The Latest in Sleep Medicine Research

Al Heuer, PhD, MBA, RRT-ACCS, RPFT, FAARC
Professor, Rutgers-SHP
Co-Owner A & T Lectures

Learning Objectives

- Review the ***Importance*** of Research in sleep medicine
- Summarize ***Key Concepts in medical research***
- Describe Strategies for ***Searching the literature.***
- Identify some more ***Recent research*** which has helped shape sleep medicine.
  - Physiology
  - Diagnostics
  - Treatment
  - Adherence
  - Cost Effectiveness
- Describe where more work needs to be done.
- Provide ***additional resources***.

Importance of Research to Sleep Medicine

- Directs how/why we practice in sleep medicine
- Helps ensure ***safe(er) and effective*** practice
- Helps build a **foundation** for future practice
- Evaluating basic scientific reports is a ***core competency*** for:
  - *Clinicians*:
  - *Educators*:
  - *Administrators*:
- Without research and the ability to assess the literature, **stagnation occurs**.

What is Research?

Investigation or experimentation aimed at the ***discovery and interpretation*** of facts, ***revision or confirmation of accepted theories***, or practical ***application of such new or revised theories*** or laws…

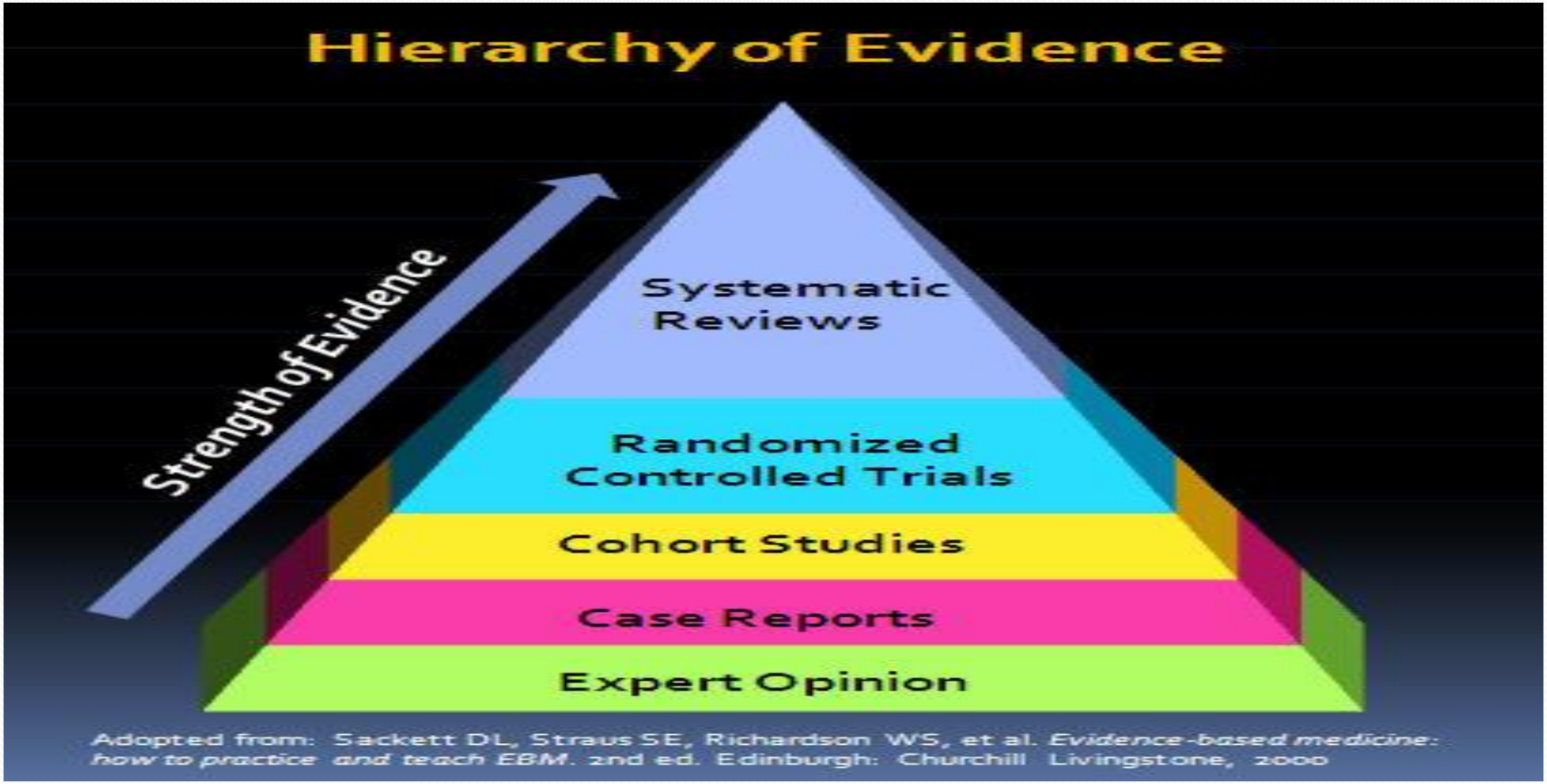
Key Terminology

- **Hypothesis:** The statement(s) being tested.
- **Subjects/Participants**: Individuals being studied.
- **Intervention:** A clinical maneuver applied to participants.
- **Blinding (Single/Double):** Hiding if subjects are receiving the intervention or the placebo.
- **Control Group** (Traditional treatment) versus **Experimental Group** (intervention being tested).
- **P-Value:** the likelihood that a particular finding is due to chance. P=0.05 (5%) or less

Types of Quantitative Research

- **Systematic Review & Meta Analysis**—Combining the results of many (well done, often RCT's) studies.
- **Randomized Controlled Trials (RCT)**:
  - Use of a control and experiential group or arm
  - Blinding - Neither researcher nor subject knows if they are getting the placebo (e.g., sugar pill) or the real intervention
  - Power analysis.
