Clinical Sleep Medicine Update: Year in Review

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MASM Fall 2017 Meeting
October 14, 2017
OBJECTIVES

• Review and understand key medical literature published in the following topics between 2016 – 2017, in order to incorporate them into medical practice:

  • Pediatrics
  • Sleep apnea, especially in relation to neurological disorders
  • Pharmacological therapy for sleep disorders
  • Insomnia & dysomnias
Year in Review:

Pediatrics

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Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients:

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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
Review Process

• SLEEP and JCSM titles from all volumes and issues in 2017 were reviewed
Sleep-Disordered Breathing

Autotitrating CPAP as a Tool for CPAP Initiation for Children

Rebecca Mihai, BAppSc (Hons) 1; Moya Vandeule, MB Bch, BAO 1; Sally Pecoraro 1; Margot J. Davey, MBBS 1,2,3; Gillian M. Nixon, MD 1,2,3

1Melbourne Children’s Sleep Centre, Monash Children’s Hospital, Melbourne, Australia; 2Department of Paediatrics, Monash University, Melbourne, Australia; 3The Ritchie Centre, The Hudson Institute of Medical Research, Melbourne, Australia

Study Objectives: Few studies have assessed autotitrating positive airway pressure (autoPAP) for treatment of obstructive sleep apnea (OSA) in children. We aimed to review our use of autoPAP for initiation of continuous positive airway pressure (CPAP) therapy in children, and compare autoPAP-derived treatment pressures to CPAP treatment pressure determined by attended polysomnography (PSG).

Methods: Retrospective review of children initiated on autoPAP from 2013 to 2015. Mean autoPAP pressure (AutoMean pressure) and average device pressure ≤ 90% of time (Auto90 pressure) were taken from downloaded data and compared to the recommended treatment pressure following titration PSG (PSG pressure).

Results: Fifty-two children started CPAP, of whom 26 (age ± standard deviation 11.9 ± 3.4 years) used autoPAP and had titration PSG. AutoPAP was used on average 84% of nights (standard deviation 20%) in the first month, with a mean ± standard deviation 6.3 ± 2.0 hours of use on nights used. The median (interquartile range) obstructive apnea-hypopnea index decreased from 16.6 (11, 35) events/h before treatment to 2.2 (0.4, 3.8) events/h on the titration PSG. Median (interquartile range) PSG pressure was 9.0 cm H2O (7.0, 10.0), AutoMean pressure was 6.3 cm H2O (5.3, 7.5), and Auto90 pressure was 8.1 cm H2O (7.1, 9.5). These were significantly different (P < .001), with the significant difference lying between AutoMean and the other two pressures. PSG pressure was greater than or equal to the AutoMean pressure in all cases, and greater than or equal to the Auto90 pressure in 20 out of 26 cases (77%).

Conclusions: AutoPAP is a safe and effective means of initiating CPAP in children. AutoMean and Auto90 pressures are usually below treatment pressure determined by titration PSG.

Keywords: autoPAP, compliance, obstructive sleep apnea, pediatrics

Study Objectives: Few studies have assessed autoPAP for treatment of OSA in children
• to review our use of autoPAP for initiation of CPAP therapy in children
• compare autoPAP-derived treatment pressures to CPAP treatment pressure determined by attended PSG

Methods: Retrospective review of children initiated on autoPAP from 2013 to 2015.
• Mean autoPAP pressure (AutoMean pressure) and average device pressure ≤ 90% of time (Auto90 pressure) were taken from downloaded data and compared to the recommended treatment pressure following titration PSG (PSG pressure).
Results:

- **52** children started CPAP, of whom **26** (age 11.9 ± 3.4 years) used AutoPAP and had titration PSG.

- **AutoPAP** used on average **84% of nights** (SD 20%) in the first month, with a mean **6.3 ± 2.0** hours of use on nights used.

- **AHI** decreased from **16.6 events/h** before treatment to **2.2 events/h** on the titration PSG.

- **Median** PSG pressure was **9.0 cm H2O** ,
- **AutoMean** pressure was **6.3 cm H2O** ,
- **Auto90** pressure was **8.1 cm H2O**.

- These were significantly different (*P* < .001), with the significant difference lying between **AutoMean** and the other two pressures.

- **PSG** pressure was greater than or equal to the **AutoMean pressure in all cases**, and greater than or equal to the **Auto90 pressure in 20 out of 26 cases** (77%).
Autotitrating CPAP as a Tool for CPAP Initiation for Children

Conclusions:

- **AutoPAP** is a safe and effective means of initiating CPAP in children.
- **AutoMean and Auto90** pressures are usually below treatment pressure determined by titration PSG.
Sleep-Disordered Breathing

High-Flow, Heated, Humidified Air Via Nasal Cannula Treats CPAP-Intolerant Children With Obstructive Sleep Apnea
Stephen Hawkins, MD; Stephanie Huston, BS; Kristen Campbell, BS; Ann Hallbower, MD

Study Objectives: Continuous positive airway pressure (CPAP) is effective but challenging for children with obstructive sleep apnea (OSA). High-flow air via open nasal cannula (HFNC) as treatment in children remains controversial. We report the efficacy of HFNC in children with OSA and CPAP intolerance, a titration protocol, and a discussion of potential mechanisms.

Methods: Patients aged 1 to 18 years with OSA (defined by obstructive apnea-hypopnea index [OAHI] greater than 1 event/h) and CPAP intolerance were enrolled. Routine polysomnography data obtained during 1 night wearing HFNC was compared with diagnostic data by Wilcoxon rank-sum test.

Results: Ten school-age subjects (representing all patients attempting HFNC at our institution to date) with varied medical conditions, moderate to severe OSA, and CPAP intolerance wore HFNC from 10 to 50 L/min of room air with oxygen supplementation if needed (room air alone for 6 of the 10). HFNC reduced median OAHI from 11.1 events/h (interquartile range 8.7–18.8 events/h) to 2.1 events/h (1.7–2.2 events/h; \( P = .002 \)); increased oxyhemoglobin saturation (SpO₂) mean from 91.3% (89.6% to 93.5%) to 94.9% (92.4% to 96.0%; \( P < .002 \)); increased SpO₂ nadir from 76.0% (67.3% to 82.3%) to 79.5% (77.2% to 86.0%; \( P = .032 \)); decreased SpO₂ desaturation index from 19.2 events/h (12.7–25.8 events/h) to 6.4 events/h (4.7–10.7 events/h; \( P = .013 \)); and reduced heart rate from 88 bpm (86–91 bpm) to 74 bpm (67–81 bpm; \( P = .004 \)). Stratified analysis of the 6 subjects with only room air via HFNC, the OAHI, obstructive hypopnea index, and mean SpO₂ still demonstrated improvements (\( P = .031 \)).

Conclusions: High-flow nasal cannula reduces respiratory events, improves oxygenation, reduces heart rate, and may be effective for CPAP intolerant children with moderate to severe OSA. Our data suggest HFNC warrants further study and consideration by payers as OSA therapy.

Keywords: CPAP intolerance, high-flow nasal cannula, obstructive sleep apnea, pediatrics

High-Flow, Heated, Humidified Air Via Nasal Cannula Treats CPAP-Intolerant Children With Obstructive Sleep Apnea

Study Objectives:

• CPAP is effective but challenging for children with OSA
• High-flow air via open nasal cannula (HFNC) as treatment in children remains controversial
• The efficacy of HFNC in children with OSA and CPAP intolerance, a titration protocol, and a discussion of potential mechanisms.

Methods:

• Patients aged 1 to 18 years with OSA (defined by OAHI > 1 event/h) and CPAP intolerance were enrolled
• Routine PSG data obtained during 1 night wearing HFNC was compared with diagnostic data by Wilcoxon rank-sum test.
High-Flow, Heated, Humidified Air Via Nasal Cannula Treats CPAP-Intolerant Children With Obstructive Sleep Apnea

Results:

- 10 school-age subjects with moderate to severe OSA, and CPAP intolerance wore HFNC from 10 to 50 L/min of room air with oxygen supplementation if needed (room air alone for 6 of the 10).
- HFNC reduced OAHI from 11.1 events/h to 2.1 events/h ($P = .002$);
- increased SpO2 mean from 91.3% to 94.9% ($P < .002$);
- increased SpO2 nadir from 76.0% to 79.5% ($P = .032$);
- decreased ODI from 19.2 events/h to 6.4 events/h ($P = .013$);
- reduced HR from 88 bpm to 74 bpm ($P = .004$).
- Stratified analysis of the 6 subjects with only room air via HFNC, the OAHI, obstructive hypopnea index, and mean SpO2 still demonstrated improvements ($P = .031$).
Conclusions:

- High-flow nasal cannula reduces respiratory events, improves oxygenation, reduces heart rate, and may be effective for CPAP intolerant children with moderate to severe OSA.
- Data suggest HFNC warrants further study and consideration by payers as OSA therapy.
Effects of Adenotonsillectomy on Parent-Reported Behavior in Children With Obstructive Sleep Apnea

Nina Hattiangadi Thomas, PhD; Melissa S. Xanthopoulos, PhD; Ji Young Kim, PhD; Justine Shults, PhD; Emma Escobar, MBA; Bruno Giordani, PhD; Elise Hodges, PhD; Ronald D. Chervin, MD, MS; Shalini Paruthi, MD; Carol L. Rosen, MD; Gerry H. Taylor, PhD; Raanan Arens, MD; Eliot S. Katz, MD; Dean W. Beebe, PhD; Susan Redline, MD; Jerilynn Radcliffe, PhD; Carole L. Marcus, MBBCh

Department of Child and Adolescent Psychiatry and Behavioral Sciences; Neurobehavioral and Biostatistical and Informatics Cores of the Clinical and Translational Research Center and Sleep Center, Children’s Hospital of Philadelphia, Philadelphia, PA; Department of Psychology and Psychiatry, University of Michigan; Department of Neurology and Sleep Disorders Center, University of Michigan; Department of Pediatrics, Saint Louis University; Department of Pediatrics, Rainbow Babies & Children’s Hospital, Case Western Reserve University School of Medicine; Department of Pediatrics, Montefiore Medical Center; Albert Einstein College of Medicine; Division of Respiratory Diseases, Boston Children’s Hospital; Department of Pediatrics, Cincinnati Children’s Hospital Medical Center; Departments of Medicine, Brigham and Women’s Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School; Children’s Hospital of Philadelphia, University of Pennsylvania

Objectives: The childhood obstructive sleep apnea syndrome (OSAS) is associated with behavioral abnormalities. Studies on the effects of OSAS treatment on behavior are conflicting, with few studies using a randomized design. Further, studies may be confounded by the inclusion of behavioral outcome measures directly related to sleep. The objective of this study was to determine the effect of adenotonsillectomy on behavior in children with OSAS. We hypothesized that surgery would improve behavioral ratings, even when sleep symptom items were excluded from the analysis.

