 15

Pain is disability

- The Global Burden of Disease Study
- Years living with disability (YLD)
  - # 1 Low back pain
  - # 2 Migraine

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017

Dx: Migraine Without Aura

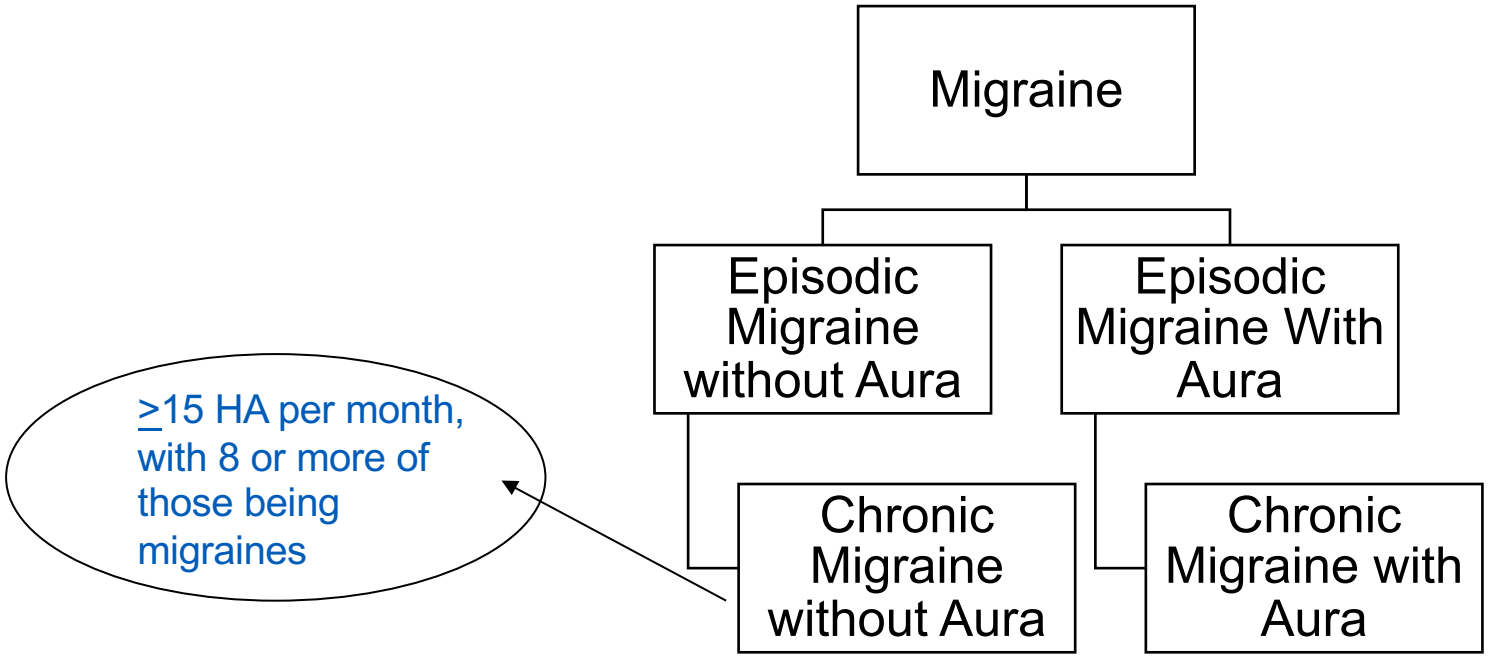
1. HA lasts 4-72 hrs
2. At least one:
    1. Nausea and/or Vomiting
    2. Light and Noise Sensitivity
3. At least two:
    1. Unilateral
    2. Pulsating/throbbing
    3. Moderate-severe pain
    4. Aggravated by movement

Dx: Migraine with Aura

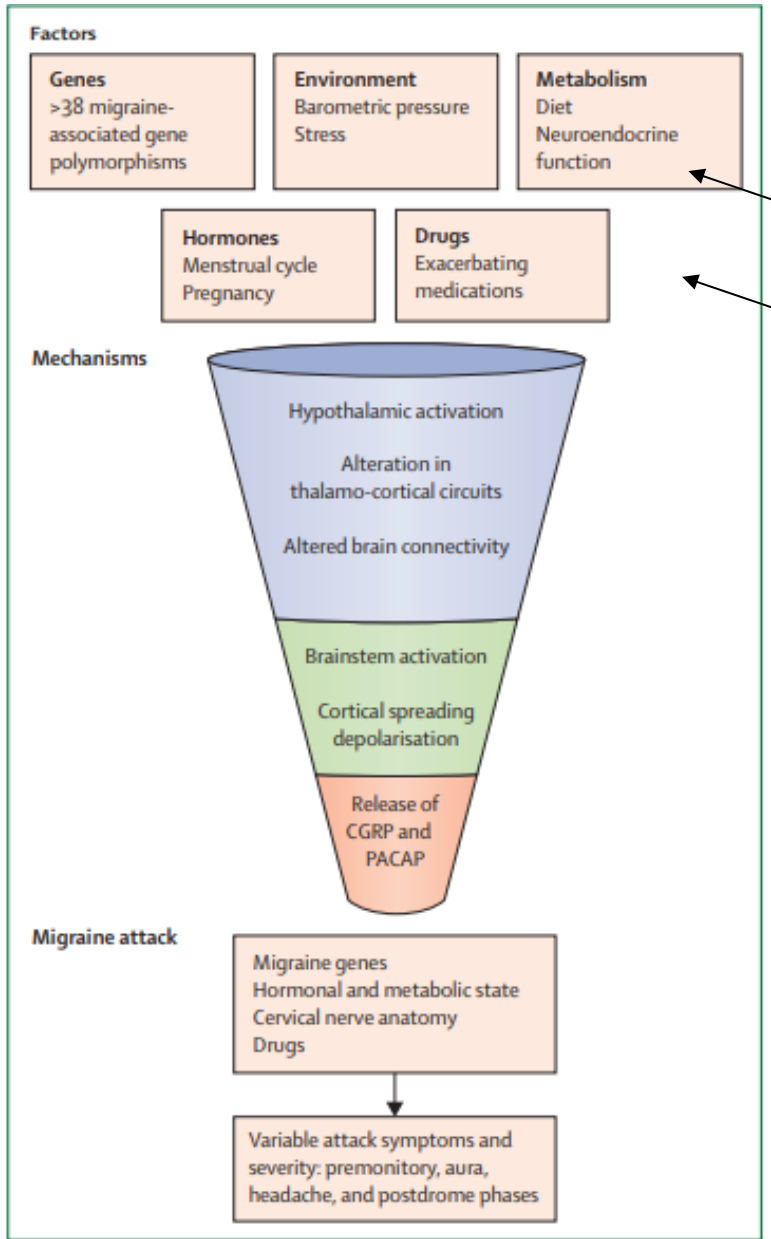
1. HA lasts 4-72 hrs
2. One or more auras of following:
    1. Visual, sensory, speech, motor, brainstem, retinal

    At least three of following:
    - Aura spreading gradually over ≥5 minutes
    - Two or more auras in succession
    - Aura may last between 5-60 min and then accompanied by headache
    - unilateral
3. At least one:
    1. Nausea and/or Vomiting
    2. Light and Noise Sensitivity
4. At least two:
    1. Unilateral
    2. Pulsating/throbbing
    3. Moderate-severe pain
    4. Aggravated by movement