- **Cohort Studies:** Following a population over many years.
- **Case Control, Case Series and Case Studies**
  - Case Study= Detailed Analysis of a single subject with the disease or condition
  - Case Series= An analysis of several subjects with the disease or condition
  - Case Control = Comparing subjects who have that condition/disease (the "cases") with patients who do not have the condition/disease but are otherwise similar (the "controls"
- **Expert Opinion**

Research (Quantitative) Design Hierarchy



The Gold Standard – Randomized Controlled trials (RCT)

- ***Randomized:*** Subjects are allocated to receive or not receive one or several clinical interventions.
  - ***Flip a coin*** to determine where subjects are allocated.
- ***Controlled:*** Compares experiential group/arm to control group/arm.
- ***Blinded:*** Nether the ***researcher nor the subject*** know whether they are getting the drug or the placebo.
  - INO Example
- ***Adequately Powered:*** Enough subjects to demonstrate an effect, or lack thereof from the intervention.
  - Power calculation can/should be done in advance (a-priori) to determine the number of subjects needed.

Recent Research in Sleep Medicine

Physiology

Diagnostics

Treatment

Adherence

Cost Considerations

Physiology: Kitamaura, et al., (2021)

- **Aim:** To assess the relationship between body composition and objective sleep parameters in male and female athletes.
- **Methods:** The body composition of 17 male and 19 female collegiate athletes were measured, and they underwent overnight home sleep monitoring.
- **Results:**
  - Male athletes studied had more muscle mass and less fat mass.
  - However, male athletes had lower sleep efficiency, longer sleep onset latency, higher arousal index, less rapid eye movement (REM) sleep, and lower percentage of slow-wave (N3) sleep in the initial non-REM sleep.
- **Conclusion: Compared to female athletes, male athletes with greater muscle volume appear to have inferior objective sleep quality,** thus implying that sleep architecture may be related to the muscle volume.