Methods: This was a secondary analysis of Child Behavior Checklist (CBCL) data, with and without exclusion of sleep-specific items, from the Childhood Adenotonsillectomy Trial (CHAT). CBCL was completed by caregivers of 380 children (7.0±1.4 [range 5–9] years) with OSAS randomized to early adenotonsillectomy (eAT) versus 7 months of watchful waiting with supportive care (WWSC).

Results: There was a high prevalence of behavioral problems at baseline; 16.6% of children had a Total Problems score in the clinically abnormal range. At follow-up, there were significant improvements in Total Problems (p < .001), Internalizing Behaviors (p = .04), Somatic Complaints (p = .01), and Thought Problems (p = .01) in eAT vs. WWSC participants. When specific sleep-related question items were removed from the analysis, eAT showed an overall improvement in Total (p = .02) and Other (p = .01) problems. Black children had less improvement in behavior following eAT than white children, but this difference attenuated when sleep-related items were excluded.

Conclusions: This large, randomized trial showed that adenotonsillectomy for OSAS improved parent-rated behavioral problems, even when sleep-specific behavioral issues were excluded from the analysis.

Keywords: obstructive sleep apnea, behavior, CBCL, CHAT
Effects of Adenotonsillectomy on Parent-Reported Behavior in Children With Obstructive Sleep Apnea

Objectives:
• The childhood OSAS is associated with behavioral abnormalities
• Studies on the effects of OSAS treatment on behavior are conflicting, with few studies using a randomized design
• Studies may be confounded by the inclusion of behavioral outcome measures directly related to sleep
• The objective of this study was to determine the effect of T&A on behavior in children with OSAS. We hypothesized that surgery would improve behavioral ratings, even when sleep symptom items were excluded from the analysis.

Methods: This was a secondary analysis of Child Behavior Checklist (CBCL) data, with and without exclusion of sleep-specific items, from the Childhood Adenotonsillectomy Trial (CHAT). CBCL was completed by caregivers of 380 children (7.0±1.4 [range 5–9] years) with OSAS randomized to early T&A versus 7 months of watchful waiting with supportive care (WWSC).
Results:

• There was a high prevalence of behavioral problems at baseline; 16.6% of children had a Total Problems score in the clinically abnormal range.

• At follow-up, significant improvements in Total Problems ($p < .001$), Internalizing Behaviors ($p = .04$), Somatic Complaints ($p = .01$), and Thought Problems ($p = .01$) in eAT vs. WWSC participants.

• When specific sleep-related question items were removed from the analysis, T&A showed an overall improvement in Total ($p = .02$) and Other ($p = .01$) problems.

• Black children had less improvement in behavior following T&A than white children, but this difference attenuated when sleep-related items were excluded.
Effects of Adenotonsillectomy on Parent-Reported Behavior in Children With Obstructive Sleep Apnea

Conclusions:
This large, randomized trial showed that T&A for OSAS improved parent-rated behavioral problems, even when sleep-specific behavioral issues were excluded from the analysis.
Effects of Melatonin and Bright Light Treatment in Childhood Chronic Sleep Onset Insomnia With Late Melatonin Onset: A Randomized Controlled Study

Annette van Maanen, MSc1; Anne Marie Meijer, PhD1; Marcel G. Smits, PhD2; Kristiaan B. van der Heijden, PhD3,4; Frans J. Oort, PhD1

1Research Institute of Child Development and Education, University of Amsterdam, Amsterdam, The Netherlands; 2Centre of Sleep-Wake Disorders and Chronobiology, Hospital Gelderse Vallei, Ede, The Netherlands; 3Department of Clinical Child and Adolescent Studies, Leiden University, Leiden, The Netherlands; 4Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Study Objectives: Chronic sleep onset insomnia with late melatonin onset is prevalent in childhood, and has negative daytime consequences. Melatonin treatment is known to be effective in treating these sleep problems. Bright light therapy might be an alternative treatment, with potential advantages over melatonin treatment. In this study, we compare the effects of melatonin and bright light treatment with a placebo condition in children with chronic sleep onset insomnia and late melatonin onset.

Methods: Eighty-four children (mean age 10.0 years, 61% boys) first entered a baseline week, after which they received melatonin (N = 26), light (N = 30), or placebo pills (N = 28) for 3 to 4 weeks. Sleep was measured daily with sleep diaries and actigraphy. Before and after treatment children completed a questionnaire on chronic sleep reduction, and Dim Light Melatonin Onset (DLMO) was measured. Results were analyzed with linear mixed model analyses.

Results: Melatonin treatment and light therapy decreased sleep latency (sleep diary) and advanced sleep onset (sleep diary and actigraphy), although for sleep onset the effects of melatonin were stronger. In addition, melatonin treatment advanced DLMO and had positive effects on sleep latency and sleep efficiency (actigraphy data), and sleep time (sleep diary and actigraphy data). However, wake after sleep onset (actigraphy) increased with melatonin treatment. No effects on chronic sleep reduction were found.

Conclusions: We found positive effects of both melatonin and light treatment on various sleep outcomes, but more and stronger effects were found for melatonin treatment.
Effects of Melatonin and Bright Light Treatment in Childhood Chronic Sleep Onset Insomnia With Late Melatonin Onset: A Randomized Controlled Study

Study Objectives:

• Chronic sleep onset insomnia with late melatonin onset is prevalent in childhood, and has negative daytime consequences.

• Melatonin treatment is known to be effective

• Bright light therapy might be an alternative treatment, with potential advantages over melatonin treatment

• Compare the effects of melatonin and bright light treatment with a placebo condition in children with chronic sleep onset insomnia and late melatonin onset.
Methods:

• 84 children (mean age 10.0 years, 61% boys) first entered a baseline week,
• after they received melatonin (N = 26), light (N = 30), or placebo pills (N = 28) for 3 to 4 weeks
• Sleep was measured daily with sleep diaries and actigraphy
• Before and after treatment children completed a questionnaire on chronic sleep reduction
• Dim Light Melatonin Onset (DLMO) was measured
• Results were analyzed with linear mixed model analyses.
Results:

• Melatonin treatment and light therapy decreased sleep latency (sleep diary) and advanced sleep onset (sleep diary and actigraphy), although for
• Sleep onset the effects of melatonin were stronger
• Melatonin treatment advanced DLMO and had positive effects on sleep latency, sleep efficiency and sleep
• WASO increased with melatonin treatment
• No effects on chronic sleep reduction were found.
Effects of Melatonin and Bright Light Treatment in Childhood Chronic Sleep Onset Insomnia With Late Melatonin Onset: A Randomized Controlled Study

Conclusions:

• Both Melatonin and Light treatment have positive effects of on various sleep outcomes

• More and stronger effects were found for Melatonin treatment.
Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content

Lauren A.E. Erland, MSc; Praveen K. Saxena, PhD

Gosling Research Institute for Plant Preservation, Department of Plant Agriculture, University of Guelph, Guelph, Ontario, Canada

Study Objectives: Melatonin is an important neurohormone, which mediates circadian rhythms and the sleep cycle. As such, it is a popular and readily available supplement for the treatment and prevention of sleep-related disorders including insomnia and jet lag. This study quantified melatonin in 30 commercial supplements, comprising different brands and forms and screened supplements for the presence of serotonin.

Methods: A total of 31 supplements were analyzed by ultraperformance liquid chromatography with electrochemical detection for quantification of melatonin and serotonin. Presence of serotonin was confirmed through analysis by ultraperformance liquid chromatography with mass spectrometry detection.

Results: Melatonin content was found to range from −83% to +478% of the labelled content. Additionally, lot-to-lot variable within a particular product varied by as much as 465%. This variability did not appear to be correlated with manufacturer or product type. Furthermore, serotonin (5-hydroxytryptamine), a related indoleamine and controlled substance used in the treatment of several neurological disorders, was identified in eight of the supplements at levels of 1 to 75 μg.

Conclusions: Melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements and an additional 26% were found to contain serotonin. It is important that clinicians and patients have confidence in the quality of supplements used in the treatment of sleep disorders. To address this, manufacturers require increased controls to ensure melatonin supplements meet both their label claim, and also are free from contaminants, such as serotonin.

Commentary: A commentary on this article appears in this issue on page 163.

Keywords: contaminant, degradation, label claim, natural health product, stability

Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content

Methods:
• A total of 31 supplements were analyzed

Results:
• Melatonin content was found to range from −83% to +478% of the labelled content.
• Additionally, lot-to-lot variable within a particular product varied by as much as 465%.
• This variability did not appear to be correlated with manufacturer or product type.
• Serotonin (5-hydroxytryptamine), a related indoleamine and controlled substance used in the treatment of several neurological disorders, was identified in 8 of the supplements at levels of 1 to 75 µg

Conclusions:
• Melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements and an additional 26% were found to contain serotonin.
• It is important that clinicians and patients have confidence in the quality of supplements used in the treatment of sleep disorders
• Manufacturers require increased controls to ensure melatonin supplements meet both their label claim, and also are free from contaminants, such as serotonin.
Delaying Middle School and High School Start Times Promotes Student Health and Performance: An American Academy of Sleep Medicine Position Statement

Nathaniel F. Watson, MD, MS; Jennifer L. Martin, PhD; Merrill S. Wise, MD; Kelly A. Carden, MD; Douglas B. Kirsch, MD; David A. Kristo, MD; Raman K. Malhotra, MD; Eric J. Olson, MD; Kannan Ramar, MD; Ilene M. Rosen, MD, MS; James A. Rowley, MD; Terri E. Weaver, PhD, RN; Ronald D. Chervin, MD, MS; for the American Academy of Sleep Medicine Board of Directors

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During adolescence, internal circadian rhythms and biological sleep drive change to result in later sleep and wake times. As a result of these changes, early middle school and high school start times curtail sleep, hamper a student’s preparedness to learn, negatively impact physical and mental health, and impair driving safety. Furthermore, a growing body of evidence shows that delaying school start times positively impacts student achievement, health, and safety. Public awareness of the hazards of early school start times and the benefits of later start times are largely unappreciated. As a result, the American Academy of Sleep Medicine is calling on communities, school boards, and educational institutions to implement start times of 8:30 am or later for middle schools and high schools to ensure that every student arrives at school healthy, awake, alert, and ready to learn.

Keywords: health, high school, middle school, performance, student

Later School Start Times: What Informs Parent Support or Opposition?

Galit Levi Dunietz, PhD, MPH\(^1\); Amilcar Matos-Moreno, MPH\(^2\); Dianne C. Singer, MPH\(^3\); Matthew M. Davis, MD, MAPP\(^3,4\); Louise M. O’Brien, PhD, MS\(^1\); Ronald D. Chervin, MD, MS\(^1\)

\(^1\)Department of Neurology and Sleep Disorders Center, University of Michigan, Ann Arbor, Michigan; \(^2\)Child Health Evaluation and Research (CHEAR) Unit, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan; \(^3\)Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; \(^4\)Institute for Healthcare Policy and Innovation University of Michigan, Ann Arbor, Michigan

**Study Objectives:** To investigate parental knowledge about adolescent sleep needs, and other beliefs that may inform their support for or objection to later school start times.