Migraine Classifications:
Episodic vs. Chronic



Migraine Review

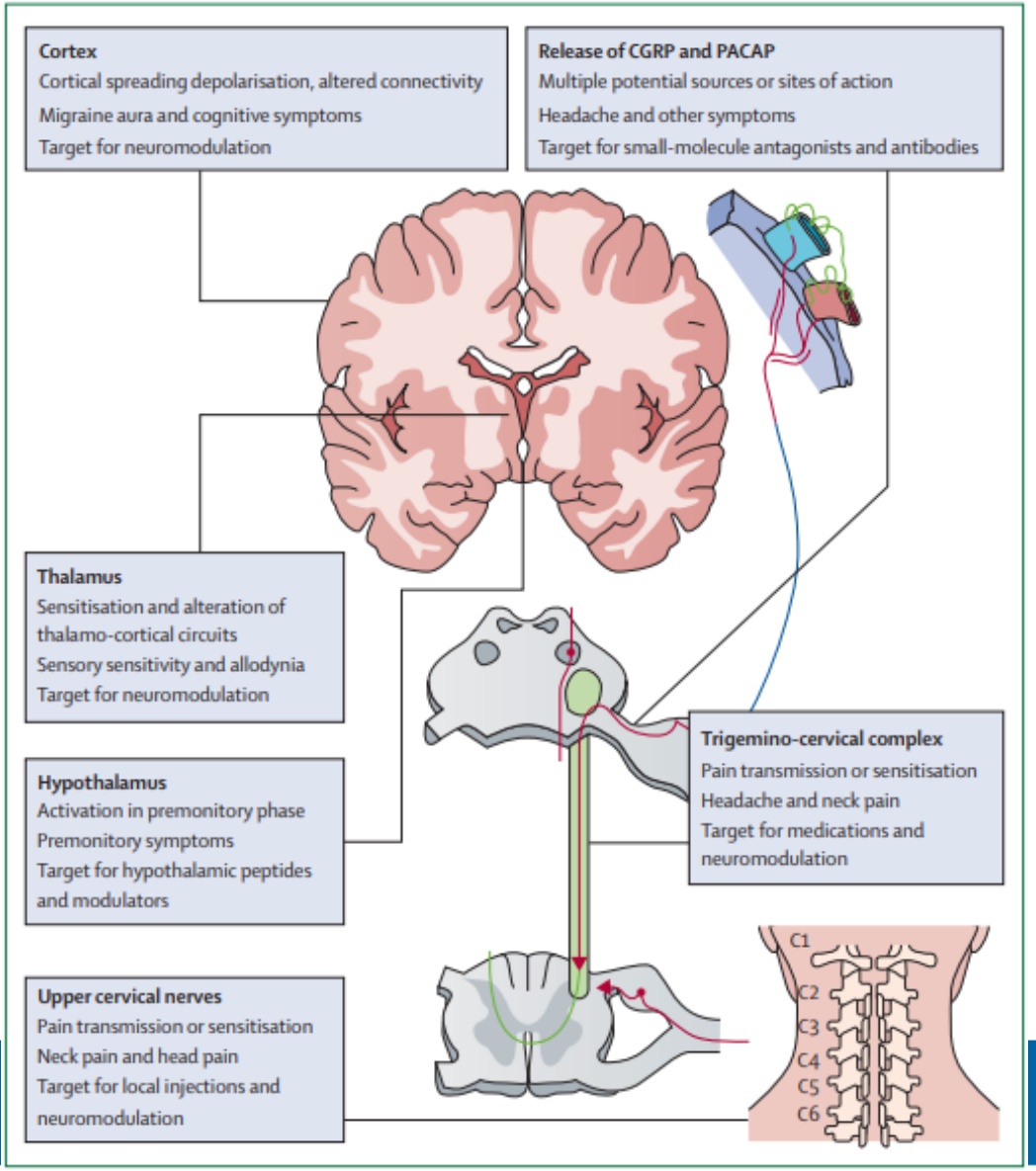


Mitochondria

SLEEP

Charles A. Lancet Neurology 2018

Migraine Pathophysiology



Charles A. Lancet Neurology 2018

Chronic migraine and Sleep

- Insomnia most common sleep disorder for individuals with chronic migraine (60-80% in adult studies)

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Yang CP, Wang SJ. Curr Pain Headache Rep 2017

Headache Triggers

40 unique triggers:

- #1: Stress
- **#2: Sleep**
- #3: Weather Changes

Pellegrino ABW et al. Cephalalgia 2017

Chicken or the Egg: Sleep or Pain First?

- Unclear – likely bidirectional influence
- However, sleep disturbance may magnify pain more than pain magnifies sleep disturbance based on prospective studies

Finan PH et al. J Pain 2013

Pathophysiology

- Sleep essential in regulation of homeostasis, including the glymphatic system
  - Waste clearing system of nociceptive substances that could potentiate migraine pain and central sensitization

Unsplash@averey

Jeff Iliff Video

Fragmented or Insufficient Sleep -> Central Sensitization

- Lack of sleep associated
  - lack of central pain inhibition
  - Increased responsiveness of central pain transmission (ascending dorsal horn pathways)

Simpson Pain 2018

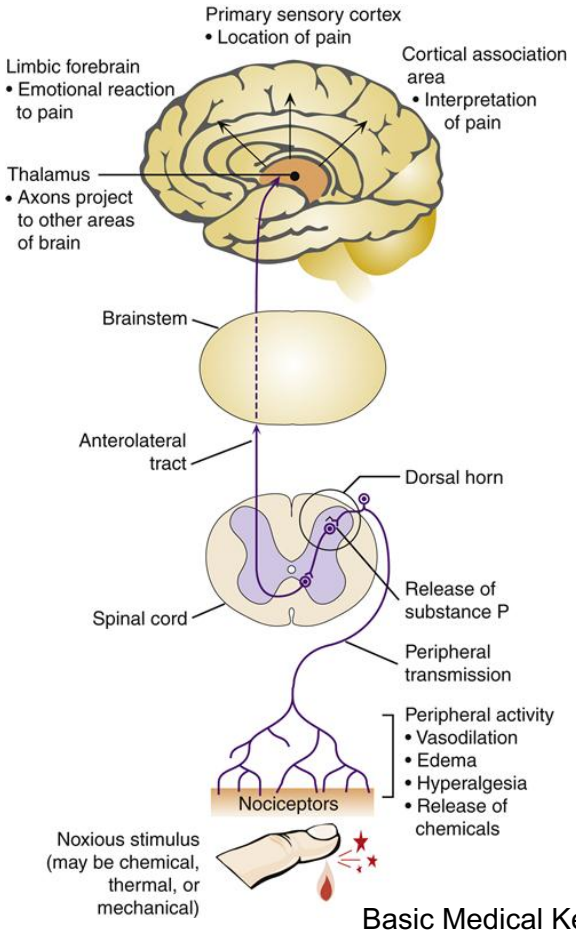
Fragmented or Insufficient Sleep = PAIN

- One night of sleep loss can reduce pain thresholds (and Vice Versa)
- Extended periods of insufficient sleep requires extended recovery periods to normalize

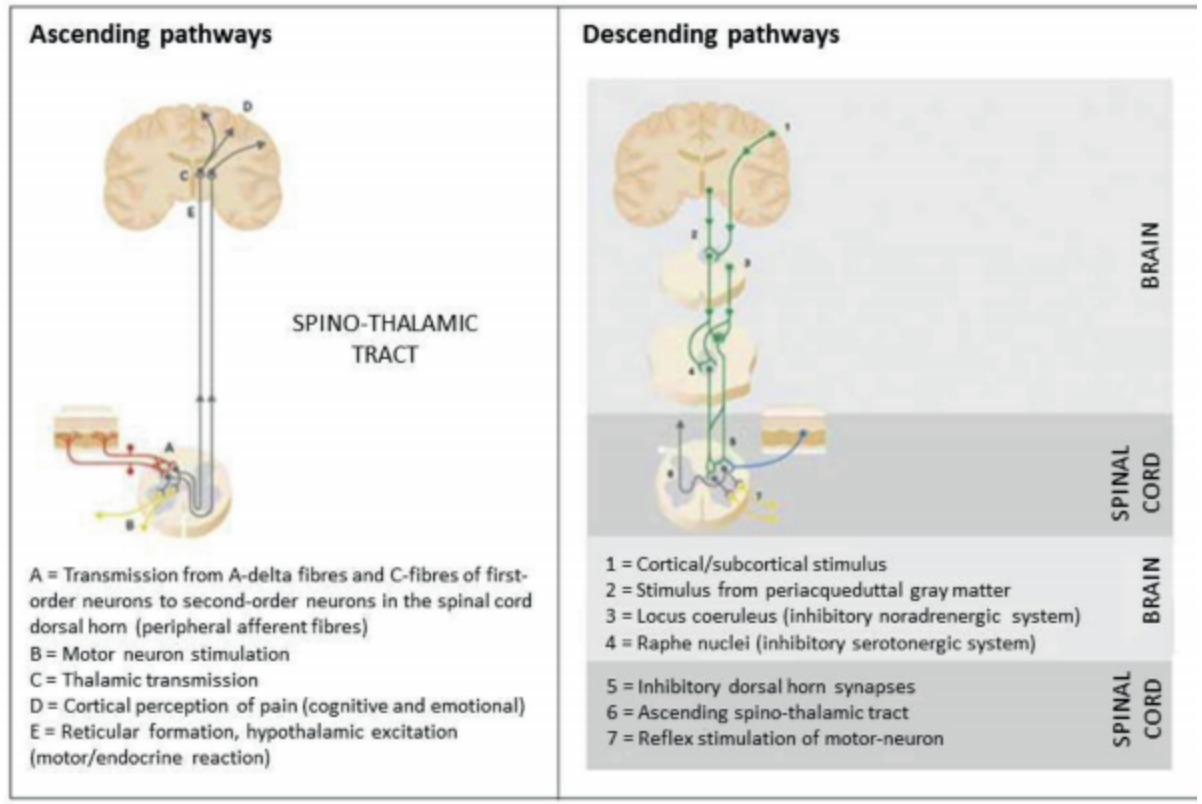
- TMJ, back pain, fibromyalgia, generalized pain, headaches, abdominal pain more commonly studied