Physiology -- Meltzer, et al (2020)

- **Aim:** To examine the impact of sleep duration on asthma in adolescents.
- **Methods:**
  - 54 adolescents with asthma (12-17 years) in a randomized study, including five nights of a "Short" sleep opportunity (time in bed: 6.5 h/night), and five nights of a "Long" sleep opportunity (time in bed: 9.5 h/night).
  - Primary outcomes were:
    - Lung function (daily peak expiratory flow rate, weekly spirometry)
    - Functional asthma outcomes (daily asthma symptoms, Asthma Control Questionnaire, PROMIS Asthma Impact Scale).
    - Markers of inflammation were also explored.
- **Results:** The short sleep group had worse morning FEV1 ($p = 0.006$),and worse symptoms; albuterol use was higher ($p < 0.05$), and asthma showed a trend towards greater negative impact on daily life ($p = 0.07$).
- **Conclusions:** ***An insufficient sleep opportunity negatively impacts objective and subjective daily symptoms of asthma in adolescents***, as well as health related quality of life. As most adolescents are significantly sleep deprived, it is important to target sleep health in the treatment of asthma.

Physiology -- Combertaldi, et al, (2021)

- **Aim:** To explore the impact of social media use on sleep disturbance in adolescents.
- **Methods:** We tested the effects of 30 min social media use on arousal and subsequent sleep in the sleep laboratory in 32 healthy young volunteers.
- **Results:** Thirty minutes of social media use immediately before sleep did not significantly increase arousal and did neither disturb objective nor subjective sleep. After social media use, participants only spent less time in sleep stage N2.
- **Conclusion:**
  - ***Social media use before sleep (controlling for effects of blue-light) had little effect on bedtime arousal and sleep quality than what was previously expected***.
  - The most notable effect appears to be the additional time spent engaging in social media use at bedtime, potentially keeping people from going to sleep.

Diagnostics -- de Goederen, et al., (2021)

- **Aim:** Unobtrusive monitoring of sleep and sleep disorders in children presents challenges. We investigated the possibility of using Ultra-Wide band (UWB) radar to measure sleep in children.
- **Methods:** Thirty-two children age 2 months to 14 years . scheduled to undergo a clinical polysomnography participated; During the polysomnography, the children's body movements and breathing rate were measured by an UWB-radar.
- **Results & Conclusion:** ***Although the current performance is not sufficient for clinical use yet, UWB radar is a promising method for non-contact sleep analysis in children***

Diagnostics -- Torstensen, et al (2021)

- **Aim:**
  - To evaluate:
    - 1) the ability of actigraphy to quantify sleep continuity measures in comparison with polysomnography in patients with hypersomnolence;
    - 2) whether actigraphy can distinguish patients with hypersomnolence, from patients with narcolepsy type 1 and from sleep-healthy controls.
    - ***Actigraphy*** is a type of wearable sleep test that tracks your movements to analyze when you are asleep and when you are awake.
- **Method:** Polysomnography, multiple sleep latency tests and actigraphy were conducted in 14 patients with narcolepsy type 1, 29 patients with hypersomnolence and 15 sleep-healthy controls.
- **Results:**
  - Actigraphy quantified several sleep continuity measures consistently with polysomnography in all the patients.
  - Actigraphy distinguished patients with hypersomnolence with from patients with narcolepsy type 1 and sleep-healthy controls.
- **Conclusion: Actigraphy is an adequate tool for establishing the amount of night sleep and supports the differential diagnosis of patients with hypersomnolence.**

Treatment: Complementary & Alternative -- Chen, et al (2021)

- **Aim:** To conduct a systematic review and meta-analysis of the effect of listening to music on sleep quality in older adults.
- **Design:** Systematic review and meta-analyses.
- **Measurements:** The primary sleep outcome was the Pittsburgh sleep quality index.
- **Results:** Five randomized control trials were included. Older adults who listened to music experienced significantly better sleep quality than those who did not listen to music.
- **Conclusions:** ***Music therapy is safe and easy to administer and can effectively improve sleep quality among older adults, particularly those listening to more sedative music.***

