Melatonin:

Role of Prolong-Release Melatonin in Neurogenerative disorders

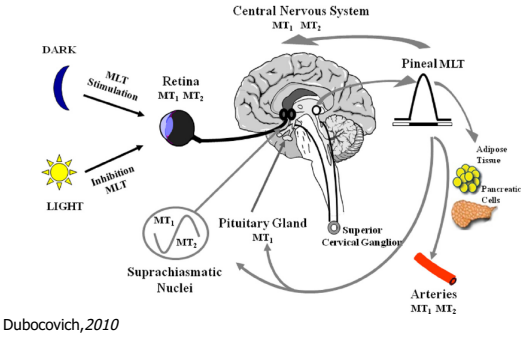
Dr. Yotin Chinvarun M.D. Ph.D.

CEP and Sleep disorder center, PMK hospital

Melatonin

- Melatonin is the "**darkness hormone**", secreted at night as we sleep
- It is the chemical messenger that transmits information about light-dark cycles to the SCN, that governs the body's biological clock and to many body organs.

Regulation of melatonin production and receptor function



Dubocovich, *2010*

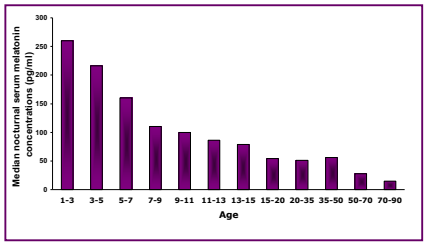
Melatonin – a key regulator of the sleep-wake cycle

- An important physiological sleep regulator
- An important cue of the internal biological clock
- Sharp increase in sleep propensity at night occurs 2 hours after the onset of endogenous melatonin
- Administration of melatonin during daytime promotes fatigue and sleep-like brain activity patterns

Melatonin secretion

- Melatonin is not a sedative, but a sign of darkness or night time
  - For example, nocturnal animals might be awake while the melatonin level is high.
- In humans, melatonin secretion related to preparation for sleep:
  - Induces heat loss
  - Reduces arousal
  - Delays production of cortisol, which increases arousal, blood pressure and blood sugar.
- Towards the morning plasma levels of melatonin decrease, sleep ends and wakefulness begins

Melatonin secretion decreases as a person ages



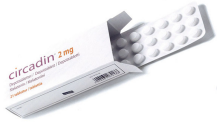
There is an age related decline in melatonin production subsequent to calcification of the pineal gland and decline in activity of the master circadian clock residing in the suprachiasmatic nuclei (SCN) of the brain

Melatonin: Pharmakokinetics

- Peak plasma concentrations of endogenous melatonin in adults reach a high of 60 to 70 pg/mL and typically occur between 2:00 and 4:00 am
- Supplementary exogenous melatonin has 15% absolute bioavailability at 2- and 4-mg oral doses
- Melatonin had rapid absorption, mean time to reach maximal concentration (Tmax) of 23 minutes
- Sustained-release melatonin (2 mg) has Tmax of 3 hours
- Terminal half- life is 3.5 to 4 hours

Prolonged-release melatonin: Circadin®

- **Prolonged-release melatonin**
  - Was introduced in 2007 in the EU and since then in other countries
  - The first and only melatonin product approved by the European Medicines Agency (EMEA)
  - Recent findings suggest that efficacy and safety are maintained for at least 3 months.
  - Works by selectively affecting melatonin receptors
  - Acts by synchronizing the biological clock and by inducing night time cues (sleep induction, blood pressure control, lowering body temperature)



Circadin® Indication and Posology

- Circadin® is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.
- The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.

Pharmacokinetic

Absorption

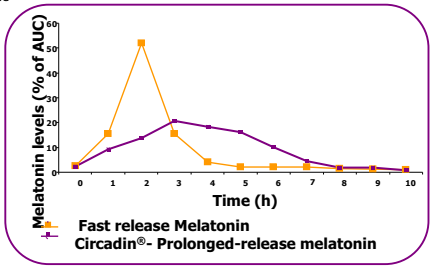
- T_{max} = 3.5–5.0 hours
- C_{max} = 1,020 pg/ml (fed state)

Biotransformation

- Liver Metabolism 12 hours
- 90% metabolised through CYP1A1 and CYP1A2 isoenzymes
- Drug interaction e.g. Cimetidine, Quinolone, Carbamazepine, Rifampicin

Circadin® Vs. Immediate-release melatonin

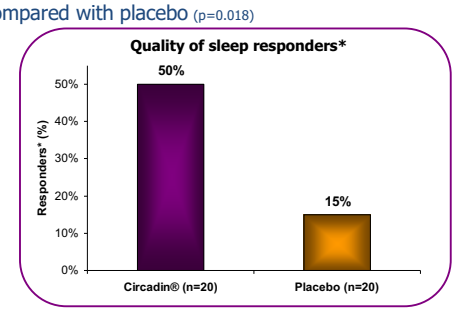
- Immediate-release melatonin has a rapid onset to high levels and is rapidly metabolised
- Prolonged-release melatonin - Circadin® circumvents both the build-up of high levels and the fast clearance of melatonin by releasing it over a predefined extended period of time