Simpson Pain 2018

Pain Transmission



Basic Medical Key



Coluzzi et al. Eur Rev Med Pharmacol sci 2017

Pain Transmission:
by Dr. Pomeranz

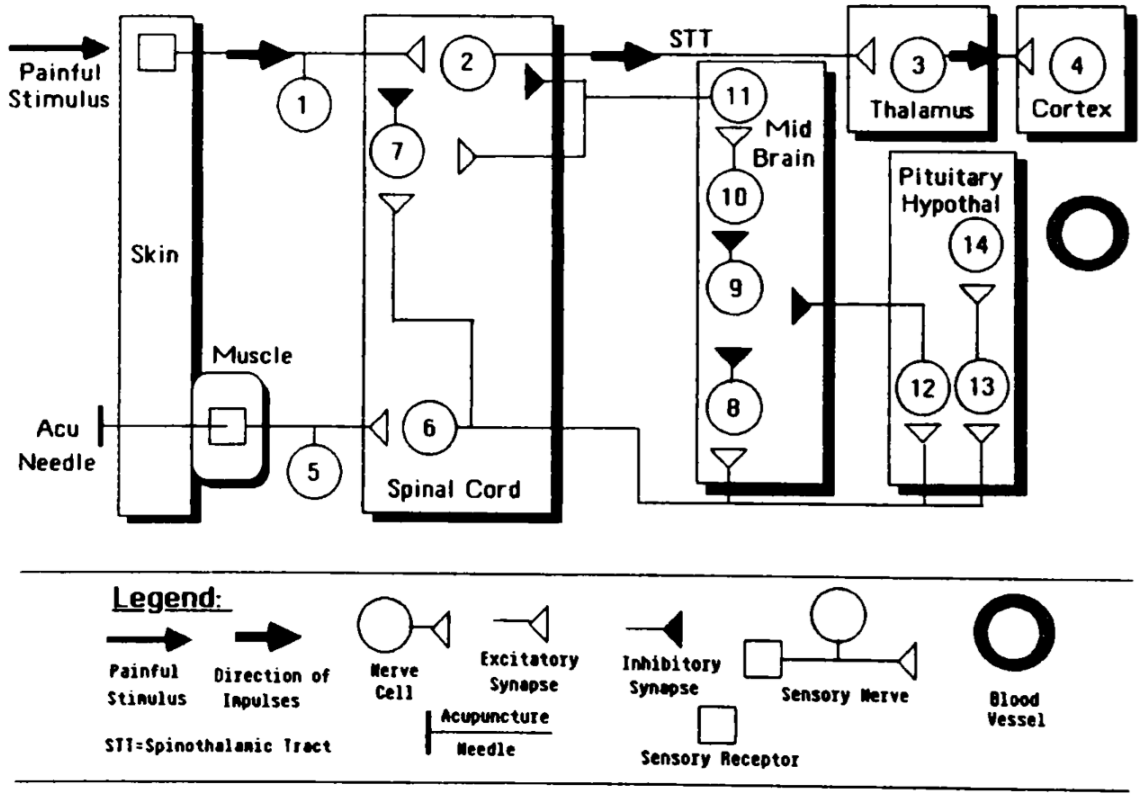
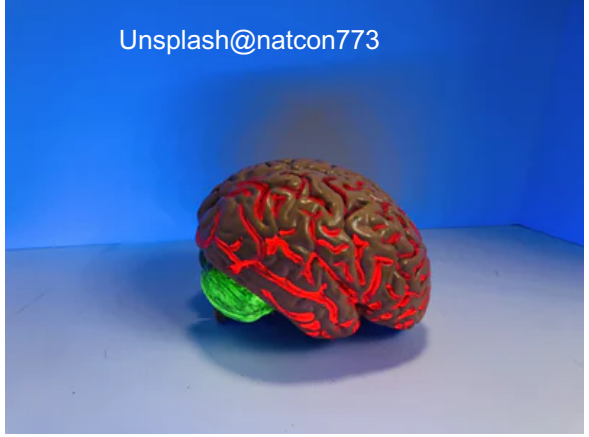


FIG. 1. Pain transmission circuit: A painful stimulus (e.g., chronic arthritic pain) activates cell 1, which sends messages along sensory nerve fibers to the spinal cord to excite cell 2. Cell 2 sends messages via the spinothalamic tract (STT) to the thalamus to excite cell 3, which in turn goes to the cerebral cortex and cell 4. The arrows indicate the flow of noxious information from cell 1 to cell 4. Open triangles are excitatory nerve terminals; filled triangles are inhibitory nerve terminals.

CAMEO study



- **Prospective longitudinal studies in adults**
  - Poor sleep quality/sleep disturbances predicts the exacerbation of migraine or the onset of migraine
- **Studied 11,699 Episodic Migraineurs vs. 1,111 Chronic Migraineurs:**
  - Chronic migraineurs more likely to report poor sleep quality than those with episodic migraines
    - sleep disturbance: CM: Mean 53.2 (SD27) vs. EM: 37.9 (SD24.3)
  - 37% were at high risk for sleep apnea: 52% Chronic, 36% Episodic
    - Particularly those with higher body mass index, men (44.4% vs. 35% of women), and older individuals

