Journal Scan

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Tolerability and efficacy of armodafinil in naïve patients with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, or narcolepsy: a 12-month, open-label, flexible-dose study with an extension period.

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STUDY OBJECTIVES: This 12-month, open-label, flexible-dose study with an extension period evaluated the tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea (OSA), shift work disorder (SWD), or narcolepsy.

METHODS: Armodafinil-naïve, adult patients with excessive sleepiness associated with treated OSA (n = 170), SWD (n = 108), or narcolepsy (n = 50) received armodafinil (100-250 mg) once daily (treated OSA or narcolepsy) or before night shifts (SWD). Patients with OSA were regular users of continuous positive airway pressure (CPAP) therapy. Efficacy measures included the Clinical Global Impression of Improvement (CGI-I) and the Epworth Sleepiness Scale (ESS).

RESULTS: Across the diagnosis groups, the most commonly occurring adverse event was headache (14%-24%). Forty-three patients (13%) and 13 patients (4%) were withdrawn because of adverse events and insufficient efficacy, respectively. Armodafinil did not adversely affect CPAP therapy. At the final visit, 80% (95% CI: 74.1, 86.7) of patients with treated OSA and 84% (72.7, 94.8) of patients with narcolepsy were rated on the CGI-I as at least minimally improved with regard to overall clinical condition; 98% (95.2, 100.0) of patients with SWD were rated as improved with regard to sleepiness during night shifts, including the commute to and from work. Armodafinil improved ESS total scores in patients with treated OSA (mean [SD] [95% CI] change from baseline, -7.3 [5.6] [-8.39, -6.30]) and patients with narcolepsy (-4.7 [6.0] [-7.41, -1.93]).

CONCLUSIONS: Armodafinil administered for 12 months or more was generally well tolerated and improved wakefulness in patients with excessive sleepiness associated with treated OSA, SWD, or narcolepsy. Armodafinil improved the overall clinical condition of patients with treated OSA or narcolepsy.

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Dysregulation of inflammatory responses by chronic circadian disruption.

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Circadian rhythms modulate nearly every mammalian physiological process. Chronic disruption of circadian

timing in shift work or during chronic jet lag in animal models leads to a higher risk of several pathologies. Many of these conditions in both shift workers and experimental models share the common risk factor of inflammation. In this study, we show that experimentally induced circadian disruption altered innate immune responses. Endotoxemic shock induced by LPS was magnified, leading to hypothermia and death after four consecutive weekly 6-h phase advances of the light/dark schedule, with 89% mortality compared with 21% in unshifted control mice. This may be due to a heightened release of proinflammatory cytokines in response to LPS treatment in shifted animals. Isolated peritoneal macrophages harvested from shifted mice exhibited a similarly heightened response to LPS in vitro, indicating that these cells are a target for jet lag. Sleep deprivation and stress are known to alter immune function and are potential mediators of the effects we describe. However, polysomnographic recording in mice exposed to the shifting schedule revealed no sleep loss, and stress measures were not altered in shifted mice. In contrast, we observed altered or abolished rhythms in the expression of clock genes in the central clock, liver, thymus, and peritoneal macrophages in mice after chronic jet lag. We conclude that circadian disruption, but not sleep loss or stress, are associated with jet lag-related dysregulation of the innate immune system. Such immune changes might be a common mechanism for the myriad negative health effects of shift work.

J Biol Rhythms. 2010 Oct;25(5):361-71.

Intrinsic activity rhythms in Macaca mulatta: their entrainment to light and melatonin.

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Mounting evidence that circadian abnormalities are a risk factor for cancer and for cardiovascular, psychiatric, and other disorders calls for in-depth investigation of intrinsic clock-dependent processes in diurnal animal models phylogenetically close to humans. Rhesus monkey (Macaca mulatta) is the most extensively studied diurnal nonhuman primate. Similar to humans, it features consolidated nighttime sleep and advanced cardiovascular, neuroendocrine, and cognitive responses. However, the intrinsic circadian rhythmicity in this species remains to be fully characterized. Here it is demonstrated that under constant dim light (~10 lx) conditions, young adult rhesus monkeys maintain robust intrinsic circadian rhythms of activity, with periods ranging from 23.4 to 25.1h. Constant environmental light of moderate intensity (~100 lx) slows down the circadian clock in rhesus monkeys. The exposure to light or melatonin shifts the phase of intrinsic circadian rhythms, with the direction and magnitude of the shift dependent on the circadian phase at which a stimulus was administered. The length of the intrinsic period largely defines an individual's chronotype (morningness or eveningness) and affects the stability of intrinsic rhythms and the phase angle of entrainment to melatonin and light. This first detailed characterization of intrinsic circadian rhythms of activity and their responses to light and melatonin in rhesus monkeys shows principal similarities to those in humans. These findings should provide new opportunities for translational research on the effects of diverse agents, environmental conditions, aging, and disease on the circadian clock and its outputs.