**Methods:** In 2014, we conducted a cross-sectional, Internet-based survey of a nationally representative sample of parents as part of the C.S. Mott Children’s Hospital National Poll on Children’s Health. Parents with teens aged 13–17 years reported their children's sleep patterns and school schedules, and whether the parents supported later school start times (8:30 AM or later). Responses associated with parental support of later school start times were examined with logistic regression analysis.

**Results:** Overall, 88% of parents reported school start times before 8:30 AM, and served as the analysis sample (n = 554). In this group, 51% expressed support for later school start times. Support was associated with current school start times before 7:30 AM (odds ratio [OR] = 3.1 [95% confidence interval (CI) 1.2, 8.4]); parental opinion that their teen’s current school start time was “too early” (OR = 3.8 [1.8, 7.8]); and agreement with American Academy of Pediatrics recommendations about school start times (OR = 4.7 [2.2, 10.1]). Support also was associated with anticipation of improved school performance (OR = 3.0 [1.5, 5.9]) or increased sleep duration (OR = 4.0 [1.8, 8.9]) with later school start times. Conversely, parents who anticipated too little time for after-school activities (OR = 0.5 [0.3, 0.9]) and need for different transportation plans (OR = 0.5 [0.2, 0.9]) were often less supportive.

**Conclusions:** Parental education about healthy sleep needs and anticipated health benefits may increase their support for later school start times. Educational efforts should also publicize the positive experiences of communities that have made this transition, with regard to limited adverse effect on after-school activity schedules and transportation.

**Keywords:** adolescents, circadian rhythms, high school, insufficient sleep, parental opinion, poll, school start times, sleep deprivation, survey

**Citation:** Dunietz GL, Matos-Moreno A, Singer DC, Davis MM, O’Brien LM, Chervin RD. Later school start times: what informs parent support or opposition? J Clin Sleep Med. 2017;13(7):889–897.
Later School Start Times: What Informs Parent Support or Opposition?

• **Study Objectives:** To investigate parental knowledge about adolescent sleep needs, and other beliefs that may inform their support for or objection to later school start times.

**Methods:**

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• Parents with teens aged 13–17 years reported their children’s sleep patterns and school schedules, and whether the parents supported later school start times (8:30 am or later)
Later School Start Times: What Informs Parent Support or Opposition?

Results:

• 88% of parents reported school start times before 8:30 am, and served as the analysis sample (n = 554)
• 51% expressed support for later school start times
• Support was associated with current school start times before 7:30 am; parental opinion that their teen’s current school start time was “too early”
• agreement with American Academy of Pediatrics recommendations about school start times
• Support also was associated with anticipation of improved school performance or increased sleep duration with later school start times
• Conversely, parents who anticipated too little time for after-school activities and need for different transportation plans were often less supportive.
Conclusions:

• Parental education about healthy sleep needs and anticipated health benefits may increase their support for later school start times.

• Educational efforts should also publicize with regard to limited adverse effect on after-school activity schedules and transportation.
Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study

Michel Lecendreux, MD1,2; Johanna Berthier, Medical Student; Jennifer Corny, PharmD; Olivier Bourdon, MD, PhD1,6; Claire Dossier, MD; Christophe Delclaux, MD, PhD1,7

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Study Objectives: Previous case reports of intravenous immunoglobulins (IVIg) in pediatric narcolepsy have shown contradictory results.

Methods: This was a nonrandomized, open-label, controlled, longitudinal observational study of IVIg use in pediatric narcolepsy with retrospective data collection from medical files obtained from a single pediatric national reference center for the treatment of narcolepsy in France. Of 56 consecutively referred patients with narcolepsy, 24 received IVIg (3 infusions administered at 1-mo intervals) in addition to standard care (psychostimulants and/or anticeptics agents), and 32 continued on standard care alone (controls).

Results: For two patients in each group, medical files were unavailable. Of the 22 IVIg patients, all had cerebrospinal fluid (CSF) hypocretin ≤ 110 pg/mL and were HLA-DQB1*06:02 positive. Of the 30 control patients, 29 were HLA-DQB1*06:02 positive and of those with available CSF measurements, all 12 had hypocretin ≤ 110 pg/mL. Compared with control patients, IVIg patients had shorter disease duration, shorter latency to sleep onset, and more had received H1N1 vaccination. Mean (standard deviation) follow-up length was 2.4 (1.1) y in the IVIg group and 3.9 (1.7) y in controls. In multivariate-adjusted linear mixed-effects analyses of change from baseline in Ullanlinna Narcolepsy Scale (UNS) scores, high baseline UNS, but not IVIg treatment, was associated with a reduction in narcolepsy symptoms. On time-to-event analysis, among patients with high baseline UNS scores, control patients achieved a UNS score < 14 (indicating remission) less rapidly than IVIg patients (adjusted hazard ratio 0.18; 95% confidence interval: 95% confidence interval: 0.03, 0.95; p = 0.043). Shorter or longer disease duration did not influence treatment response in any analysis.

Conclusions: Overall, narcolepsy symptoms were not significantly reduced by IVIg. However, in patients with high baseline symptoms, a subset of IVIg-treated patients achieved remission more rapidly than control patients.

Commentary: A commentary on this article appears in this issue on page 363.

Keywords: cataplexy, child, immunoglobulin, immunomodulation, narcolepsy

Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study

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Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study

Results:
• For 2 patients in each group, medical files were unavailable.
• Of the 22 IVIg patients, all had CSF hypocretin ≤ 110 pg/mL and were HLA-DQB1*06:02 positive.
• Of the 30 control patients, 29 were HLA-DQB1*06:02 positive and of those with available CSF measurements, all 12 had hypocretin ≤ 110 pg/mL.
• Compared with control patients, IVIg patients had shorter disease duration, shorter latency to sleep onset, and more had received H1N1 vaccination.
• Mean follow-up length was 2.4 y in the IVIg group and 3.9 y in controls.
• High baseline Narcolepsy Scale scores, but not IVIg treatment, was associated with a reduction in narcolepsy symptoms.
• Among patients with high baseline Narcolepsy Scale scores, control patients achieved a UNS score < 14 (indicating remission) less rapidly than IVIg patients (p = 0.043).
  Shorter or longer disease duration did not influence treatment response in any analysis.

Conclusions: Overall, narcolepsy symptoms were not significantly reduced by IVIg. However, in patients with high baseline symptoms, a subset of IVIg-treated patients achieved remission more rapidly than control patients.
The Relationship Between Caffeine, Sleep, and Behavior in Children

Emily J. Watson, Bachelor of Psychology (Honors); Siobhan Banks, PhD; Alison M. Coates, PhD; Mark J. Kohler, PhD

1Centre for Sleep Research, School of Psychology, University of South Australia, Adelaide, South Australia, Australia; 2Alliance for Research in Exercise, Nutrition and Activity, School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia

Study Objectives: To examine caffeine consumption from various dietary sources in a cohort of Australian children and the relationship between caffeine consumption, sleep, and daytime behavior.

Methods: Children aged 8 to 12 years and their parents/guardians completed a battery of questionnaires. Children completed a caffeine questionnaire while parents completed questionnaires regarding demographics, sleep, and behavior.

Results: The final sample consisted of 309 children (mean ± standard deviation [SD] age 10.6 ± 1.3 years, male = 48%) and corresponding parent reports. On average a mean ± SD 10.2 ± 17.4 mg/day of caffeine was consumed with a range of zero to 151 mg/day. Of the children who consumed caffeine (87% of the sample), the largest contributor was coffee and tea; making up 41% of total caffeine intake, and sodas (soft drinks) contributed to 40% of caffeine intake. Total caffeine consumption was significantly associated with sleep routine (r = 0.152); morning tiredness (r = 0.129); restless sleep (r = 0.113); and internalizing behavioral problems (r = 0.128). Using path analysis, caffeine consumption was positively associated with morning tiredness (β = 0.111, P = .050) which was positively associated with internalizing behaviors (β = 0.432, P < .001). The addition of sleep routine and restless sleep to the model led to a complete mediation of caffeine consumption on morning tiredness, as well as a partial mediation of the association between morning tiredness and internal behaviors.

Conclusions: In 8- to 12-year-olds the primary sources of caffeine are coffee/tea and sodas. Overall mean caffeine consumption is small by adult standards but has an effect on behavior and sleep in children. The effect on behavior is mediated by disrupted sleep, indicating that caffeine is a contributor to sleep problems and related behavior in children.

Keywords: behavior, caffeine, internalizing behaviors, morning tiredness, path analysis, restless sleep, school-aged children, sleep, sleep routine

The Relationship Between Caffeine, Sleep, and Behavior in Children

**Study Objectives:** To examine caffeine consumption from various dietary sources in a cohort of Australian children and the relationship between caffeine consumption, sleep, and daytime behavior.

**Methods:**
- Children aged 8 to 12 years and their parents/guardians completed a battery of questionnaires.
- Children completed a caffeine questionnaire while parents completed questionnaires regarding demographics, sleep, and behavior.
The Relationship Between Caffeine, Sleep, and Behavior in Children

Results:
• The final sample consisted of 309 children (10.6 ± 1.3 years, male = 48%) and corresponding parent reports.
• On average a mean ± SD 10.2 ± 17.4 mg/day of caffeine was consumed with a range of zero to 151 mg/day.
• Of the children who consumed caffeine (87% of the sample) - coffee and tea (41% of total caffeine intake) - sodas (soft drinks) contributed to 40% of caffeine intake.
• Total caffeine consumption was significantly associated with - sleep routine ($r = 0.152$);
  - morning tiredness ($r = 0.129$);
  - restless sleep ($r = 0.113$); and
  - internalizing behavioral problems ($r = 0.128$).
• Caffeine consumption was positively associated with **morning tiredness** ($P = .050$) which was positively associated with **internalizing behaviors** ($P < .001$).
The Relationship Between Caffeine, Sleep, and Behavior in Children

Conclusions:
• In 8- to 12-year-olds the primary sources of caffeine are coffee/tea and sodas
• Overall mean caffeine consumption is small by adult standards but has an effect on behavior and sleep in children
• The effect on behavior is mediated by disrupted sleep, indicating that caffeine is a contributor to sleep problems and related behavior in children
Year in Review:
Sleep Apnea & Neurological Diseases

Virginia Skiba, MD
Senior Staff Physician
Associate Program Director, Sleep Medicine Fellowship
Medical Director, Cottage Lab
Henry Ford Health Sleep Disorders and Research Center
Detroit, MI
**Conflict of Interest Disclosures for Speakers**

1. I do not have any relationships with any entities *producing, marketing, re-selling, or distributing* health care goods or services consumed by, or used on, patients, OR

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
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2. I have the following relationships with entities *producing, marketing, re-selling, or distributing* health care goods or services consumed by, or used on, patients:

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
OSA and Neurological Diseases: Objectives

1. To review the 2017 AASM Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea

2. To review recent data on OSA and stroke
   • Associations between OSA and stroke
   • Treatment of OSA and impact on stroke

3. To review recent data on OSA and cognitive disorders
   • Associations between OSA and cognitive disorders
   • Treatment of OSA and impact on cognition

4. To review recent data on use of CPAP for treatment of OSA and reduction of cardiovascular complications
OSA and AASM Practice Guidelines:

Testing for OSA
Good Practice Statements:

• Diagnostic testing for OSA should be performed in conjunction with a comprehensive sleep evaluation and adequate follow-up.