Sleep Apnea Association with Migraine

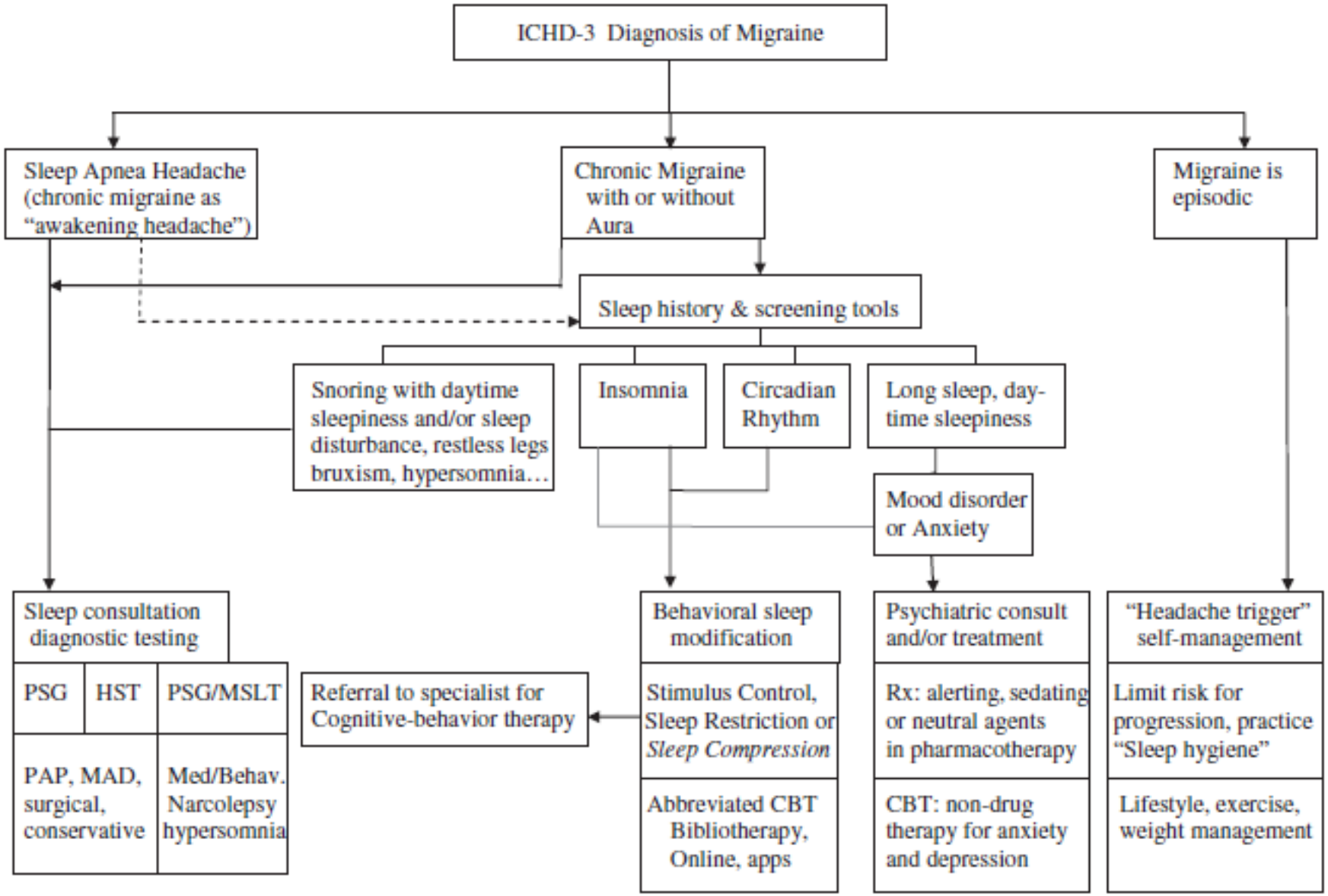
- Ages to 20-44 year olds
  - increased association of sleep apnea with migraine in population cohort study (aHR: 2.71 for men, 2.29 for women)

Harnod T et al. Medicine 2015

Sleep Apnea Headache

1. **HA present upon awakening after sleep**
2. **Sleep apnea diagnosed**
3. **One of the following:**
    1. Recurs on >15 days/mo
    2. Bilateral, Pressure, No nausea, no light/noise sensitivity
    3. Resolves within 4 hrs
4. **Two of the following:**
    1. HA temporally related to worsening sleep apnea
    2. HA improves with improvement of sleep apnea

Photo by Unsplash @Yuris - Yuris Alhumady



Rains 2018, Headache

Adolescent Studies

- 69 adolescents with primary HA disorders (90% migraine, 10% Tension-Type) evaluated for sleep complaints with School Sleep Habits Q
  - 65.7% with insufficient total sleep
  - 23.3% with daytime sleepiness
  - 41% with difficulty falling asleep
  - 38% with night awakenings

Gilman DK et al. Headache 2007

Adolescent Studies

- HA intensity and duration
  - associated with longer sleep onset delay
  - sleep problem behaviors
- HA intensity
  - associated with nightmares
  - staying up all night
  - difficulty with early morning awakenings

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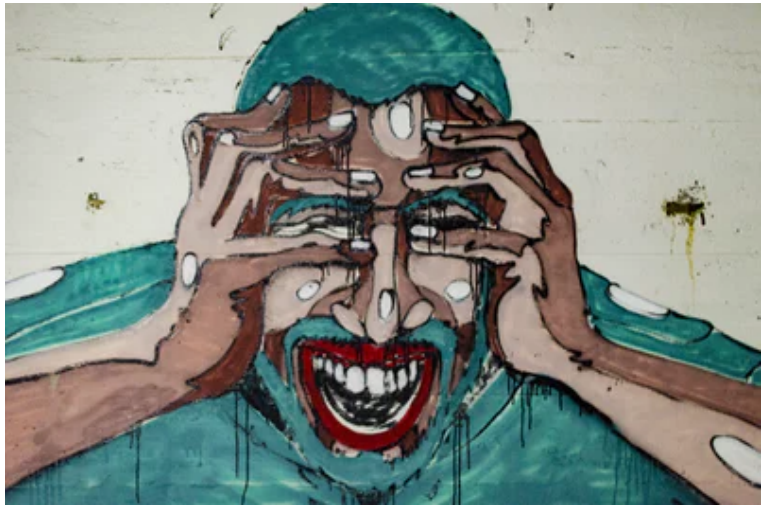

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Later School Start Date

- 256 high schoolers (115 starting at 8:30 am or later, 141 starting earlier than 8:30 am)
- Late: 7 (5) HA days/month vs. 8 (7) HA days/month not significant
- Median total hrs of sleep was 5.6 hrs for both groups
- High school start time did not have a large effect on HA frequency in high school students starting later.

Gelfand et al. Headache 2019

Narcolepsy and Migraine

- Increased prevalence of migraine in narcoleptic patients: 44% of women and 23% of men with migraine have narcolepsy
  - Study sample of 100 patients with migraine – Stanford Centre for Narcolepsy Sleep Inventory
  - Migraine prevalence two to fourfold increase in narcolepsy patients
  - Narcolepsy symptoms identified 12+/- 11.4 yrs years prior to onset of migraine symptoms

Dahmen N et al. Cephalagia 2003

Chronic pain and Sleep Impairment

- Pediatric pain prevalence: 11-38%
- Sleep problems in childhood increase risk of developing pain 2-3 years later
- Mental health symptoms partially mediate sleep and chronic pain

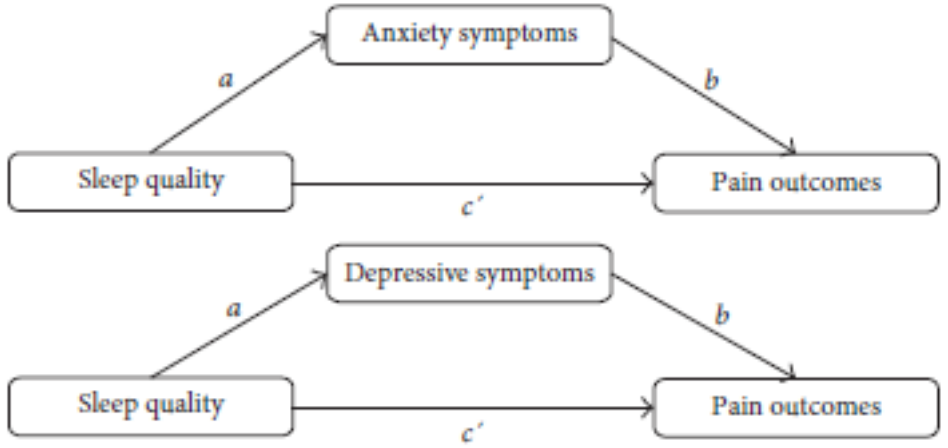


FIGURE 1: Proposed mediation models.