Sleep. 2010 Sep;33(9):1210-6.

Insomnia symptoms and daytime function in stable heart failure.

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OBJECTIVES: To evaluate insomnia symptoms and the extent to which they are associated with clinical and demographic patient characteristics, daytime symptoms, and functional performance in patients with stable heart failure (HF).

DESIGN: Cross-sectional, observational.

SETTING: Five structured HF disease management programs in the Northeastern U.S.

PARTICIPANTS: 173 stable chronic HF patients

INTERVENTIONS: N/A.

MEASUREMENTS AND RESULTS: Full polysomnography was obtained for one night in participants' homes. Participants completed the six-minute walk test, Medical Outcomes Study SF-36,

Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Multi-Dimensional Assessment of Fatigue Scale, Centers for the Epidemiological Studies of Depression Scale, and questionnaire items eliciting insomnia symptoms (self-reported difficulty initiating and maintaining sleep and waking too early in the morning). Over half of HF patients reported insomnia symptoms. These were associated with increased daytime symptoms (depression, fatigue), excessive daytime sleepiness, and functional performance in models that statistically controlled for clinical and demographic covariates. These relationships were not explained by sleep disordered breathing.

CONCLUSIONS: Insomnia symptoms are common in patients with stable heart failure and are associated with daytime symptoms and decrements in functional performance.

Psychosom Med. 2010 Oct;72(8):755-62. Epub 2010 Sep 14.

Overnight changes of immune parameters and catecholamines are associated with mood and stress.

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OBJECTIVES: To test the hypothesis that a nocturnal decrease of secretion of inflammation markers and catecholamines would be associated with mood and stress variables even after controlling for objective sleep variables.

METHODS: A total of 130 healthy volunteers participated in this study, spending 2 nights in the Gillin Laboratory of Sleep and Chronobiology at the University of California, San Diego, General Clinical Research Center. Blood samples were obtained before sleep (10:30 PM) and after awakening (6:30 AM) on the first day, and these samples were assayed for inflammatory biomarkers and catecholamines. On the second night, polysomnographic records were scored for objective sleep variables, e.g., total sleep time and wake after sleep onset. Self-rating scales for mood, stress, depression, and daily hassles were administered the second day.

RESULTS: The nocturnal decrease in interleukin-6 was smaller in people who reported more negative mood or fatigue and greater in those who reported more uplift events (e.g., with Profile of Mood States fatigue r(p) = -.25 to -.30). People with high stress or high depression levels had smaller nocturnal decreases of epinephrine. That relationship was even stronger when partial correlations were used to control for morning level and sleep variables. The associations between nocturnal changes of C-reactive protein, soluble tumor necrosis factor-receptor I, and norepinephrine with psychological states were nonremarkable.

CONCLUSIONS: The analyses of nocturnal change scores (difference scores) add substantial information compared with the traditional analyses of morning levels of immune variables and catecholamines alone. Subjective well-being is significantly associated with a greater nocturnal decrease of interleukin-6 and epinephrine. More research on nocturnal adaptation processes is warranted.

Adv Ther. 2010 Nov;27(11):796-813. Epub 2010 Sep 6.

Jet lag, circadian rhythm sleep disturbances, and depression: the role of melatonin and its analogs.