• Polysomnography is the standard diagnostic test for the diagnosis of OSA in adult patients in whom there is a concern for OSA based on a comprehensive sleep evaluation.
Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An AASM Clinical Practice Guideline

Recommendations:

1. We recommend that clinical tools, questionnaires and prediction algorithms **not** be used to diagnose OSA in adults, in the absence of polysomnography or home sleep apnea testing. (STRONG)

2. We recommend that **polysomnography**, or home sleep apnea testing with a technically adequate device, be used for the diagnosis of OSA in **uncomplicated adult patients** presenting with signs and symptoms that indicate an increased risk of **moderate to severe OSA**. (STRONG)

3. We recommend that if a single **home sleep apnea test** is negative, inconclusive, or technically inadequate, **polysomnography** be performed for the diagnosis of OSA. (STRONG)
Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An AASM Clinical Practice Guideline

4. We recommend that polysomnography, rather than home sleep apnea testing, be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia. (STRONG)

5. We suggest that, if clinically appropriate, a split-night diagnostic protocol, rather than a full-night diagnostic protocol for polysomnography be used for the diagnosis of OSA. (WEAK)

6. We suggest that when the initial polysomnogram is negative and clinical suspicion for OSA remains, a second polysomnogram be considered for the diagnosis of OSA. (WEAK)
OSA and stroke:
Associations
OSA and Stroke:  
Background Studies on Associations

• Sleep Heart Health Study and Wisconsin Sleep Cohort Study showed an association between OSA and stroke, in both retrospective and prospective studies (OSA increases risk of stroke about 2 fold)  
  • The association was strongest for moderate and severe OSA, but was also seen in mild OSA

• Severe obstructive sleep apnea (AHI > 30) increases the risk of ischemic stroke in the elderly population (>70 yo), independent of known confounding factors

• Cardioembolic stroke is more common in patients with OSA (72%) vs controls (33%) and a-fib is more common in OSA patients (59%) than controls (24%)

• Nocturnal hypoxemia is associated with white matter hyperintensities
OSA and Stroke:
Background Studies con’t

• Wake up stroke is more common in OSA patients

• The only baseline characteristics that differ between stroke patients with and without OSA are: neck size, facial weakness, dysarthria (not ESS, Berlin questionnaire, BMI)
OSA and Stroke: Recent Studies on Associations

• In a retrospective study of 134 patients with acute stroke, atrial fibrillation was found more often in OSA patients (41% vs 20%), while there was no difference in atherothrombosis and small vessel disease mechanisms (OSA= AHI>15)

• In a retrospective cross-sectional study of 283 patients with suspected OSA, moderate to severe OSA was independently related with presence of intracranial arterial stenosis (defined as >50% narrowing of ICA, MCA, ACA, PCA, VA and BA on MRA imaging)
  • stenosis seen in 7% with no OSA, 15% mild OSA, 30% moderate or severe OSA

• In a cross sectional study of 170 patients, moderate to severe OSA was associated with cerebral small vessel disease, including white matter hyperintensities

OSA and Stroke: Recent Studies on Testing

- In a prospective observational study, 102 patients with acute stroke completed unattended sleep testing using ApneaLink Plus (either in the hospital or outpatient), within mean 25 days of a stroke
  - OSA was detected in 63%
  - **80% had analyzable data** (higher BMI and more disability trended towards short recordings)
  - Mean time from study recruitment to HSAT was 1.7 days
  - CPAP was initiated 34 of 52 subjects (65%), average time to set up was **62 days from recruitment**

➢ Testing for OSA in the acute setting is feasible with unattended polysomnography

OSA and Stroke: Recent Studies on Recovery

• A prospective study tested 99 subjects with acute stroke with a portable study (Apnea Link) and found OSA worsens neurological recovery:
  • Mean NIHSS scores were not significantly different at admission, but at discharge OSA group had higher mean NIHSS score
  • Presence of OSA was associated with worse functional outcome (mRS) at admission, discharge, 3 months and last follow up

OSA and Stroke:

Treatment with CPAP
OSA and Stroke:
Background Studies on Treatment

- There have been several studies conducted on stroke patients in **acute rehabilitation**, showing small or no differences in functional outcomes
  - Limited by small numbers and un-blinded studies
OSA and Stroke: Recent Studies on Treatment

• Treatment with CPAP during inpatient rehabilitation is feasible:
  • 30 stroke rehabilitation patients were recruited and treated with auto CPAP or sham CPAP (nasal mask with a high leak, delivering 0.75-1 cm water)
  • Average CPAP use was 3.7 hrs a night, 50% subjects had at least 4 hrs of use
  • There was a trend towards improved outcome in active CPAP group (Functional Independence Measure)

OSA and Cognitive Disorders: Associations
OSA and Cognitive Disorders: Background Studies on Associations

• A meta-analysis of 25 studies comparing cognitive performance in adults with OSA with that of healthy controls suggested that those with OSA performed worse on domains of vigilance and executive function, but associations with memory, visual, and motor skills were inconsistent.
  • In older men living in the community, mild-to-moderate SDB was associated with cognitive decline over 3 years.
  • In older women living in the community, SDB was associated with an 85% increased risk of mild cognitive impairment or dementia after 5 years of follow-up.

• A retrospective study of 2,636 men followed for 3.4 years found nocturnal hypoxemia was associated with decline in MMSE

• Another retrospective study of 559 healthy older adults found OSA was associated with a weak decline in attention domain
OSA and Cognition: Recent Studies on Associations

- Compared to healthy controls, OSA subjects were found to have higher amyloid deposition on PET scans (N=19 in each group)
- 1,667 subjects were followed for 15 years and underwent at-home sleep testing, OSA (4% definition) was not associated with risk of dementia (as defined by hospitalization codes and examinations)
  - 1,083 of those underwent detailed neuropsychological testing, those with severe OSA were at higher risk for developing AD or MCI (Risk Ratio 1.43-2.35 depending on adjustment models)

OSA and Cognitive Disorders:
Treatment with CPAP
OSA and Cognitive Disorders: Background Studies on Treatment

• Trials show some improvements in attention and executive function in otherwise healthy patients treated with CPAP.

• 1,105 healthy adults with OSA were treated with active or sham CPAP and significant differences were found in executive and frontal lobe function at 2 months only (no changes in domains of learning, memory, attention, psychomotor function were found).

• Patients with OSA have been found to have younger onset of MCI but in only some of the sub-analysis use of CPAP was shown to delay the age of MCI onset.

• Several prospective studies found treatment with CPAP in patients with AD and OSA provides slight improvements or slowed decline on neuropsychological testing (studies only involved 10-50 subjects).
OSA and Cognitive Disorders: Recent Studies on Treatment

- Prospective study compared 55 patients with newly diagnosed moderate to severe OSA, half treated with CPAP and half treated with lifestyle modifications, to matched healthy adults and compared neurocognitive testing and imaging at 1 month
  - Median CPAP use was 5 hrs/night
  - Subjects who used CPAP showed improvements in right thalamus size (activation of the thalamic system acts as functional interface between arousal and attentional regulation), decreased ESS scores and improved episodic memory

OSA and CPAP:
Cardiovascular Outcomes
CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*
Methods

• Subjects:
  • 2,717 adults, 45-75 yo, in Australia
  • Moderate to severe OSA (portable study, 4% desat) AND coronary or cerebrovascular disease
  • Excluded if ESS >15, severe hypoxemia <80% for >10% TRT

• Randomized to:
  • CPAP use (auto CPAP for 1 week, then fixed to the 90%ile pressure)
  • Usual care alone

• Duration: mean follow up 3.7 yrs

• Endpoints:
  • Primary endpoint: death from cardiovascular causes, MI, stroke or hospitalization for ACS, heart failure or TIA
  • Secondary endpoints: other cardiovascular outcomes, health-related quality of life, snoring symptoms, daytime sleepiness, and mood.
Results

• Subjects
  • Mean age 61 yo, 81% male, 63% Asian, 25% white
  • Mean CPAP use 3.3 hrs/night, 42% used for >4 hrs/night
  • Mean AHI 29

• Primary endpoint: no difference - 17% CPAP group and 15% in control group had a cardiovascular event

• Secondary endpoints: CPAP reduced daytime sleepiness, anxiety and depression scores and improved health-related quality of life and mood

• Patients who were adherent to CPAP therapy (>4hrs/night) had a lower risk of stroke than those in the control group
Conclusion

- Low average use of 3.3 hrs/night
- Severe hypoxemia excluded
- CPAP use of >4/hrs a night had lower risk of stroke
Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis

Jie Yu, MD; Zien Zhou, MD; R. Doug McEvoy, MD; Craig S. Anderson, PhD; Anthony Rodgers, PhD; Vlado Perkovic, PhD; Bruce Neal, PhD

Methods

• Study inclusion:
  • MEDLINE, EMBASE, and the Cochrane Library were searched for randomized clinical trials that included reporting of major adverse cardiovascular events or deaths
  • At least 12 weeks of follow up

• Main outcomes:
  • Composite of major adverse cardiovascular events: acute coronary syndrome (ACS) events, stroke
  • Cause-specific outcomes of: fatal or nonfatal ACS, stroke, hospitalization for unstable angina, fatal or hospitalized heart failure
  • All-cause death, cardiovascular death, non-cardiovascular death
Results

• **Subjects**
  • 10 trials (10 CPAP, 1 ASV; included 2016 NEJM paper) with sleep apnea, N=7,266
  • Trials were reviewed by 2 authors
  • Mean age 60.9 yo, 80% men, mean BMI 30

• **Outcome**
  • 356 major adverse cardiovascular events and 613 deaths
  • Results published after 2010 except for 1 trial
  • 9 studies compared CPAP to standard care, 1 to sham CPAP
  • Sample size of 83-2,717 participants
  • Median follow up 6-68 months
  • 9 studies used in-lab PSG, 1 study used portable sleep study for diagnosis
  • Inclusion criteria AHI > 7.5-20/hr
  • Mean adherence to CPAP ranged from 1.4 to 6.6 hrs per day
Results

• There was no significant association of PAP with major adverse cardiovascular events, cardiovascular death, all-cause death, ACS, stroke, and heart failure

• The meta-regression analyses identified no association between the length of follow-up, adherence to PAP, baseline AHI, and the relative risks of events reported for the individual trials
Figure 2. Meta-analysis of the Association of Positive Airway Pressure With Cardiovascular Events and Death