King S et al. Pain 2011
Pavlova M et al. Pain Res Mangmt 2017

Most Common Co-morbidities in Relationship to Migraines

- **Depression is 2.2 to 4.0 fold to be more likely in patients with migraine compared to general population**
  - Martin PR et al. Behav Res Ther. 2015
- **Prevalence of depression is 6.9% for individuals with migraine**
  - Lampl C et al. J Headache Pain 2016
- **In adolescents/young adults, major depressive disorder and generalized anxiety disorder higher prevalence in those with migraine versus those without (55% vs. 22%, p<.0001)**
  - Dindo LN et al. Int J Behav Med. 2017
- **Anxiety present in 6.1% in individuals without headache versus 19.1% in individuals with migraine**
  - Lampl et al. J Headache Pain 2016
- **Odds ratio of 3.5-5.3 for generalized anxiety disorder in migraine**
  - Hamelsky, Lipton. Headache 2006

Preventive Supplements/Medications Affecting Sleep

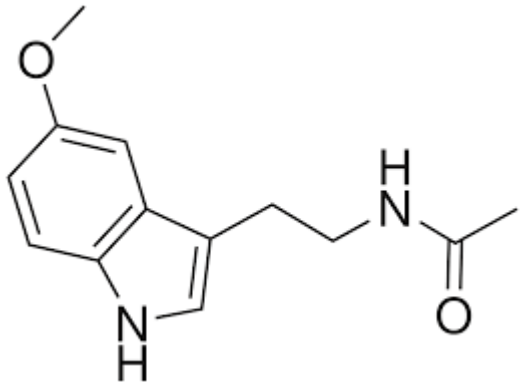
Topiramate	Amitriptyline	Gabapentin	Melatonin	Tizanidine
• Reports of daytime sleepiness • somnambulism	• Decreased sleep latency • Daytime somnolence (Liu) • Periodic limb movements (Goerke)	• Increased slow wave sleep • Increased REM • Reduced nighttime awakenings • Greater sleep duration (Jain 2014)	• Reduced sleep onset latency • Nocturnal enuresis • Daytime sleepiness • Intense Dreams	• Side effect: Sedation

Liu et al. Sleep Med 2017
Goerke et al. Pharmopsych. 2013
Jain SV Epilepsia 2014

Preventives and Sleep Abnormalities

CoQ10 (Ubiquinol)	Beta Blockers: propranolol	CGRP Antagonists
• Reports of delayed sleep onset • Increased energy	• Suppression of nighttime melatonin • Sleep Disturbance • Reports of somnambulism	• Fatigue • Particularly those predisposed to autoimmune disease

Melatonin



- Melatonin may affect migraine pathways
  - Anti-inflammatory
  - Shares similar structure to indomethacin (indole)
  - Membrane stabilizer
  - Inhibits dopamine release (but may increase RLS symptoms)
  - Antagonizes glutamate
  - Suppress CGRP release (known vasodilatory inflammatory substance involved in migraine pain)

Long R et al. Medicine 2018

Melatonin

Melatonin Biomarker study in children

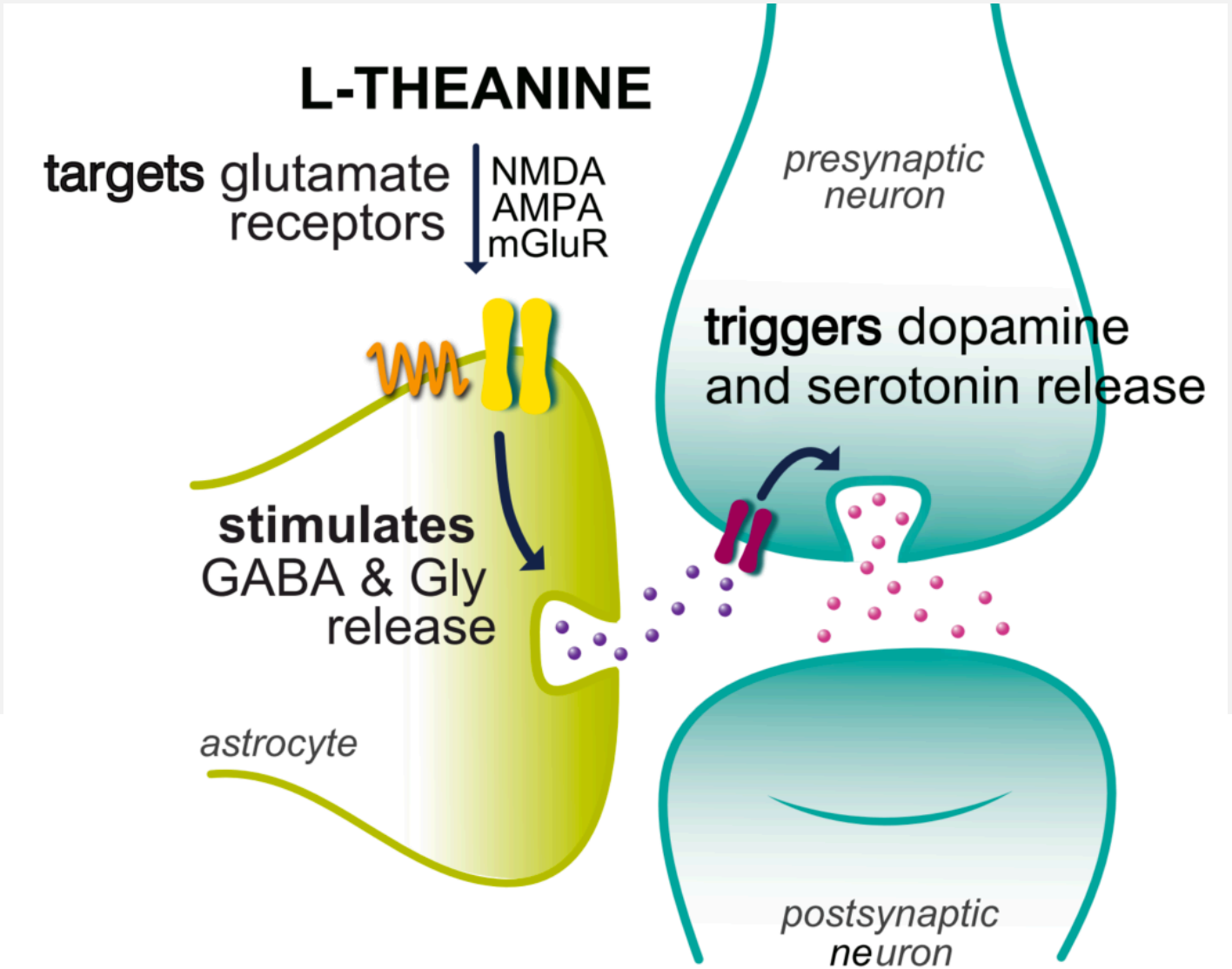
- 21 children, 5-17 yo
- Melatonin metabolite 6-sulfatoxymelatonin (aMT6s) in urine was assayed and results from nights preceding migraine were compared to nights preceding a non-headache day
- Mean aMT6s levels lower the night before for individuals with premonitory symptoms of noise sensitivity, nausea, and irritability
- Melatonin biomarker did not predict a migraine attack

Berger et al. Headache 2019

Melatonin

- Migraine prophylaxis (Takes 8-12 weeks to take effect)
- Melatonin 3 mg-10 mg nightly
- RCT's: possibly more effective than amitriptyline, same efficacy as valproic acid, better than placebo