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Traveling through several time zones results in a constellation of symptoms known as jet lag. These include reduced alertness, daytime fatigue, loss of appetite, reduced cognitive skills, and disruption of the sleep/wake cycle. In susceptible air travel passengers, jet lag may exacerbate affective illness and result in psychiatric morbidity. Dysregulation of circadian rhythms and melatonin secretion represent the common underlying factor in jet lag and other circadian disorders. Recent studies have established the effectiveness of strategically timed administration of melatonin and appropriate timed exposure to environmental schedules including light in counteracting the dysregulation (chronobiologic actions). With the introduction of melatonergic agonists such as ramelteon and tasimelteon, which have both a stronger affinity for MT• and MT, melatonin receptors and a

longer half-life, new therapeutic options now exist for treating the sleep disturbances associated with jet lag. The melatonin analogs are unique inasmuch as they can also enhance daytime alertness. The recently introduced melatonergic antidepressant agomelatine, which has established its supremacy over other antidepressants in having a significant chronobiologic activity, represents a good choice for treating depressive symptoms that are associated with jet lag.

Acta Anaesthesiol Scand. 2010 Nov;54(10):1157-63. doi: 10.1111/j.1399-6576.2010.02296.x. Epub 2010 Sep 3.

Circadian aspects of post-operative morbidity and mortality.

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It has been well established that there exists a circadian concentration of cardiovascular, cerebrovascular and cardiopulmonary events. The aim was to describe aspects of circadian variation in relation to cardiovascular, cerebrovascular and thromboembolic diseases and to describe the literature concerning post-operative circadian disturbances. We also present the literature concerning circadian variation in post-operative morbidity and mortality. PubMed and the Cochrane database were searched for papers using a combination of 'circadian,''surgery,''post-operative,''mortality' and 'morbidity.' Eleven relevant studies were found, and seven of these were excluded due to the use of time of surgery and not time of morbidity or mortality as the main variable. The results from the four articles showed a circadian distribution of morbidity and mortality that mimics the one seen without surgery. There is a peak incidence of myocardial ischemia, fatal thromboembolism and sudden unexpected death in themorning hours. A circadian variation exists in post-operative morbidity and mortality. The observed circadian variation in post-operative morbidity andmortality may warrant a chronopharmacological approach to patients in the perioperative period. The underlying pathophysiological mechanisms should be the focus for future studies.

J Psychopharmacol. 2010 Nov;24(11):1577-601. Epub 2010 Sep 2.

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders.

Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, Britton TC, Crowe C, Dijk DJ, Espie CA, Gringras P, Hajak G, Idzikowski C, Krystal AD, Nash JR, Selsick H, Sharpley AL, Wade AG.

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Sleep disorders are common in the general population and even more so in clinical practice, yet are relatively poorly understood by doctors and other health care practitioners. These British Association for Psychopharmacology guidelines are designed to address this problem by providing an accessible up-to-date and evidence-based outline of the major issues, especially those relating to reliable diagnosis and appropriate treatment. A consensus meeting was held in London in May 2009. Those invited to attend included BAP members, representative clinicians with a strong interest in sleep disorders and recognized experts and advocates in the field, including a representative from mainland Europe and the USA. Presenters were asked to provide a review of the literature and identification of the standard of evidence in their area, with an emphasis on meta-analyses, systematic reviews and randomized controlled trials where available, plus updates on current clinical practice. Each presentation was followed by discussion, aimed to reach consensus where the evidence and/or clinical experience was considered adequate or otherwise to flag the area as a direction for future research. A draft of the proceedings was then circulated to all participants for comment. Key subsequent publications were added by the writer and speakers at draft stage. All comments were incorporated as far as possible in the final document, which represents the views of all participants although the authors take final responsibility for the document.

J Clin Sleep Med. 2010 Aug 15;6(4):330-5.

Napping, nighttime sleep, and cardiovascular risk factors in mid-life adults.

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STUDY OBJECTIVES: To evaluate the relations between sleep characteristics and cardiovascular risk factors and napping behavior, and to assess whether daytime napping leads to subsequent better or worse sleep.

METHODS: The sample consisted of 224 (African American, Caucasian, and Asian) middle-aged men and women. Sleep measures included nine nights of actigraphy and sleep diaries, sleep questionnaires, and one night of polysomnography to measure sleep disordered breathing.

RESULTS: More frequent napping was associated with shorter nighttime sleep duration averaged across the nine nights of actigraphy (especially among African Americans), more daytime sleepiness, more pain and fatigue by diary, and increased body mass index and waist circumference. Shorter nighttime sleep duration was associated with taking a nap during the next day and taking a nap was associated with less efficient sleep the next night.