<table>
<thead>
<tr>
<th>Source</th>
<th>Positive Airway Pressure</th>
<th>Control</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Positive Airway Pressure</th>
<th>Favors Control</th>
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<td></td>
<td>Events or Deaths, No.</td>
<td>Participants, No.</td>
<td>Events or Deaths, No.</td>
<td>Participants, No.</td>
<td>Random-Effects Model</td>
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<td>0.34 (0.04-1.29)</td>
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<td>0</td>
<td>42</td>
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<td>57</td>
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<td>2272</td>
<td>187</td>
<td>2250</td>
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<td>1759</td>
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<td>Overall (P&lt;sup&gt;2&lt;/sup&gt; = 0.36, P = 0.68)</td>
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<td>2272</td>
<td>320</td>
<td>2250</td>
<td>0.92 (0.71-1.23)</td>
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<td>666</td>
<td>133</td>
<td>659</td>
<td>1.19 (1.02-1.39)</td>
</tr>
<tr>
<td>Huang et al.,&lt;sup&gt;22&lt;/sup&gt; 2015</td>
<td>0</td>
<td>42</td>
<td>1</td>
<td>41</td>
<td>0.33 (0.01-1.97)</td>
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<tr>
<td>Parra et al.,&lt;sup&gt;23&lt;/sup&gt; 2015</td>
<td>6</td>
<td>57</td>
<td>9</td>
<td>69</td>
<td>0.81 (0.21-3.25)</td>
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<tr>
<td>McEvoy et al.,&lt;sup&gt;24&lt;/sup&gt; 2016</td>
<td>40</td>
<td>1359</td>
<td>43</td>
<td>1358</td>
<td>0.93 (0.81-1.42)</td>
</tr>
<tr>
<td>Pecker et al.,&lt;sup&gt;25&lt;/sup&gt; 2016</td>
<td>122</td>
<td>122</td>
<td>9</td>
<td>122</td>
<td>0.78 (0.10-7.02)</td>
</tr>
<tr>
<td>Overall (P&lt;sup&gt;2&lt;/sup&gt; = 0.00, P = 0.80)</td>
<td>324</td>
<td>3622</td>
<td>289</td>
<td>3621</td>
<td>1.13 (0.99-1.29)</td>
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<tr>
<td>Noncardiovascular death</td>
<td></td>
<td></td>
<td></td>
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<td>Bradley et al.,&lt;sup&gt;16&lt;/sup&gt; 2005</td>
<td>4</td>
<td>128</td>
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<td>130</td>
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<td>357</td>
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<td>366</td>
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<tr>
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<td>1</td>
<td>195</td>
<td>0</td>
<td>196</td>
<td>3.02 (0.12-73.57)</td>
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<tr>
<td>McMillan et al.,&lt;sup&gt;20&lt;/sup&gt; 2014</td>
<td>1</td>
<td>140</td>
<td>1</td>
<td>138</td>
<td>0.99 (0.06-15.60)</td>
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<tr>
<td>Cowie et al.,&lt;sup&gt;21&lt;/sup&gt; 2015</td>
<td>33</td>
<td>666</td>
<td>35</td>
<td>659</td>
<td>0.93 (0.39-2.38)</td>
</tr>
<tr>
<td>Parra et al.,&lt;sup&gt;23&lt;/sup&gt; 2015</td>
<td>6</td>
<td>57</td>
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<td>69</td>
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<td>1359</td>
<td>23</td>
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<td>0.85 (0.34-2.24)</td>
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<td>122</td>
<td>2</td>
<td>122</td>
<td>2.00 (0.37-10.72)</td>
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<tr>
<td>Overall (P&lt;sup&gt;2&lt;/sup&gt; = 0.80, P = 0.39)</td>
<td>71</td>
<td>3024</td>
<td>84</td>
<td>3038</td>
<td>0.85 (0.60-1.19)</td>
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Figure 3. Meta-analysis of the Association of Positive Airway Pressure With Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Source</th>
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<th>Risk Ratio (95% CI), Random-Effects Model</th>
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<td>Participants, No.</td>
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<tr>
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<td>195</td>
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<td>McMillan et al, 2014</td>
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<td>140</td>
<td>3</td>
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<td>Huang et al, 2015</td>
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<tr>
<td>Parra et al, 2015</td>
<td>2</td>
<td>57</td>
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<tr>
<td>McEvoy et al, 2016</td>
<td>42</td>
<td>1359</td>
<td>39</td>
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<tr>
<td>Peker et al, 2016</td>
<td>11</td>
<td>122</td>
<td>8</td>
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<tr>
<td>Overall (I² = 10.20%, P = .35)</td>
<td>63</td>
<td>2272</td>
<td>64</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbé et al, 2012</td>
<td>3</td>
<td>357</td>
<td>2</td>
</tr>
<tr>
<td>McMillan et al, 2014</td>
<td>1</td>
<td>140</td>
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<td>Huang et al, 2015</td>
<td>0</td>
<td>42</td>
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<tr>
<td>Parra et al, 2015</td>
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<td>57</td>
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<td>McEvoy et al, 2016</td>
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<td>1359</td>
<td>68</td>
</tr>
<tr>
<td>Peker et al, 2016</td>
<td>3</td>
<td>122</td>
<td>6</td>
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<tr>
<td>Overall (I² = 0.00%, P = .51)</td>
<td>77</td>
<td>2077</td>
<td>89</td>
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<tr>
<td>Hospitalization for unstable angina</td>
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<td></td>
<td></td>
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<tr>
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<td>357</td>
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<tr>
<td>McEvoy et al, 2016</td>
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<td>1359</td>
<td>90</td>
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<td>Overall (I² = 0.00%, P = .37)</td>
<td>116</td>
<td>1716</td>
<td>101</td>
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<td>Cowie et al, 2015</td>
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<td>Peker et al, 2016</td>
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<td>Overall (I² = 0.00%, P = .88)</td>
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<td>2546</td>
<td>326</td>
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Risk Ratio (95% CI)
Figure 5. Association of Positive Airway Pressure With Vascular Outcomes and Deaths in Trial Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Positive Airway Pressure</th>
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<th>Heterogeneity</th>
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<td>Participants, No.</td>
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<td>3</td>
<td>1694</td>
<td>135</td>
</tr>
<tr>
<td>Adherence</td>
<td>&lt;1 h/d</td>
<td>3</td>
<td>141</td>
<td>1694</td>
</tr>
<tr>
<td></td>
<td>≥1 h/d</td>
<td>4</td>
<td>28</td>
<td>578</td>
</tr>
<tr>
<td>Outcomes</td>
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<td>163</td>
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<tr>
<td></td>
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<td>315</td>
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<td>Major adverse cardiovascular events plus</td>
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<td>240</td>
<td>1694</td>
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<td>Adherence</td>
<td>&lt;1 h/d</td>
<td>3</td>
<td>240</td>
<td>1694</td>
</tr>
<tr>
<td></td>
<td>≥1 h/d</td>
<td>4</td>
<td>75</td>
<td>578</td>
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</tr>
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<td>247</td>
<td>213</td>
</tr>
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<td></td>
<td>≥1 h/d</td>
<td>4</td>
<td>4</td>
<td>578</td>
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<tr>
<td>Sleep apnea</td>
<td>5</td>
<td>29</td>
<td>1917</td>
<td>35</td>
</tr>
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<td>222</td>
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<td>≥1 h/d</td>
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<td>Sleep apnea</td>
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<td>Outcome</td>
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Risk Ratio (95% CI)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reference No. for Included Studies</th>
<th>No. of Participants</th>
<th>Pooled Mean Difference, Random-Effects Model (95% CI)</th>
<th>Heterogeneity P², %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>18, 20, 22, 24</td>
<td>1510 1507</td>
<td>-0.20 (-2.29 to 1.89)</td>
<td>61.50</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>18, 20, 22, 24</td>
<td>1481 1477</td>
<td>-0.21 (-1.06 to 0.65)</td>
<td>0.00</td>
<td>.80</td>
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<tr>
<td>Body mass index</td>
<td>17, 18, 20, 22</td>
<td>677 692</td>
<td>0.36 (-0.17 to 0.88)</td>
<td>0.00</td>
<td>.91</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>18, 20</td>
<td>276 275</td>
<td>0.02 (-0.11 to 0.07)</td>
<td>56.70</td>
<td>.13</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>18, 20</td>
<td>266 267</td>
<td>0.02 (-0.14 to 0.19)</td>
<td>0.00</td>
<td>.46</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>18, 20</td>
<td>263 264</td>
<td>0.05 (-0.23 to 0.14)</td>
<td>0.00</td>
<td>.60</td>
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<td>Triglycerides, mmol/L</td>
<td>18, 20</td>
<td>274 276</td>
<td>0.04 (-0.14 to 0.23)</td>
<td>33.60</td>
<td>.22</td>
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<tr>
<td>Glucose, mmol/L</td>
<td>18, 20</td>
<td>275 276</td>
<td>-0.09 (-0.40 to 0.23)</td>
<td>0.00</td>
<td>.95</td>
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<tr>
<td>Hemoglobin A₁c, %</td>
<td>18, 20</td>
<td>268 267</td>
<td>-0.04 (-0.27 to 0.18)</td>
<td>0.00</td>
<td>.90</td>
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<td>ESS score</td>
<td>17, 19, 20, 22, 24</td>
<td>2169 2116</td>
<td>-1.92 (-2.79 to -1.06)</td>
<td>91.50</td>
<td>.00</td>
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<tr>
<td>SAQLI score</td>
<td>18, 20</td>
<td>288 282</td>
<td>0.51 (0.31 to 0.70)</td>
<td>8.70</td>
<td>.29</td>
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<td>EQ-SD score</td>
<td>18, 24</td>
<td>1362 1336</td>
<td>0.00 (-0.02 to 0.03)</td>
<td>0.00</td>
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<td>Component scores</td>
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<tr>
<td>SF-36 score, physical</td>
<td>18, 23, 24</td>
<td>1446 1426</td>
<td>1.91 (-1.01 to 4.83)</td>
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<td>SF-36 score, mental</td>
<td>18, 23, 24</td>
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<td>HADS score, anxiety</td>
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<td>HADS score, depression</td>
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<td>1334 1306</td>
<td>-0.70 (-1.09 to -0.31)</td>
<td>21.90</td>
<td>.26</td>
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</table>
CONCLUSIONS AND RELEVANCE  The use of PAP, compared with no treatment or sham, was not associated with reduced risks of cardiovascular outcomes or death for patients with sleep apnea. Although there are other benefits of treatment with PAP for sleep apnea, these findings do not support treatment with PAP with a goal of prevention of these outcomes.
Meta-Analysis of Cardiovascular Outcomes With Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea

Ahmed S. Abuzaid, MD\textsuperscript{a}, Haitham S. Al Ashry, MD\textsuperscript{b,*}, Ayman Elbadawi, MD\textsuperscript{c}, Ha Ld, MD\textsuperscript{c}, Marwan Saad, MD\textsuperscript{d}, Islam Y. Elgendy, MD\textsuperscript{e}, Akram Elgendy, MD\textsuperscript{e}, Ahmed N. Mahmoud, MD\textsuperscript{e}, Amgad Mentias, MD\textsuperscript{f}, Amr Barakat, MD\textsuperscript{g}, and Chitra Lal, MD\textsuperscript{b}