Long R et al. Medicine 2018



GABA, L-theanine Supplements

Decreased sleep latency and prolonged sleep duration in mice studies

Kim Pharm Biol 2019

Diet Sleep and Headaches

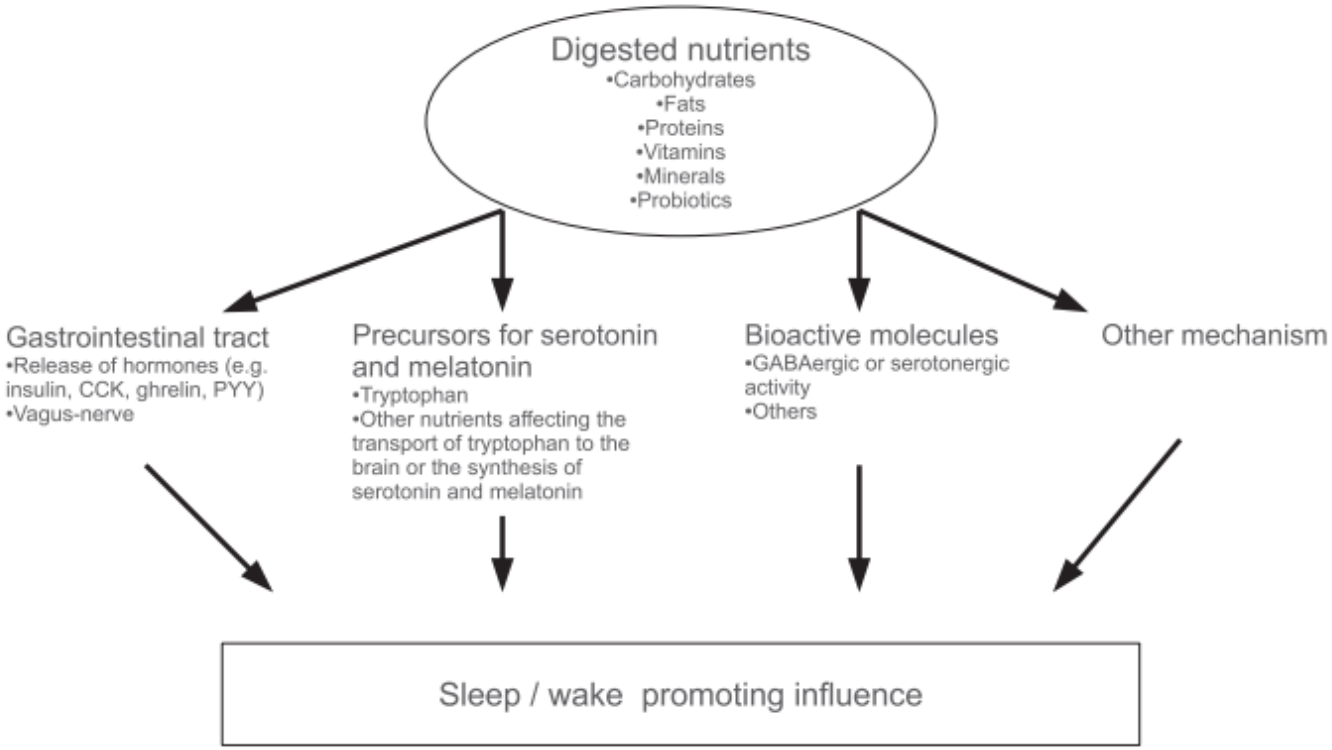
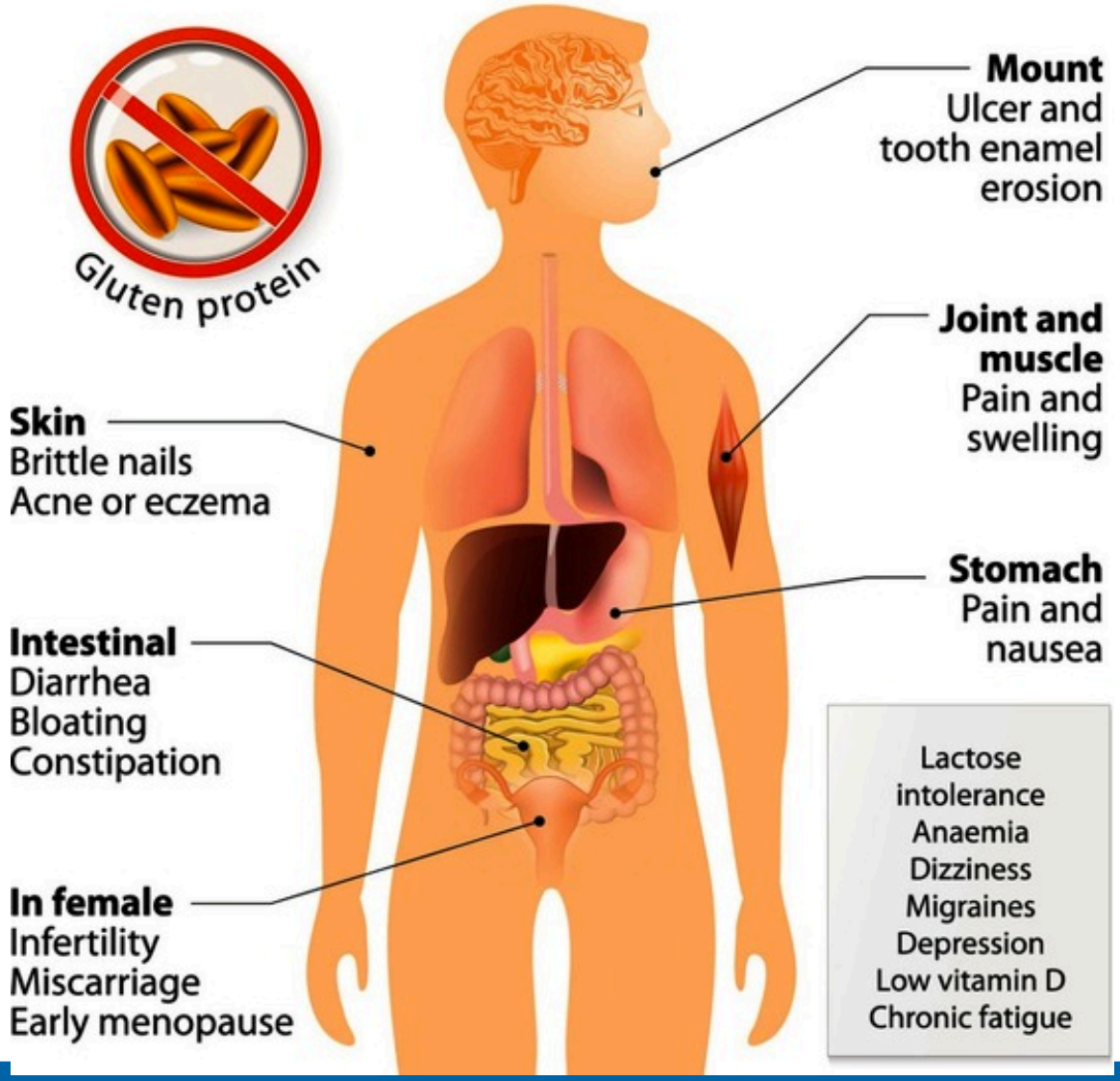


Fig. 1 – Dietary factors promote sleep via circulating intestinal hormones, by stimulating the synthesis of serotonin and melatonin, acting on GABAergic or serotonergic neurons or via other unidentified mechanisms.

Peuhkuri et al. Nutrition Research 2012

Celiac disease: headaches/sleep

- Sleep disorders common in both celiac disease and headache disorders



Iron and Headaches

- Ferritin, Iron Panel, CBC
- Ferritin: 50-70 optimal level
- Low iron/ferritin associated with morning headaches, poor sleep, restless leg/periodic limb movements