Treatment: Complementary & Alternative -- Cândido Dos Reis, et al., (2021)

- **Aim:** To evaluate the effectiveness of Auricular acupuncture (AA) in reducing the symptoms of sleep disorders and anxiety .
- **Design:** This was a nonrandomized clinical trial in which AA was administered to patients who had one of three sleep disorders.
- **Results:**
  - Reduction in sleep disorder symptoms was confirmed.
  - There was also a reduction in mean anxiety score symptoms.
- **Conclusion:** ***AA was effective in reducing sleep disorder symptoms and our data suggests some relief of symptoms of anxiety.***

Treatment: Complementary & Alternative -- Ong (2020)

- **Background & Aim:** There is a substantial body of evidence on the use of mindfulness-based (meditation) interventions (MBIs) for insomnia and sleep disturbances. There are now several randomized controlled trials now published.
- **Design:** Systematic literature review
- **Results/Conclusion:**
  - Collectively, there is a general support for the effectiveness of MBIs on self-reported patient outcomes.
  - The quality of studies varies and the findings on objective measures are equivocal.
  - ***Further research is needed to examine biological correlates associated with mindfulness practice, whether the timing of meditation practice is related to sleep outcomes, who is likely to succeed with MBI.***

Treatment: Nutrition -- Zhao, et al., (2020)

- Aim: To explore the role of nutritional supplements in enhancing sleep quality
- Methods: Systematic review of the literature
- Results/Conclusion(S):
  - Nutrition can profoundly affect the hormones and inflammation status which directly or indirectly contribute to insomnia.
  - Specific examples include:
    - Ensure ***adequate Vitamin D*** - Is often deficient in people with OSA--2-5,000 IU's per day
    - Increase ***magnesium*** intake--100-200 mg before going to sleep.
    - Try ***5HTP***- is a precursor to the hormone serotonin
    - ***Chamomile Tea-***One of the simplest natural home remedies for sleep apnea is a cup of chamomile tea before you go to sleep. The substances found in chamomile are believed to help the nerves relax, which makes it easier for us to sleep.
    - ***Almonds***-Among the best natural home remedies for sleep apnea, we need to mention almond. This small ingredient can supple the body with a high amount of magnesium that enables the muscles to relax more.
    - ***Turmeric***-With anti-inflammatory quality, turmeric is claimed to fight against the inflammation that can take place in your respiratory system. This will reduce the times you stop breathing at night. When mixing it with warm milk, you have one of the best natural home remedies for sleep apnea.

Treatment: Jun, et al, (2021)

- **Aim:** To synthesize and ***evaluate current non-pharmacological sleep interventions for critically ill adult patients in intensive care units*** and provide recommendations for future studies in this area.
- **Methods:** A systematic literature published from 2012-2020.
- **Results:**
  - Interventions involved use of **earplugs, an eye mask, white noise, music, aromatherapy, massage, acupressure, light intensity, a sleep hygiene protocol, quiet time and minimization of nursing care.**
  - Non-pharmacological interventions improved sleep quality.
- **Conclusions: Non-pharmacological sleep interventions can have a positive influence on sleep quality in critically ill patients, but more research is needed to determine their effectiveness.**

Treatment: Medications: Wichniak, et al., (2021)

- **Aim:** ***The aim of this article is to compare the effect of hypnotics and the anti-depressant, trazodone on sleep.***
- **Methods**: Systematic Review which included 11 studies.
- **Results:** Trazodone is very effective in the treatment of sleep-maintenance insomnia, especially in patients with comorbid mental disorders or treated with activating antidepressants. Hypnotics and trazodone have the opposite effect on deep sleep.
- **Conclusion:** ***Trazodone increases the duration and quality of deep sleep. In contrast, hypnotics decrease slow-wave activity, a biomarker of deep sleep*****.**