CONCLUSIONS: Napping in middle-aged men and women is associated with overall less nighttime sleep in African Americans and lower sleep efficiency as measured by actigraphy, and increased BMI and central adiposity. These findings point to the importance of measuring of napping in understanding associations of sleep with cardiovascular risk.

J Psychopharmacol. 2010 Aug;24(2 Suppl):5-14.

Clock genes at the heart of depression.

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The rhythms of life are ever pervasive, touching almost every aspect of our lives. We are finely tuned to the cycle of light and dark, so that we normally sleep during the night and are active during the day. Physiological rhythms are, however, not just slaves to the solar day, but are actually generated endogenously within the suprachiasmatic nuclei in the hypothalamus and are entrained via the retina. The circadian timing system is organized hierarchically with the suprachiasmatic nuclei providing neural and/or hormonal cues to the various organ systems, allowing them to express their own rhythmic physiological output. There is now a substantial body of evidence emerging that disruption of rhythmicity through altered sleep/wake patterns and exposure to light, or through endogenous disruption of key determinants of endogenous rhythms, can be detrimental to health. Circadian rhythm disturbances have long been associated with mood disorders, especially delayed sleep onset, and evidence is accumulating that alterations to the cellular timing system may underpin some aspects of the disorders. For example, mice carrying mutations in either Clock or per2 spend less time immobile in swim tests, which has been suggested as mimicking mania. In humans, single nucleotide polymorphisms in Clock and other clock genes have been associated with depression. With this increasing knowledge we may predict that new antidepressant drugs will emerge that, as a primary or secondary mechanism of action, target and correct abnormalities in the circadMian timing system.

J Rheumatol. 2010 Oct;37(10):2156-66. Epub 2010 Aug 3.

Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study.

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OBJECTIVE: To determine the effects of sodium oxybate (SXB) on sleep physiology and sleep/wake-related

symptoms in patients with fibromyalgia syndrome (FM).

METHODS: Of 304 patients with FM (American College of Rheumatology tender point criteria) in the screened study population, 209 underwent polysomnography, 195 were randomized, and 151 completed this 8-week, double-blind, placebo-controlled study of SXB 4.5 g and 6 g/night. We evaluated changes in objective sleep measures and subjective symptoms, including daytime sleepiness [Epworth Sleepiness Scale (ESS)], fatigue visual analog scale (FVAS), sleep [Jenkins Scale for Sleep (JSS)], and daytime functioning [Functional Outcome of Sleep Questionnaire (FOSQ), SF-36 Vitality domain, and Fibromyalgia Impact Questionnaire (FIQ) general and morning tiredness].

RESULTS: Pretreatment screening revealed an elevated incidence of maximum alpha EEG-intrusion > 24 min/hour of sleep (66%), periodic limb movements of sleep (20.1% e" 5/hour), and moderate to severe obstructive sleep apnea disorder (15.3% apnea-hypopnea index e" 15/hour). Compared with placebo, both doses of SXB achieved statistically significant improvements in ESS, morning FVAS, JSS, FOSQ, SF-36 Vitality, and FIQ general and morning tiredness; both doses also demonstrated decreased rapid eye movement (REM) sleep (all p d" 0.040). SXB 6 g/night improved afternoon, evening and overall FVAS, reduced wakefulness after sleep onset, and increased Stage 2, slow-wave, and total non-REM sleep (all p d"0.032) versus placebo. Moderate correlations (e" 0.40) were noted between changes in subjective sleep and pain measures. Adverse events occurring significantly more frequently with SXB than placebo were nausea, pain in extremity, nervous system disorders, dizziness, restlessness, and renal/urinary disorders (including urinary incontinence).

CONCLUSION: This large cohort of patients with FM demonstrated that SXB treatment improved EEG sleep physiology and sleep-related FM symptoms. 12. J Biol Rhythms. 2010 Aug;25(4):288-96.Sex differences in phase angle of entrainment and melatonin amplitude in humans.

J Biol Rhythms. 2010 Aug;25(4):288-96.

Sex differences in phase angle of entrainment and melatonin amplitude in humans.

Cain SW, Dennison CF, Zeitzer JM, Guzik AM, Khalsa SB, Santhi N, Schoen MW, Czeisler CA, Duffy JF.