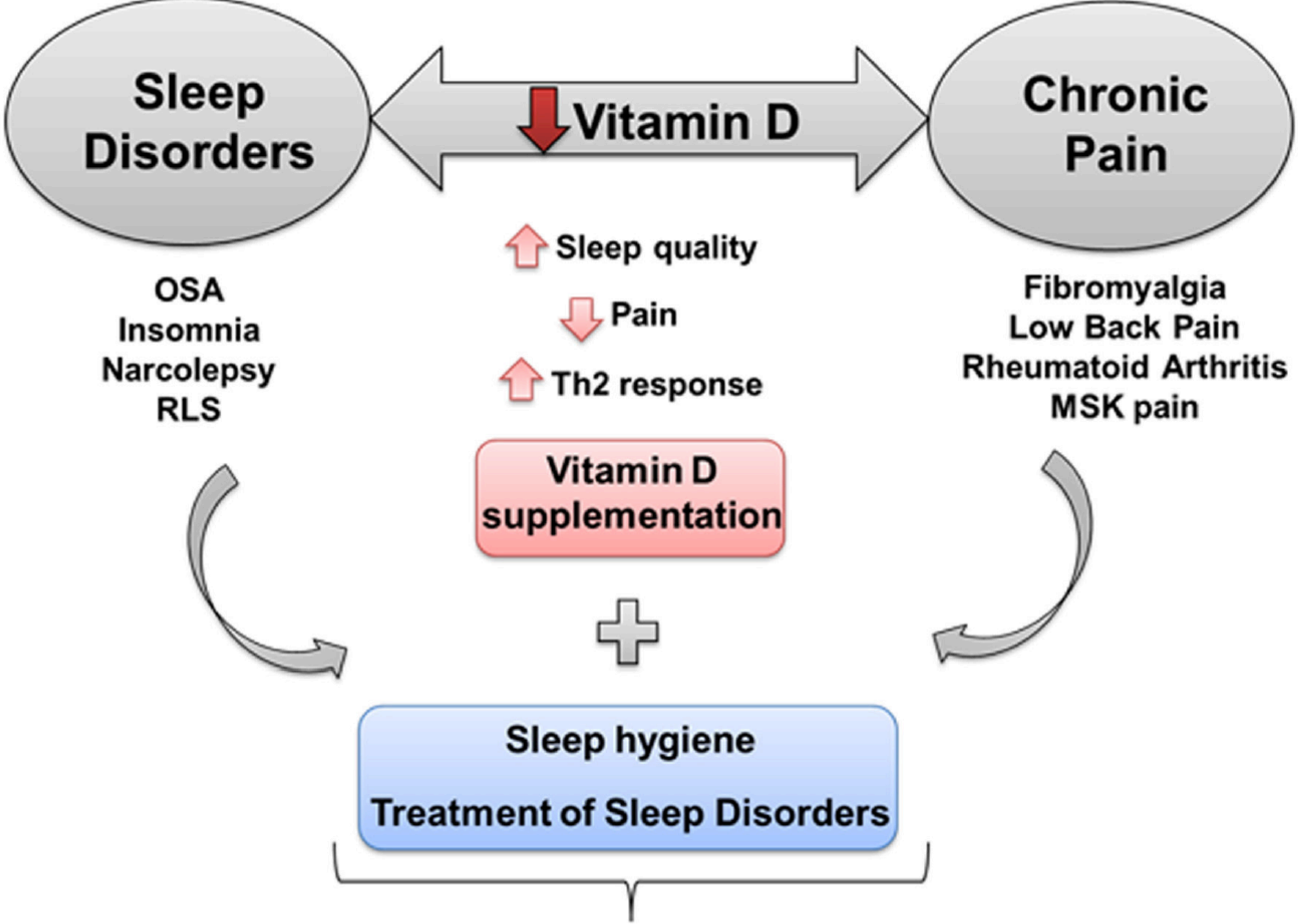
Treatment: 2-6 mg/kg/day

- Start slow and low (18-65 mg elemental iron per day with Vitamin C, most can't tolerate on empty stomach)
  - May have to buy OTC or ask pharmacy for lower elemental iron formulation
  - increase every week until 2 mg-6 mg/kg/day
  - repeat ferritin/iron panel in 3 months

Vitamin D Sleep and Pain

- Vitamin D insufficiency related to lower pain thresholds
- Vitamin D supplementation decreases pediatric migraine frequency
- Vitamin D lower in RLS, insomnia

Oliveira J Endocrinology 2017


Sleep Disorders
Vitamin D
Chronic Pain
Sleep quality
Pain
Th2 response
OSA
Insomnia
Narcolepsy
RLS
Fibromyalgia
Low Back Pain
Rheumatoid Arthritis
MSK pain
Vitamin D supplementation
Sleep hygiene
Treatment of Sleep Disorders

Acupuncture for Headaches and Sleep

- Acupuncture
  - Beneficial for prevention of migraines and tension-type headaches in two Cochrane reviews
  - Possible benefit for insomnia comparing acupuncture to sham acupuncture
    - 30 studies, 2363 participants MD –0.79, 95% CI-1.38, -0.19, I(2)=49% in Pittsburgh Sleep Quality Index
  - Acupuncture compared to benzodiazepine receptor agonists
    - MD -2.76, 9%CI -3.67, -1.85, I(2)=94% in PSQI

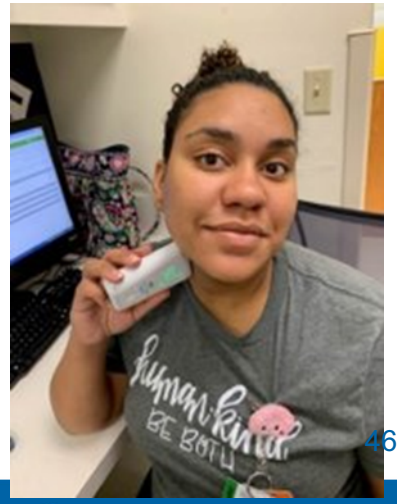
1. Linde K, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev. 2016 Jun 28
2. Linde K et al. , Acupuncture for the prevention of tension-type headache. Cochrane Database Syst Rev. 2016 Apr 19
3. Shergis JL et al. Complement Ther Med. 2016

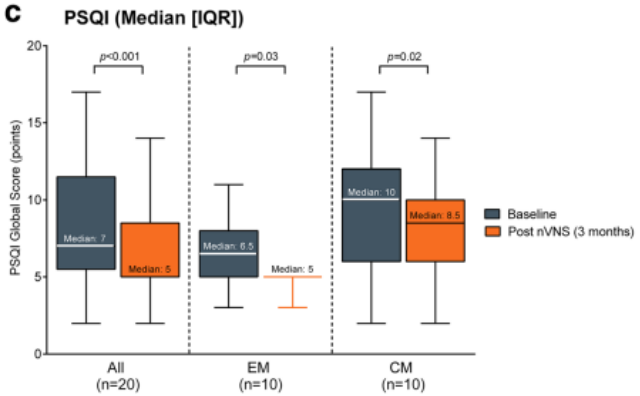
Acupuncture

- Six weekly sessions in CMH Headache Relief Clinics

Neuromodulation and Sleep

- **Cefaly®**
  - Transcutaneous supraorbital (trigeminal nerve) stimulator
  - Sedation is a side-effect
- **Gammacore™**
  - non-invasive vagus nerve stimulator
  - Open-label, prospective study:
  - 20 adult patients with episodic (10) or chronic migraine (10)
  - two two-minute sessions twice daily for 3 months
  - Significant improvements in the Pittsburgh Sleep Quality Index



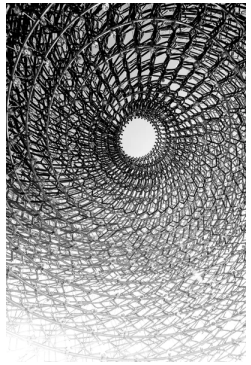


LOVE WILL.

Knife TM et al. J Head Pain. 2015

Children's Mercy

Clinical Hypnosis



- Not “Mind Tricks”
- A self-regulation strategy using self-directed suggestions to facilitate the mind-body connection, ultimately cultivating a sense of awareness and positive well-being
- Likely beneficial for headaches based on retrospective and prospective randomized study
- Systematic review for insomnia – evidence limited but promising results

Jong MC et al. Eur J Pediatr 2019
Kohen DP. Am J Clin Hyp 2011
Kohen DP, Zajac R. J Pediatr. 2007
Chamine I et al. J Clin Sleep Med. 2018

Aromatherapy for Sleep and Headaches

- Headaches:
  - Lavender aromatherapy 47 patients (cases/controls) x 15 min decreased headache severity on VAS pain scale from 3.6±2.8 to 1.6±1.6 (p<.0001) compared to control group (liquid paraffin)
- Sleep:
  - Meta-analysis of 12 studies
    - Aromatherapy improved sleep quality (effect size (Z)=3.716, 95% confidence interval [CI], 0.540-1.745; p<.001), inhalation aromatherapy (Z=6.107, 95% CI, 0.792-1.541; p<.001) better than massage therapy (Z=2.205, 95% CI, 0.128-2.166; p<.027)