Treatment--Upper Airways Stimulation for OSA

- Strollo, Soose, Maurer, et, al, NEJM, (2014)
  - **Method:** Multicenter, prospective, single-group, cohort design, surgically implanted an upper-airway stimulator in 126 patients with OSA apnea who did not tolerate CPAP therapy.
  - **Results/Conclusion**: In this uncontrolled cohort study, ***upper-airway stimulation led to significant improvements in objective (AHI scores) and subjective measurements.***
- Soose, Woodson, Gillespie, et al (2018)
  - **Method:** Prospective, multicenter, cohort study of patients with moderate to severe OSA .
  - **Results/Conclusion:** Patients with moderate to severe OSA and body mass index ≤ 32 kg/m2, hypoglossal cranial nerve stimulation therapy **can provide significant improvement in important sleep related quality-of-life outcome measures** and the effect is maintained across a 2-y follow-up period.

Upper Airways Stimulation for OSA

CPAP Adherence -- Rotenberg (2016)

- **Background:** CPAP however is known to have problems with adherence, with many patients eventually abandoning the device.
- **Aim:** To assess secular trends in CPAP adherence over the long term to see if there have been meaningful improvements in adherence in response to multiple interventions proposed to do so.
- **Methods:** A systematic literature review of literature.
- **Results: Based on the combined results of 82** papers over a 20 year period, ***the overall CPAP non-adherence rate based on a 7-h/night sleep time that was 34.1 %.*** There was no significant improvement over the 20 year time frame. Behavioral intervention improved adherence rates by ~1 h per night on average.
- **Conclusions:**
  - ***The rate of CPAP adherence remains persistently low over twenty years worth of reported data.***
  - ***No clinically significant improvement in CPAP adherence was seen even in recent years despite efforts toward behavioral intervention and patient coaching.***
  - ***This low rate of adherence is problematic, and calls into question the concept of CPAP as gold-standard of therapy for OSA.***

CPAP Adherence-Shapiro (2021)

- **Background**: Many factors contribute to continuous positive airway pressure (CPAP) nonadherence, affecting health care burden. The original CPAP-SAVER study enrolled 66 CPAP-naive participants and showed high 1-month adherence and significantly higher apnea beliefs and CPAP attitude for the intervention group.

- **Purpose and Methods:** Thirty-three participants from the original CPAP-SAVER study were recruited for a 3-year follow-up to determine adherence, examine the intervention effect, and identify adherence-associated factors.

- **Results:**
  - ***Adherence rates dropped to 54.5% at 3 years. Beliefs*** and attitudes were significant factors associated with adherence.
  - Life satisfaction was significantly higher at present compared with before wearing CPAP ($t = 5.17$, $p < .001$).

- **Conclusion & Implications:** The authors recommend intervention with a focus on apnea beliefs, CPAP attitude, and long-term support to promote CPAP adherence. Focus on CPAP attitude and beliefs and enhanced support early in the obstructive sleep apnea (OSA) treatment trajectory may promote long-term adherence and subsequently reduce the health care burden of OSA disease.

CPAP Adherence – Patel (2021)

- **Background:** CPAP effectiveness is limited by suboptimal adherence. Prior studies of adherence have focused on middle-aged men.
- **Aim**: To determine whether CPAP adherence vary by age and sex.
- **Methods:** Retrospective use of telemonitoring data from 789,260 CPAP patients age 18 to 90, between 2015 and 2018.
- **Results: O*verall adherence by US Centers of Medicare & Medicaid Services criteria was 72.6%***, but it varied dramatically by age and sex,
  - ***Ranged from 51.3% in 18- to 30-year-old women to 80.6% in 71- to 80-year-old men.***
  - Patterns of use over the first 90 days demonstrated that younger age groups had peak CPAP use by the 2nd night, with a subsequent decay in use, which was greatest among 18- to 30-year-old women.
  - In contrast, older patients steadily increase use, and then they have much slower decays in use over time.
  - Younger, but not older, patients have lower use of CPAP on weekends compared with weekday nights.
- **Conclusion**:
  - **CPAP adherence varies substantially by demographics, with 18- to 30-year-old women having the lowest.**
  - **The pattern of use over the first 90 days also varies substantially by age and sex.**
  - **Further research to understand and address the causes of disparities is crucial.**