(Am J Cardiol 2017;120:693–699)
Methods

• Study inclusion
  • Search of PubMed, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials for randomized controlled trials comparing CPAP with medical therapy alone in patients with OSA who reported cardiovascular outcomes of interest through December 2016
  • Data extracted by 2 authors

• Outcomes
  • Primary: major adverse cardiac events
  • Other: cardiac mortality, myocardial infarction, angina pectoris, stroke, and transient ischemic attack
Results

• Subjects
  • 4 randomized controlled trials included (1 that was not included in JAMA; 2016 NEJM included)
  • 3,780 subjects
  • Mean age 61%, 74% men
  • mean AHI 33.75
  • Duration of follow up and mean CPAP use not reported

• Outcomes
  • 174 of 1,882 (9%) patients assigned to the CPAP group experienced major adverse cardiac events compared with 186 of 1,898 (10%) allocated to the control group (RR 0.94, 95% CI 0.78 to 1.15, p = 0.93)
  • In 3 studies, subgroup analysis was done among patients who used CPAP more than 4 hours versus no CPAP. Meta-analysis of these subgroups did show less risk of major adverse cardiac events with >4 hours of adherence (RR 0.70, 95% CI 0.52 to 0.94, p = 0.02)
Major adverse cardiovascular event

\[ \geq 4 \text{ hrs/night} \]
Cardiac mortality

Myocardial Infarction

Angina
Figure 6. Forest plot evaluating the relative risk of stroke between CPAP versus control group of OSA patients.

Figure 7. Forest plot evaluating the relative risk of transient ischemic attack between CPAP versus control group of OSA patients.
Conclusion

In conclusion, compared with medical therapy alone, utilization of CPAP in patients with OSA is not associated with improved cardiac outcomes except in patients who wore it for >4 hours.
Final Thoughts

• There is ample data on association between OSA and serious cardiovascular and neurologic events

• Several trials reported improvements with CPAP use on improved cognition, reduced risk of dementia, stroke and cardiovascular events
  • However many studies include a small number of subjects, don’t have a control group and are not randomized

• Recent meta-analysis shows lack of consistent reduced cardiovascular events with CPAP use
  • However many studies are limited by short follow up, inadequate CPAP use
Concluding Thoughts

• Discussions with patients?
  • CPAP should be offered for symptomatic improvement in EDS
  • CPAP may improve cognition in individual patients
  • We need to emphasize the importance of proven therapies, such as blood pressure lowering, lipid lowering, and antiplatelet therapy in patients with sleep apnea, who should be treated according to established guidelines

• Need for more research
  • Older studies included different patients (more severe OSA based on different definitions, medical management of chronic conditions was different)
  • Randomized with a control group on maximal medical management
  • Active group needs to be adherent with CPAP… is more than 4 hrs needed?
References

Practice Guidelines

OSA and Stroke: Associations


**Stroke and CPAP**

**OSA and Cognitive Disorders: Associations**


CPAP and Cognitive Disorders:


CPAP and Cardiovascular Outcomes:


Year in Review:
Pharmacology

Afifa Shamim-Uzzaman, MD
Director, AAVA Sleep Center
Assistant Professor, University of Michigan
Ann Arbor, MI
Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients:

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<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
Agents Reviewed

• Pitolisant
  • H3R reverse agonist

• JSP-110 ([R]-2-amino-3-phenylpropylcarbamate hydrochloride)
  • Formerly known as ADX-N05
  • phenylalanine-derived wake promoting agent
  • dopamine and norepinephrine reuptake inhibitor
  • differs from modafinil in that it inhibits reuptake at dopamine and norepinephrine transporters
  • differs from traditional stimulants such as D-amphetamine in that JZP-110 does not promote the release of norepinephrine

• TAAR1
  • Trace amine-associated receptor agonist
Pitolisant
The European Medicines Agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use

Marta Kollb-Sielecka a,*, Pierre Demolis a, b, Joseph Emmerich a, b, Greg Markey a, c, Tomas Salmonson a, d, Manuel Haas a

a European Medicines Agency (EMA), London, United Kingdom
b National Agency for the Safety of Medicines and Health Products (ANSM), France
c Medicines and Healthcare Regulatory Agency (MHRA), London, United Kingdom
d Läkemedelsverket, Medical Products Agency, Uppsala, Sweden

Table 2
Overview of main studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study features</th>
<th>Doses</th>
<th>N</th>
<th>ESS change from baseline</th>
<th>% responders</th>
<th>Cataplexy reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmony I</td>
<td>Randomized double-blind; patients with narcolepsy with or without cataplexy; 8 weeks</td>
<td>9–36 mg/day</td>
<td>94</td>
<td>$-3.3 [-5.83; -0.83]; p &lt; 0.05$</td>
<td>71%</td>
<td>$0.38 [0.16; 0.93]; p = 0.034$</td>
</tr>
<tr>
<td>Harmony Ibis</td>
<td>Randomized double-blind; patients with narcolepsy with or without cataplexy; 8 weeks</td>
<td>4.5–18 mg/day</td>
<td>165</td>
<td>$-1.94 [-4.05; -0.07]; p = 0.065$</td>
<td>66.7%</td>
<td>$-1.00 [-2.12; 0.128] p = 0.077$</td>
</tr>
<tr>
<td>Harmony CTP</td>
<td>Randomized double-blind; patients with narcolepsy with cataplexy; 7 weeks</td>
<td>4.5–36 mg/day</td>
<td>105</td>
<td>$-3.41 [-4.95; -1.87]; p &lt; 0.0001$</td>
<td>68.6%</td>
<td>$0.512 [0.435; 0.603]; p &lt; 0.0001$</td>
</tr>
</tbody>
</table>

ESS, Epworth Sleepiness Scale.
Fig. 1. Changes in Epworth Sleepiness Scale Score (ESS) (mean ± SEM) from Baseline to week 8 in Harmony 1 study [Dauvilliers, 2013].

Fig. 2. Changes in weekly cataplexy episodes (geometric mean) from baseline to week 7 in Harmony CTP study.
Harmony III

- Phase III, naturalistic, open-label, prospective, longitudinal, uncontrolled trial, to assess the long-term safety of pitolisant in the treatment of EDS in patients with narcolepsy with or without cataplexy.
- The maximal dose received during the study was 36 mg/day in 88% of patients.
- The ESS change from baseline to final visit at month 12 was about 4.3 points.
- Responders’ rate (defined as ESS $\leq 10$ or $\text{ESSF} - \text{ESSB} \geq 3$) was 64.7%.
Ongoing Trials with Pitolisant

• HARMONY IV (NCT 01789398):
  • Pitolisant as an add-on to sodium oxybate

• Trial NCT01067235
  • Pitolisant as an add on to modafinil

Both trials have been completed but results are not yet available
Can I purchase or bring drug or device products from a foreign country to the U.S.?

U.S. Citizens:

In most circumstances, it is illegal for individuals to import drugs or devices into the U.S. for personal use because these products purchased from other countries often have not been approved by FDA for use and sale in the U.S. For example, a drug approved for use in another country but not approved by FDA would be considered an unapproved drug in the U.S. and, therefore, illegal to import.

FDA cannot ensure the safety and effectiveness of medicine purchased over the Internet from foreign sources, storefront businesses that offer to buy foreign medicine for you, or during trips outside the U.S. For these reasons, FDA recommends only obtaining medicines from legal sources in the U.S.

Are there any circumstances when I could purchase or bring an unapproved drug or device into the U.S.?

FDA has guidance for personal importation of drug or device products. Below provides information regarding situations for which this might be allowed:

- Product is not for treatment of a serious condition and there is no known significant health risk (Over the Counter, OTC); and

- Product is for the treatment of a serious condition (Prescription Drug Products):
  - The product is for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means.
  - There is no known commercialization or promotion of the product to persons residing in the U.S.
  - The product does not represent an unreasonable risk.
  - The consumer affirms in writing that the product is for personal use.
  - The quantity is generally not more than a three month supply and either:
    - a. Provide the name and address of the doctor licensed in the U.S. responsible for your treatment with the product, or
    - b. Provide evidence that the product is for the continuation of a treatment begun in a foreign country.
JZP-110 (aka ADX-N05)
JZP-110

Inclusion Criteria:
- Adults between 18 and 65 years of age
- Confirmed narcolepsy with or without cataplexy
- ESS ≥ 10
- Mean Sleep Latency ≤ 10 min in 4 of 5 naps on the MWT

Exclusion Criteria:
- Lactating or pregnant women
- Medical disorder other than narcolepsy with EDS
- Significant cardiovascular disease
- Phenylketonuria or hypersensitivity to phenylalanine-derived products
- BMI > 34
- Excessive caffeine use 1 week prior to study
- Nictoine dependence
- Drug or alcohol abuse within prior 2 years
- Any sedating or stimulating product
- SSRI or anticonvulsant use in prior 14 days
- Any other concurrent investigational drug use

Withdrawals d/t AE: conversion d/o, acute cholecystitis, anxiety flare

Figure 1—Study design.
Introduction: Trace amines (TAs) are endogenous amino acid metabolites that are structurally similar to the biogenic amines. TAs are endogenous ligands for trace amine-associated receptor 1 (TAAR1), a GPCR that modulates dopaminergic, serotonergic, and glutamatergic activity. Selective TAAR1 agonists have been shown to have pro-cognitive, antipsychotic-like, anti-addiction, stress-reducing, weight-reducing, glucose-lowering and wake-promoting activities. We used Taar1 knockout (KO) and over-expressing (OE) mice and TAAR1 agonists to elucidate the role of TAAR1 in sleep/wake.

Methods: EEG, EMG, body temperature (Tb) and locomotor activity (LMA) were recorded in Taar1 KO, OE and WT mice. Following a 24h recording to characterize baseline sleep/wake, mice were sleep-deprived (SD) for 6h. In separate experiments, mice were given three doses of the TAAR1 partial agonist RO5263397, caffeine, modafinil or vehicle p.o.

Results: Baseline wakefulness was modestly increased in OE compared to WT mice. Baseline theta (4.5-9Hz) and low gamma (30-60Hz) activity was elevated in KO compared to OE mice in NREM and REM sleep. Following SD, both KO and OE mice exhibited a homeostatic sleep rebound. In WT mice, RO5263397 increased waking and reduced NREM and REM sleep, decreased gamma power during wake and NREM, and decreased Tb without affecting LMA; these effects were absent in KO mice and potentiated in OE mice. By contrast, caffeine increased wake time, NREM gamma power, and LMA in all strains compared to vehicle; this effect was attenuated in KO and potentiated in OE mice. Subsequent studies confirmed that motor activation and gamma band activity increases induced by caffeine or modafinil are attenuated in KO mice compared to WT.