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Studies of sex differences in the timing of human circadian rhythms have reported conflicting results. This may be because the studies conducted to date have not controlled for the masking effects of the rest activity cycle on the circadian rhythms being assessed. In the present analysis of data collected under controlled conditions, we examined sex differences in the timing of circadian rhythms while minimizing masking from behavioral and environmental factors using a constant routine (CR) protocol. All participants (28 women and 28 men paired by habitual wake time; age range, 18 30 years) maintained a regular self selected sleep wake schedule at home prior to the study. After 3 baseline days in the laboratory, participants began a CR. Women were found to have a significantly higher melatonin amplitude and lower temperature amplitude than men. While sleep timing was the same between the 2 groups, the timing of the circadian rhythms of core body temperature and pineal melatonin secretion was earlier relative to sleep time in women as compared to men. Sleep therefore occurred at a later biological time for women than men, despite being at the same clock time. Given that sleep propensity and structure vary with circadian phase and are impacted by circulating melatonin, these findings may have important implications for understanding sex differences in sleep timing and duration, diurnal preference, and the prevalence of sleep disorders such as insomnia.

Eur J Endocrinol. 2010 Sep;163(3):383-90. Epub 2010 Jun 29.

Sleeping during the day: effects on the 24-h patterns of IGF-binding protein 1, insulin, glucose, cortisol, and growth hormone.

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BACKGROUND: Disturbed sleep is a major risk factor for metabolic disturbances, including type 2 diabetes, but the involved mechanisms are still poorly understood. We investigated how an acute shift of sleep to the daytime affected IGF-binding protein 1 (IGFBP1), which is a risk factor for diabetes.

METHODS: Seven healthy men (age, 22-32 years) participated in a night sleep condition (sleep 2300-0700 h) and a day sleep condition (0700-1500 h) with hourly blood samples taken for 25 h (starting at 1900 h) and isocaloric meals every 4th hour awake. The blood samples were analyzed for IGFBP1, insulin, GH, glucose, and cortisol.

RESULT: The acute shift of sleep and meal timing (to 8 h) shifted the 24-h patterns of IGFBP1, glucose, insulin, and GH to a similar degree. However, the day sleep condition also resulted in elevated levels of IGFBP1 (area under curve (AUC)+22%, $P<0.05$), and reduced glucose levels (AUC-7%, $P<0.05$) compared with nocturnal sleep. Sleeping during the day resulted in elevated cortisol levels during early sleep and reduced levels in late sleep, but also in increased levels the subsequent evening ($P's<0.05$).

CONCLUSION: Sleep-fasting seems to be the primary cause for the elevation of IGFBP1, irrespective of sleep timing. However, sleeping during the day resulted in higher levels of IGFBP1 than nocturnal sleep, suggesting altered metabolism among healthy individuals, which may have implications for other groups with altered sleep/eating habits such as shift workers. Moreover, sleep and meal times should be accounted for while interpreting IGFBP1 samples.

Cochrane Database Syst Rev. 2010 May 12;(5):CD008508.

Caffeine for the prevention of injuries and errors in shift workers.

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BACKGROUND: Sleepiness leads to a deterioration in performance and attention, and is associated with an increased risk of injury. Jet lag and shift work disorder are circadian rhythm sleep disorders which result in sleepiness and can elevate injury risk. They create a need for individuals to operate at times which are different to those dictated by their circadian rhythms. Consequently there is also a need for interventions to help ensure that these persons can do so safely. Caffeine has a potential role in promoting alertness during times of desired wakefulness in persons with jet lag or shift work disorder, however its effects on injury and error are unclear.

OBJECTIVES: To assess the effects of caffeine for preventing injuries caused by impaired alertness in persons with jet lag or shift work disorder.

SEARCH STRATEGY: We searched the Cochrane Injuries Group Specialised Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE, PsycINFO, CINAHL, TRANSPORT (to July 2008); and PubMed databases (to April 2010). We also searched the Internet and checked reference lists of relevant papers.

SELECTION CRITERIA: Randomised controlled trials investigating the effects of caffeine on injury, error or cognitive performance in people with jet lag or shift work disorder.

DATA COLLECTION AND ANALYSIS: Two authors independently screened search results and assessed full texts for inclusion. Data were extracted and risk of bias was assessed. Estimates of treatment effect (odds ratio and standardised mean difference (SMD)) and 95% confidence intervals (CI) were calculated and pooled using the fixed-effect model.