CPAP Adherence & Outcomes: Wickwire, et al., (2021)

- **Aim(s)**: To examine:
  - (1) the impact of adherence to continuous positive airway pressure (CPAP) therapy on risk for cardiovascular (CVD) events among a nationally representative sample of older adults with obstructive sleep apnea (OSA), and
  - (2) the heterogeneity of this effect across subgroups defined by race, sex, and socioeconomic status.

- **Methods:** Retrospective cohort study among 5024 Medicare beneficiaries aged ≥ 65 years with OSA (2009-2013). Monthly indicators of CPAP adherence (charges for machines, masks, or supplies) were summed over 25 months to create a CPAP adherence variable. New CVD events (ischemic heart disease, cardiac and peripheral procedures) were modeled as a function of CPAP adherence using generalized estimating equations. Heterogeneity of the effect of CPAP on new CVD events was evaluated based on race, sex, and socioeconomic status.

- **Results:**
  - 1678 (33%) demonstrated new CVD events.
  - CPAP adherence was associated with reduced risk of new CVD events
  - There were no significant differences in the protective effect of CPAP based on race, sex, or socioeconomics.

- **Conclusions:** In this national study of older adult Medicare beneficiaries with OSA, ***CPAP adherence was associated with greatly reduced risk for CVD events. This risk reduction was consistent across race, sex, and socioeconomic subgroups.***

Adherance: Complementary and Alternative. Kalwala, et al., (2021)– CBT use did ***not*** enhance PAP adherence

BEYOND THE BLUE:
What Fellows Are Reading in Other Journals

Alternative and Complementary Treatments for Obstructive Sleep Apnea

Christopher R. Kawala, Christopher J. Humphreys, Tanya Khaper, and Clodagh M. Ryan

Sleep Medicine Program, Division of Respirology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Recommended Reading from the University of Toronto Sleep Medicine Fellows; Clodagh M. Ryan, M.D., Director of the Sleep Fellowship Program

ORCID IDs: 0000-0003-0874-8251 (C.R.K.); 0000-0002-2372-965X (C.M.R.).

Ong JC, *et al.* A Randomized Controlled Trial of CBT-I and PAP for Obstructive Sleep Apnea and Comorbid Insomnia: Main Outcomes from the MATRICS Study. *Sleep* (1)

Reviewed by Christopher R. Kawala

The occurrence of comorbid insomnia in association with obstructive sleep apnea (OSA) is prevalent (2) and linked to poorer positive airway pressure (PAP) acceptance and adherence (3). Cognitive behavioral therapy for insomnia (CBT-I) in combination with PAP therapy (4, 5) has demonstrated efficacy for the treatment of comorbid insomnia and OSA. Moreover, in one study, those who received CBT-I prior to PAP treatment had better nightly PAP use (5). The primary aim of the MATRICS study was to compare differences in PAP adherence and insomnia symptoms between concomitant CBT-I and PAP and PAP alone in participants with comorbid insomnia and sleep apnea. The secondary aim was to determine if concurrent initiation of both therapies was superior to sequential therapy.

The study randomized 121 adults with OSA and comorbid insomnia to one of three arms. The CBT-I protocol consisted of four weekly individual 50-minute sessions. In arm A, participants received CBT-I before the initiation of PAP therapy (i.e., sequential). In arm B, participants received concurrent CBT-I and PAP therapy (i.e., concurrent), and in arm C, participants were treated with PAP alone (i.e., standard treatment).