Conclusion: TAAR1 overexpression increases wakefulness whereas TAAR1 partial agonism strongly increases wakefulness and reduces NREM and REM sleep. These results indicate a modulatory role for TAAR1 in sleep/wake and cortical activity and suggest TAAR1 as a novel target for wake-promoting therapeutics.

Support (If Any): NIH R01 NS082876.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>First Line Therapy</th>
<th>Second Line Therapy</th>
</tr>
</thead>
</table>
| EDS               | Modafanil/Armodafanil | For disabling EDS on 1\(^{\text{st}}\)-line therapy:  
                   + Intermediate-release methylphenidate  
                   For partial responders having pm difficulty:  
                   + Short-acting stimulant  
                   (methylphenidate preferred)  
                   For nonresponders already on stimulants:  
                   switch to  
                   Long-acting stimulant  
                   (Adderall XR preferred) |
| EDS and Cataplexy | Suvorexant            | + SNRI, SSRI, or TCA  
                   Preferred: venlafaxine |
Melatonin
REMFresh (CRA-Melatonin)- REMAKT Trial

• IPP-technology:
  • Hydrogel matrix coating allows for rapid release of melatonin from the surface of the tablet in the acidic (stomach) environment
  • Higher pH (small intestine), after proper hydration, allows continuous release of the active melatonin and acidic moiety into the intestinal lumen
• Allows for:
  ➢ Burst release and absorption of approximately 50% of the melatonin within the first 3 hours, facilitates sleep onset.
  ➢ Sustained release and absorption of approximately 50% of the remaining melatonin within the next 4 hours helps with sleep maintenance
• Tmax 1.5 hours
• Median plateau time (sleep maintenance time) = 6.7 hours vs 3.7 hours (IR-melatonin)

N = 10
Significant variation in melatonin content between brands.

Significant difference in melatonin concentration between different formulations.

Difference in melatonin content varied from 1.25 to 113% from lot-to-lot, within the same brand.

<table>
<thead>
<tr>
<th>Product code</th>
<th>Lot</th>
<th>Serotonin present, µg</th>
<th>Standard error, µg</th>
<th>Absolute % difference between lots</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>1</td>
<td>7.422</td>
<td>0.689</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7.33</td>
<td>0.496</td>
<td></td>
</tr>
<tr>
<td>E-1</td>
<td>1</td>
<td>6.462</td>
<td>1.028</td>
<td>60.90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.12</td>
<td>0.349</td>
<td></td>
</tr>
<tr>
<td>G-3</td>
<td>1</td>
<td>2.9</td>
<td>0.252</td>
<td></td>
</tr>
<tr>
<td>G-5</td>
<td>1</td>
<td>74.27</td>
<td>12.94</td>
<td>22.40</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>59.31</td>
<td>1.274</td>
<td></td>
</tr>
<tr>
<td>J-1</td>
<td>1</td>
<td>36.86</td>
<td>0.929</td>
<td>113.64</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10.15</td>
<td>0.724</td>
<td></td>
</tr>
<tr>
<td>N-2</td>
<td>1</td>
<td>5.158</td>
<td>0.404</td>
<td>15.26</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.01</td>
<td>0.552</td>
<td></td>
</tr>
<tr>
<td>Q-1</td>
<td>1</td>
<td>3.73</td>
<td>0.614</td>
<td></td>
</tr>
<tr>
<td>R-1</td>
<td>1</td>
<td>1.21</td>
<td>0.372</td>
<td></td>
</tr>
</tbody>
</table>
Restifffic
RESTIFFIC

• Wraps around foot, can be tightened or loosened depending on pressure needed
• Targets Pressure on Abductor Hallucis & Flexor Hallucis Brevis Muscles
RESTIFFIC – Clinical Trial

• Single 8-week single-arm, open-label, clinical trial with a repeated measures design conducted between April 2009 and August 2012 in 2 offices in Erie, PA.

IRLSS Scores:
• Decreased from 25.05±5.33 (“Severe”) to 7.83±6.33 (“Mild”) from first day to last day (69% decrease in average IRLSS scores)

Sleep loss due to RLS symptoms:
• Decreased from 119.5 minutes to 22.1 minutes per night.

Clinical Global Impression Scale:
• All patients improved; none became worse.
• 90% of patients were “much improved” or “very much improved.”
• 60% of patients showed complete or nearly complete remission of all symptoms.
• 93% of patients showed no side effects.
“Okay, so that one’s not right for me either... Is Zythoranex right for me?”
Year in Review: Insomnia

J. Andrew Berkowski, MD
Assistant Professor of Neurology
Michigan Medicine & VA Ann Arbor Health System
Ann Arbor, MI
Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients:

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
CBT-I in 2016-17

• CBT-I is effective for everything!!!

• CBT-I works in any situation!
CBT-I effective for insomnia and co-morbid onychomycosis

Journal of Appendages and Sleep

https://dailyhealthpost.com/essential-oil-sleep-foot-spray/
CBT-I effective for insomnia in head football coaches during NCAA season

Journal of B1G Sports Physiology

Article Selection

Scope and impact
Focus on major sleep journals
  • Sleep
  • Journal of Clinical Sleep Medicine
  • Sleep Medicine
Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline

Michael J. Sateia, MD1; Daniel J. Buysse, MD2; Andrew D. Krystal, MD, MS3; David N. Neubauer, MD4; Jonathan L. Heald, MA5

1Geisel School of Medicine at Dartmouth, Hanover, NH; 2University of Pittsburgh School of Medicine, Pittsburgh, PA; 3University of California, San Francisco, San Francisco, CA; 4Johns Hopkins University School of Medicine, Baltimore, MD; 5American Academy of Sleep Medicine, Darien, IL
AASM Clinical Practice Guideline

Purpose:
• Commissioned by AASM Board of Directors
• No previous clinical guidelines
• Estimated 3.5—7% of patients receive prescription medications for sleep disturbance
AASM Clinical Practice Guideline

Methods:
• Four expert reviewers
• Systematic review of clinical trials
• GRADE system

Considerations:
• Efficacy
• Adverse effects
• Evaluation of efficacy v. adverse effects
• Recommendations for future investigations

AASM Clinical Practice Guideline

Results:
• WEAK strength of recommendation for all medications
• Does NOT mean effect or lack thereof is weak
AASM Clinical Practice Guideline

**FOR** chronic sleep initiation insomnia (versus no treatment):

- Eszopiclone
- Ramelteon
- Temazepam
- Triazolam
- Zaleplon
- Zolpidem
AASM Clinical Practice Guideline

**FOR** chronic sleep maintenance insomnia (versus no treatment):

- Doxepin
- Eszopiclone
- Suvorexant
- Temazepam
- Zolpidem
AASM Clinical Practice Guideline

**AGAINST** chronic sleep initiation & maintenance insomnia (versus no treatment):

- Diphenhydramine
- Melatonin
- Tiagabine
- Trazodone
- Tryptophan
- Valerian
Trazodone

- 50 mg trial with moderate quality of evidence
- Improvement to SL, TST, and WASO did not meet clinical significance
- Significant headache and somnolence
Diphenhydramine

- Two RCTs of 50 mg
- Improvement to SL, TST, SE, subjective awakenings, and sleep quality did not meet clinical significance
- Increased drowsiness and dizziness; one study showed rebound effect
- Absence of efficacy and minimal evidence for adverse effects
Prevalence, Correlates, and Predictors of Insomnia in the US Army prior to Deployment

Daniel J. Taylor, PhD; Kristi E. Pruiksma, PhD; Willie J. Hale, PhD; Kevin Kelly, MD; Douglas Maurer, DO; Alan L. Peterson, PhD; Jim Mintz, PhD; Brett T. Litz, PhD; Douglas E. Williamson, PhD; STRONG STAR Consortium

1Department of Psychology, University of North Texas, Denton, TX; 2Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX; 3Carl R. Dernall Army Medical Center, Fort Hood, TX; 4South Texas Veterans Healthcare System, San Antonio, TX; 5Department of Psychology, University of Texas at San Antonio, San Antonio, TX; 6Department of Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio, San Antonio, TX; 7Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA; 8Department of Psychiatry, Boston University School of Medicine, Boston, MA; 9Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; 10Durham VA Medical Center, Durham, NC
Insomnia in US Army

Purpose:
Prevalence, correlates, and predictors of insomnia prior to deployment
Insomnia in US Army

Methods:
• Fort Hood in Killeen, Texas
• Cross-section study
• 4101 active duty personnel
• ~45 minute self-report survey battery
Insomnia in US Army

Surveys include:

• Insomnia Severity Index
• Beck Anxiety Inventory
• PTSD checklist
• Alcohol Use Disorders Identification
• 9 others
Insomnia in US Army

Results:
• 19.9% had ISI ≥ 15 (clinical insomnia-moderate to severe)
• Highest in Native Americans
• 21.0% in enlisted personnel v. 4.9% in officers
Table 6—Predictors from simultaneous logistic regression analysis for variables predicting insomnia.

<table>
<thead>
<tr>
<th>Predictor Variable (Measure)</th>
<th>B</th>
<th>SE B</th>
<th>Wald</th>
<th>P</th>
<th>Odds Ratio</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.03</td>
<td>0.34</td>
<td>0.01</td>
<td>0.930</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>0.80</td>
<td>0.12</td>
<td>44.43</td>
<td>&lt; 0.001</td>
<td>2.22</td>
<td>1.75</td>
<td>2.80</td>
</tr>
<tr>
<td>Depression</td>
<td>0.89</td>
<td>0.14</td>
<td>38.93</td>
<td>&lt; 0.001</td>
<td>2.43</td>
<td>1.84</td>
<td>3.22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.84</td>
<td>0.14</td>
<td>37.68</td>
<td>&lt; 0.001</td>
<td>2.31</td>
<td>1.77</td>
<td>3.01</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>0.60</td>
<td>0.11</td>
<td>29.82</td>
<td>&lt; 0.001</td>
<td>1.82</td>
<td>1.47</td>
<td>2.26</td>
</tr>
<tr>
<td>Headaches</td>
<td>0.72</td>
<td>0.16</td>
<td>21.59</td>
<td>&lt; 0.001</td>
<td>2.06</td>
<td>1.52</td>
<td>2.79</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.51</td>
<td>0.14</td>
<td>13.22</td>
<td>&lt; 0.001</td>
<td>1.66</td>
<td>1.26</td>
<td>2.18</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>0.39</td>
<td>0.11</td>
<td>12.12</td>
<td>&lt; 0.001</td>
<td>1.48</td>
<td>1.19</td>
<td>1.84</td>
</tr>
<tr>
<td>Extremity pain</td>
<td>0.39</td>
<td>0.12</td>
<td>10.74</td>
<td>0.001</td>
<td>1.48</td>
<td>1.17</td>
<td>1.87</td>
</tr>
<tr>
<td>Head injury</td>
<td>0.44</td>
<td>0.14</td>
<td>9.33</td>
<td>0.002</td>
<td>1.55</td>
<td>1.17</td>
<td>2.05</td>
</tr>
<tr>
<td>Vertical cohesion</td>
<td>−0.31</td>
<td>0.11</td>
<td>7.20</td>
<td>0.007</td>
<td>0.74</td>
<td>0.59</td>
<td>0.92</td>
</tr>
<tr>
<td>Childhood physical neglect</td>
<td>0.29</td>
<td>0.12</td>
<td>5.45</td>
<td>0.020</td>
<td>1.33</td>
<td>1.05</td>
<td>1.70</td>
</tr>
<tr>
<td>Back pain</td>
<td>0.26</td>
<td>0.12</td>
<td>4.80</td>
<td>0.029</td>
<td>1.30</td>
<td>1.03</td>
<td>1.65</td>
</tr>
<tr>
<td>Number of times married</td>
<td>0.30</td>
<td>0.14</td>
<td>4.38</td>
<td>0.036</td>
<td>1.35</td>
<td>1.02</td>
<td>1.79</td>
</tr>
<tr>
<td>Tangible social support</td>
<td>−0.27</td>
<td>0.13</td>
<td>4.14</td>
<td>0.042</td>
<td>0.77</td>
<td>0.59</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Insomnia in US Army