EFFECTS OF AROMATHERAPY ON SLEEP IMPROVEMENT 65

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kim(2009)	6.155	0.565	0.319	5.049	7.261	10.903	0.000
Kim, Kim & Park(2007)	0.684	0.291	0.085	0.114	1.255	2.352	0.019
Park et al.(2010)	1.269	0.330	0.109	0.621	1.916	3.839	0.000
Park et al.(2012)	1.344	0.286	0.082	0.783	1.904	4.701	0.000
Seo & Chang(2009)	0.927	0.281	0.079	0.376	1.479	3.294	0.001
Yang, Kang, & Kim(2011)	0.549	0.259	0.067	0.042	1.056	2.121	0.034
Won & Chae(2011)	-0.563	0.315	0.099	-1.180	0.053	-1.790	0.073
Lee(2008)	1.185	0.317	0.100	0.564	1.806	3.739	0.000
Lee & Hwang(2011)	0.874	0.256	0.065	0.373	1.376	3.419	0.001
Lee, Lee, & Kim(2011)	0.324	0.248	0.061	-0.162	0.810	1.308	0.191
Jung & Jeon(2004)	0.000	0.329	0.108	-0.645	0.645	0.000	1.000
Choi & Lee(2012)	1.847	0.360	0.130	1.141	2.552	5.128	0.000
	1.142	0.307	0.094	0.540	1.745	3.716	0.000

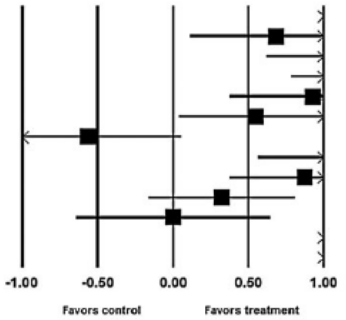


FIG. 2. Effect size of aromatherapy related to sleep. Subgroup inhalation: heterogeneity: $tau^2=0.09$, $Q=8.04$, $df=4$ ($p=0.090$), $I^2=50.23\%$. CI, confidence interval; df, degree of freedom.

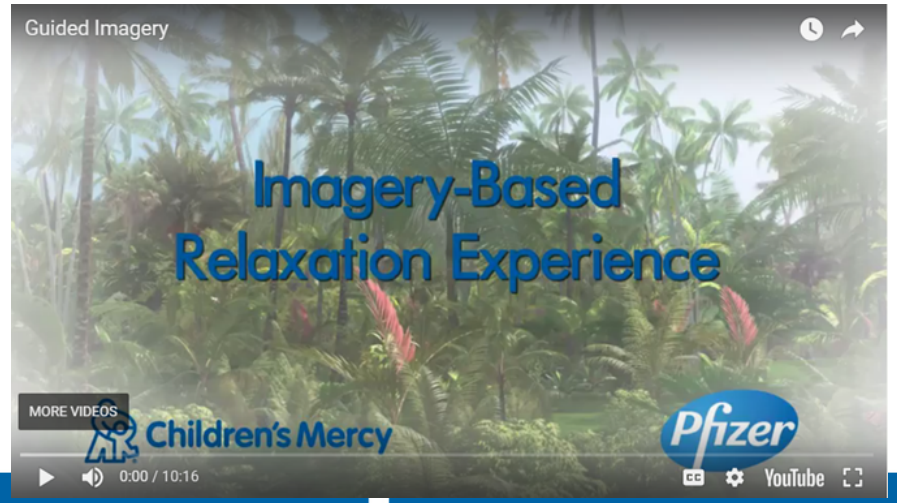
Sasannejad et al. Eur Neurol 2012
Hwang E, Shin S. J Altern Complement Med 2015

Biofeedback

- Biofeedback reduces pediatric migraine frequency compared to waiting-list control participants (MD – 1.97, 95% CI – 2.72, -1.21, p<.00001)
- Biofeedback for chronic insomnia – unclear, need more studies

Stubberud A et al. Pediatrics 2016
Melo DLM et al. Appl Psychophysiol Biofeedback 2019

Active Relaxation: WWW.HeadacheReliefGuide.Com

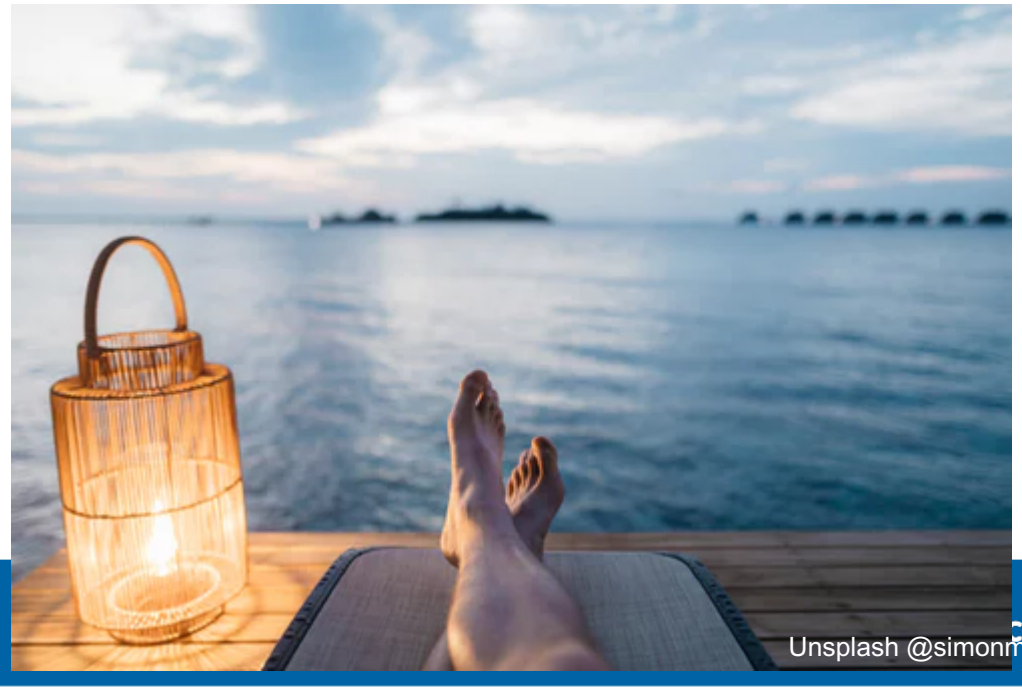


Mannix LK et al. Headache 1999

Meyer B et al. J Headache Pain. 2016

Active Relaxation and Sleep

- Mindfulness Meditation may mildly improve sleep
  - Meta-analysis of 6 RCTs: 330 participants, improved total wake time and sleep quality, sleep onset latency, sleep efficiency
  - Improvements in PSQI noted (absolute value of SMD range: 0.44-1.09, all $p<0.05$)



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Gong H et al. J Psychosom Res 2016

Healthy Sleep Hyginne Recommendations.

Healthy Sleep Hygiene 'Top Ten' Recommendations (*source: UCSD Center for Pulmonary and Sleep Medicine patient information handout*)[66]
1. Don't go to bed until you are sleepy. If you aren't sleepy, get out of bed and do something else until you become sleepy.
2. Regular bedtime routines/rituals help you relax and prepare your body for bed (reading, warm bath, etc.).
3. Try to get up at the same time every morning (including weekends and holidays).
4. Try to get a full night's sleep every night, and avoid naps during day if possible (if you must nap, limit to 1 h and avoid nap after 3 p.m.).
5. Use the bed for sleep and intimacy only; not for any other activities such as TV, computer or phone use, etc.
6. Avoid caffeine if possible (if must use caffeine, avoid after lunch).
7. Avoid alcohol if possible (if must use alcohol, avoid right before bed).
8. Do not smoke cigarettes or use nicotine, ever.
9. Consider avoiding high-intensity exercise right before bed (extremely intense exercise may raise cortisol, which impairs sleep).
10. Make sure bedroom is quiet, as dark as possible, and a little on the cool side rather than warm (similar to a cave).

Top Two Sleep Hygiene Recommendations

1. ROUTINE
2. Keep it Cool!

Summary and Key Points

- Headache management is multi-modal, comprehensive, and integrative (collaborative/interprofessional)
- Sleep dysfunction contributes to chronification/refractory headaches
- Early intervention is key with preventive, abortive, lifestyle, integrative management
- Disability is high in people living with migraine
  - Keep kids in school, teach them functioning despite living with pain