The study found no significant difference in objective PAP adherence between the treatment arms. Participants in arms A and B reported significant changes from baseline for two outcome measures: a reduction in Insomnia Severity Index scores ($P = 0.0009$) and a greater percentage of patients deemed "good sleepers" based on a Pittsburgh Sleep Quality Index Score < 5 ($P = 0.044$). There were no differences between the sequential and concurrent treatment models on any outcome measure.

This study failed to demonstrate a beneficial effect of CBT-I on PAP adherence, which is inconsistent with the results from a prior study (5). Specifically, participants in this trial used PAP on average for 2.6 hours/night, below the recommended adherence of 4 hours/night. A *post hoc* analysis showed that those with mild OSA used PAP less frequently compared with participants with moderate-to-severe OSA. The aforementioned study by Sweetman and colleagues excluded patients with mild OSA (5), and this could explain the divergent findings in PAP adherence. Differences in participant motivation to undergo treatment for OSA may also contribute to the findings. In summary, although CBT-I is an effective strategy for reducing insomnia severity and improving subjective sleep quality in patients with comorbid insomnia and OSA, this study does not support the implementation of CBT-I to augment PAP adherence. ■

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Correspondence and requests for reprints should be addressed to Clodagh M. Ryan, M.D., 9N-967 Toronto General Hospital, Toronto, ON, M5G 2N2, Canada. E-mail: clodagh.ryan@uhn.ca.

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Cost Effectiveness: Pachito (2022)

- **Aim:** To synthesize findings of economic evaluations investigating cost-effectiveness of continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA) and of strategies of organization of care related to CPAP therapy.

- **Methods**: Scoping review with searches conducted in MEDLINE, CRD, LILACS, and Embase in August 2020.
- **Results:**
  - Of 34 studies, 3 concluded that CPAP is less costly and more effective when compared to usual care.
  - Most studies indicated that CPAP is associated with better health outcomes, but at higher prices.
  - Three studies assessed the effects of organizing CPAP therapy in primary care, which was cost-effective or cost-saving.

- **Conclusions**: ***Compared to usual care, CPAP is cost-effective after the second year of treatment, when indicated for moderate-to-severe OSA. CPAP therapy may be even more cost-effective by using different strategies of organization of care.***

Education: Sullivan et al., (2021)

- **Aims:** To understand the sleep medicine educational exposure among parent specialties of sleep medicine fellowships.
- **Methods:** Target respondents were program directors of family medicine, otolaryngology, psychiatry, neurology, pediatrics, and pulmonary and critical care training programs in the US. The survey was based on the Sleep Education Survey, a peer-reviewed, published survey created by the American Academy of Neurology Sleep Section. (18-question survey was emailed via Survey Monkey)
- **Results:**
  - A total of 1228 programs were contacted, and 479 responses were received for an overall response rate of 39%.
  - Pulmonary/critical care and neurology reported the highest percentages of sleep medicine rotation as an option for housestaff (85.7% and 90.8%, respectively), and pulmonary and critical care had the highest portion of programs indicating a rotation requirement (75.4%).
  - Teaching format was a mixture of didactic lectures, sleep center/laboratory exposure, and case reports, with lectures being the most common format. Didactics averaged 4.75 h/y.
  - Few programs reported trainees subsequently pursuing sleep medicine fellowship (<10% produced a fellow over 5 years), and even fewer reported having a trainee who pursued grant funding for sleep-related research over 5 years.
- **Conclusions:** ***There is wide variability and overall low exposure to sleep medicine education among physician education programs in the United States.***

Take Home Points

- There has been much research done in sleep medicine.
- The researched has helped shape this aspect of healthcare practice.
- Some research has more scientific merit than others.
- Understanding how to identify, evaluate and integrate strong research is an important skill-set.
- The research is changing all the time based on new discoveries so it's important to keep up to date

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