Clinical Significance:
• 19.9% is slightly lower than previous studies but higher than the 13% in a similar civilian population
• Co-morbidities are not causality and may reflect interrelationship
• Insomnia is a health problem among active duty military

SCIENTIFIC INVESTIGATIONS

Veterans Affairs Primary Care Provider Perceptions of Insomnia Treatment

Christi S. Ulmer, PhD, CBSM1,2; Hayden B. Bosworth, PhD1,2; Jean C. Beckham, PhD3,4; Anne Germain, PhD5; Amy S. Jefferys, MStat6; David Edelman, MD1,6; Stephanie Macy, BS1; Angela Kirby, MA4; Corrine I. Voils, PhD7,8

1Durham VA Health Services Research and Development, Durham, North Carolina; 2Duke University Department of Psychiatry and Behavioral Sciences, Durham, North Carolina; 3Duke University School of Nursing, Durham, North Carolina; 4Veterans Affairs VISN 6 Mental Illness Research, Education, and Clinical Center, Durham, North Carolina; 5University of Pittsburgh, Department of Psychiatry, Pittsburgh, Pennsylvania; 6Department of Medicine, Duke University Medical Center, Durham, North Carolina; 7William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin; 8Department of Surgery, University of Wisconsin-Madison, Madison, Wisconsin
VA Primary Care Perception

Purpose:
• Insomnia within the largest integrated health system
• Assess primary care diagnosis and treatment
VA Primary Care Perception

Methods:
• 9 VA medical centers in Veteran’s Integrated Service Network 6 (mid-Atlantic)
• Internet survey of primary care providers
VA Primary Care Perception

Results:
• 51/381 providers (or 13%) responded
• 58.8% respondents estimated the prevalence of insomnia to be 20—39%
• 31.4% respondents thought higher than 40%
### VA Primary Care Perception

**Table 4**—Insomnia documentation in the medical record.

<table>
<thead>
<tr>
<th></th>
<th>Encounter Form (%)</th>
<th>CPRS Problem List (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Most of the time</td>
<td>43.1</td>
<td>29.4</td>
</tr>
<tr>
<td>Sometimes</td>
<td>29.4</td>
<td>47.1</td>
</tr>
<tr>
<td>Rarely</td>
<td>13.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Never</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Missing</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

CPRS = Computerized Patient Reporting System.
<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide the veteran with guidance on healthy sleep habits.</td>
<td>76.5</td>
</tr>
<tr>
<td>Offer the veteran pharmacotherapy, such as hypnotics or antidepressants.</td>
<td>70.6</td>
</tr>
<tr>
<td>Adjust or change medications that may contribute to insomnia.</td>
<td>66.7</td>
</tr>
<tr>
<td>Referral to a sleep specialist within my VA facility.</td>
<td>52.9</td>
</tr>
<tr>
<td>Referral to a VA provider who has been trained in cognitive behavioral therapy for insomnia.</td>
<td>29.4</td>
</tr>
<tr>
<td>Written materials focused on helping with insomnia.</td>
<td>29.4</td>
</tr>
<tr>
<td>Internet-based or electronic self-management resources for insomnia.</td>
<td>7.8</td>
</tr>
<tr>
<td>Referral to a sleep specialist at another VA facility.</td>
<td>2.0</td>
</tr>
<tr>
<td>Referral to a sleep specialist outside of the VA.</td>
<td>2.0</td>
</tr>
<tr>
<td>No response</td>
<td>0.0</td>
</tr>
<tr>
<td>Response</td>
<td>% Endorsed</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>No, I have never heard of it</td>
<td>15.7</td>
</tr>
<tr>
<td>Yes, I have heard of it but I don't really know how it works.</td>
<td>43.1</td>
</tr>
<tr>
<td>Yes, I have heard of it and have a general understanding of how it works.</td>
<td>29.4</td>
</tr>
<tr>
<td>Yes, I have heard of it and have a very good understanding of how it works.</td>
<td>5.9</td>
</tr>
<tr>
<td>Yes, I use it in my practice.</td>
<td>3.9</td>
</tr>
<tr>
<td>Missing</td>
<td>2.0</td>
</tr>
</tbody>
</table>

CBT-I = cognitive behavioral therapy for insomnia.
VA Primary Care Perception

Clinical Significance:
• Insomnia is considered as secondary to other conditions
• Despite access to CBT-I, this first-line treatment is off the radar
• Similar to non-VA settings
Effectiveness of Benzodiazepine Receptor Agonists in the Treatment of Insomnia: An Examination of Response and Remission Rates

Vivek Pillai, PhD1; Thomas Roth, PhD1; Timothy Roehrs, PhD1; Kenneth Moss, MD1; Edward L. Peterson, PhD2; Christopher L. Drake, PhD1

1Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI; 2Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, MI
BzRAs: Response & Remission

Purpose:
Assessment of “real-world” effectiveness of benzodiazepine receptor agonists
BzRAs: Response & Remission

Methods:
• Email survey from Henry Ford Health System database
• Outpatients with insomnia diagnosis in past two years and BzRA prescribed
• Assessed with reference to pre-treatment and during treatment
BzRAs: Response & Remission

Methods:

- Insomnia Severity Index (ISI)
  - Responders: decrease in ISI ≥ 6
  - Remitters: ISI < 11
- Levels of sleep disturbance including wake after sleep onset (WASO) and sleep onset latency (SOL)
BzRAs: Response & Remission

Results:
• 76.7% responders for ISI
• 47.7% remission
• Dose unrelated to response and remission
• 88.6% had a medical or psychiatric co-morbidity
BzRAs: Response & Remission

- SOL > 30
- WASO > 30
- WASO > 60
- SOL > 30 and/or WASO > 60

Proportion (%)

- Untaxed
- On BzRAs
BzRAs: Response & Remission

Clinical Significance:
• Patients frequently respond to BzRAs but most do not remit from insomnia disorder
• (CBT-I is effective for insomnia!)
Three-Year Follow-Up Comparing Cognitive Behavioral Therapy for Depression to Cognitive Behavioral Therapy for Insomnia, for Patients With Both Diagnoses

Kerstin Blom, LP, PhD; Susanna Jernelöv, LP, PhD; Christian Rücker, MD, PhD; Nils Lindefors, MD, PhD; Viktor Kaldo, LP, PhD

1Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; 2Section of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Purpose:
• Historically, focus of treatment has been on depression over insomnia
• Mounting evidence for co-morbid rather than “secondary” insomnia
• Long-term follow up of internet-based CBTs (ICBT) in patients with co-morbidity
Methods:
• 43 adults with major depression and insomnia
• Randomized to ICBT-I or ICBT-D
• 36 month follow-up
• Primary outcome: Self-Rated Montgomery Åsberg Depression Rating Scale (MADRS-S) and ISI
CBT-I v. CBT-D

Results:
• CBT-I was superior to CBT-D for insomnia
• No significant difference between CBT-I and CBT-D for depression
Clinical significance:

• Treatment of insomnia is important to recovery from depression

• Insomnia is not secondary to depression and should be treated independently

• Supposition: insomnia has specific treatments whereas depression can improve via many treatment modalities
European guideline for the diagnosis and treatment of insomnia

DIETER Riemann1, Chiara Baglioni1, Claudio Bassetti2, Bjørn Bjorvatn3, Leja Dolenc Grose1j4, Jason G. Ellis5, Colin A. Espie6, Diego Garcia-Borreguero7, Michaela Gjerstad8, Marta Gonçalves9, Elisabeth Hertenstein1, Markus Jansson-Frojmark10, Poul J. Jennum11, Damien Leger12, Christoph Nissen1,2,13, Liborio Parrino14, Tiina Paunio15, Dirk Pevernage16, Johan Verbraeken17, Hans-Gunter Weiß18, Adam Wichniak19, Irina Zavalko20, Erna S. Arnardottir21,†, Oana-Claudia Deleanu22,†, Barbara Strazisar23,†, Marielle Zoetmulder24,† and KAI SPIEGELHALDER1

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European Guideline for Insomnia

Purpose:
• Task force from European Sleep Research Society
• Provide clinical recommendations for the managements of adults with insomnia
European Guideline for Insomnia

Methods:

• Systematic review of all meta-analyses on adult insomnia through June 2016

• Use of the GRADE system‡

European Guideline for Insomnia

Diagnostic Recommendations (all strong):
• Medical history and examination
• Psychiatric/psychological history
• Sleep history
• Actigraphy
• Polysomnography
European Guideline for Insomnia

Treatment recommendations:
• CBT-I should be first-line for chronic insomnia (strong recommendation, high quality evidence)
• CBT-I and Bz/BzRAs comparable short term (≤ 4 weeks) (weak, moderate)
• Online or self-administered CBT-I is effective but likely less so than in-person CBT-I
• CBT-I and hypnotics more effective in short term than CBT-I alone
• CBT-I more effective in maintenance phase than CBT-I with pharmacotherapy
European Guideline for Insomnia

Treatment recommendations:
• Antihistamines, antipsychotics, melatonin, and herbal supplements (e.g. valerian) are not recommended (strong to weak, low to very low)
• Light therapy, exercise, mindfulness, and hypnosis need further study but are promising
• Complementary and alternative therapies (e.g. homeopathy, acupuncture) are not recommended (weak, very-low)
Clinical algorithm

Patient with sleep onset and/or sleep maintenance disturbance/early morning awakening and associated daytime impairment

Clinically significant impairment?
- yes
  - Sleep pattern in synchrony with circadian rhythm?
    - yes
      - Intake of substances that affect sleep?
        - yes
          - Change of medication
            - Abstinence Withdrawal
        - no
          - Comorbid somatic or mental disorder?
            - yes
              - Treatment of comorbid disorder AND insomnia
            - no
              - Treatment of insomnia with CBT-I as first-line option

- no
  - Psychoeducation, prevention
CBT-I effective for insomnia in heads of state with access to nuclear devices

International Journal of Sleep & Politics

References


QUESTIONS