MAIN RESULTS: Thirteen trials were included. None measured an injury outcome. Two trials measured error, and the remaining trials used neuropsychological tests to assess cognitive performance. The trials assessing the

impact on errors found that caffeine significantly reduced the number of errors compared to placebo. The pooled effect estimates on performance by cognitive domain suggest that, when compared to placebo, caffeine improved concept formation and reasoning (SMD -0.41; 95% CI -1.04 to 0.23), memory (SMD -1.08; 95% CI -2.07 to -0.09), orientation and attention (SMD -0.55; 95% CI -0.83 to -0.27) and perception (SMD -0.77; 95% CI -1.73 to 0.20); although there was no beneficial effect on verbal functioning and language skills (SMD 0.18; 95% CI -0.50 to 0.87). One trial comparing the effects of caffeine with a nap found that there were significantly less errors made in the caffeine group. Other trials comparing caffeine with other active interventions (for example nap, bright light, modafinil) found no significant differences. There is a high risk of bias for the adequacy of allocation concealment and presence of selective outcome reporting amongst the trials.

AUTHORS' CONCLUSIONS: Caffeine may be an effective intervention for improving performance in shift workers however, there are no trials from which we can assess its effect on injuries. The results largely originate from studies involving young participants under simulated conditions, and the extent to which the findings are generalisable to older workers and real world shift work is unclear. Based on the current evidence, there is no reason for healthy individuals who already use caffeine within recommended levels to improve their alertness to stop doing so. The assessment of the relative effects of caffeine to other potential countermeasures should be a focus of future research.

Circ Res. 2010 Feb 19;106(3):447-62.

Circadian rhythms and metabolic syndrome: from experimental genetics to human disease.

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The incidence of the metabolic syndrome represents a spectrum of disorders that continue to increase across the industrialized world. Both genetic and environmental factors contribute to metabolic syndrome and recent evidence has emerged to suggest that alterations in circadian systems and sleep participate in the pathogenesis of the disease. In this review, we highlight studies at the intersection of clinical medicine and experimental genetics that pinpoint how perturbations of the internal clock system, and sleep, constitute risk factors for disorders including obesity, diabetes mellitus, cardiovascular disease, thrombosis and even inflammation. An exciting aspect of the field has been the integration of behavioral and physiological approaches, and the emerging insight into both neural and peripheral tissues in disease pathogenesis. Consideration of the cell and molecular links between disorders of circadian rhythms and sleep with metabolic syndrome has begun to open new opportunities for mechanism-based therapeutics.

J Clin Sleep Med. 2010 Oct 15;6(5):458-66.

The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder,or narcolepsy: an open-label extension study.

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STUDY OBJECTIVES: Armodafinil is a wakefulness-promoting medication. Its efficacy and tolerability have been established in 12-week studies of patients with excessive sleepiness (ES) associated with treated obstructive sleep apnea (OSA), shift work disorder (SWD), or narcolepsy. This study evaluated the tolerability and efficacy of armodafinil for > or = 12 months.

METHODS: Patients with ES associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week, double-blind studies were eligible for this multicenter, open-label study of > or = 12 months' duration of treatment with armodafinil (50 to 250 mg/day). Adverse events and other criteria of tolerability were monitored throughout the study. Efficacy assessments included the Clinical Global Impression of Change (CGI-C), Brief Fatigue Inventory (BFI), and Epworth Sleepiness Scale (ESS).

RESULTS: Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients (420/743) completed 12 months or more of

treatment. Discontinuations due to adverse events occurred in 13% of patients (95/743) during the initial 12-month period. Throughout the > or = 12-month study, adverse events were generally of mild-to-moderate intensity; headache (25% [180/731]), nasopharyngitis (17% [123/731]), and insomnia (14% [99/731]) were the most common. Modest increases were observed in vital sign measurements (blood pressure [3.6/2.3 mm Hg], heart rate [6.7 beats per minute]) across all patient groups; most of the changes occurred by month 3. Improvements from baseline in efficacy assessments started at month 1 and were maintained throughout the study.

CONCLUSIONS: Armodafinil remained effective and was generally well tolerated. Increased monitoring of blood pressure may be appropriate in patients on armodafinil. Armodafinil represents an option for long-term treatment of patients with ES associated with treated OSA, SWD, or narcolepsy.