EPAR, Assessment report for Circadin. Procedure No.EMEA/H/C/695

Circadin® : Efficacy

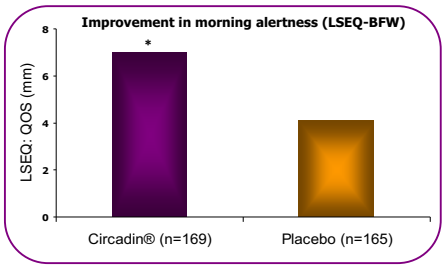
- Circadin® improves patient reported quality of sleep compared with placebo (p=0.018)



responder= *> 10 mm* LSEQ-QOS
Luthringer, 2009.

Circadin® : Efficacy

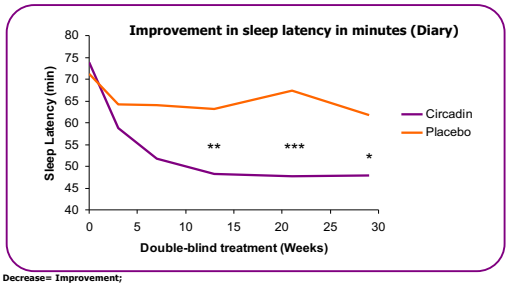
- Circadin® improves morning alertness (LSEQ-BFW) compared with placebo (p=0.038)*



Wade et al. 2007;

Circadin® efficacy (long term 6 months)

- The efficacy of Circadin® is maintained or enhanced during in the long term treatment (p<0.001)*



Decrease= Improvement;
Mean (95%CI) Treatment Effect: -8.0 (-12.4, -3.7), *<0.05 ; **<0.01;***<0.001

Circadin® re-adjusts sleep-wake cycle

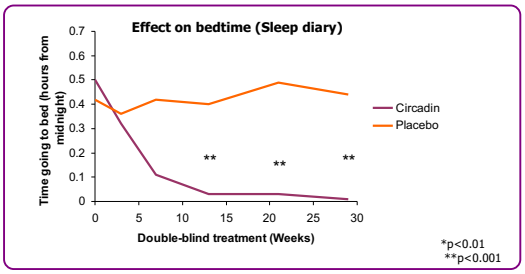
Circadin® (prolonged-release melatonin)

restores the physiological melatonin level and thereby the circadian sleep-wake cycle

It may take several days to restore the physiological circadian sleep-wake cycle – hence treatment efficacy builds up to synchronize the endogenous biological clock. Some patients need up to 3 months to attain the full response

Circadin re-adjusts the body clock

- Late sleepers experience a significant shift to an earlier bedtime with Circadin® compared to placebo



Data on Neurim file

Circadin® - Low level of adverse events

MedDRA System Organ Class/ Preferred Term	Circadin (N=1850) N	%	Rate of Pts With AE per 100 Pt Weeks	Placebo (N=1575) N	%	Rate of Pts With AE per 100 Pt Weeks
ABDOMINAL PAIN	21	(1.1)	0.069	11	(0.7)	0.104
ABDOMINAL PAIN UPPER	18	(1.0)	0.059	20	(1.3)	0.189
CONSTIPATION	23	(1.2)	0.075	14	(0.9)	0.132
DIARRHOEA	58	(3.1)	0.190	29	(1.8)	0.273
NAUSEA	34	(1.8)	0.111	27	(1.7)	0.255
VOMITING	28	(1.5)	0.092	14	(0.9)	0.132
ASTHENIA	37	(2.0)	0.121	19	(1.2)	0.179
INFLUENZA	26	(1.4)	0.085	14	(0.9)	0.132
LOWER RESPIRATORY TRACT INFECTION	37	(2.0)	0.121	19	(1.2)	0.179
NASOPHARYNGITIS	75	(4.1)	0.245	48	(3.0)	0.453
PHARYNGITIS	37	(2.0)	0.121	20	(1.3)	0.189
SINUSITIS	18	(1.0)	0.059	8	(0.5)	0.075
UPPER RESPIRATORY TRACT INFECTION	56	(3.0)	0.183	20	(1.3)	0.189
URINARY TRACT INFECTION	40	(2.2)	0.131	12	(0.8)	0.113
ARTHRALGIA	68	(3.7)	0.222	29	(1.8)	0.273
BACK PAIN	74	(4.0)	0.242	23	(1.5)	0.217
MUSCLE CRAMP	21	(1.1)	0.069	10	(0.6)	0.094
NECK PAIN	21	(1.1)	0.069	10	(0.6)	0.094
PAIN IN EXTREMITY	30	(1.6)	0.098	18	(1.1)	0.170
HEADACHE	107	(5.8)	0.350	101	(6.4)	0.952
MIGRAINE	18	(1.0)	0.059	18	(1.1)	0.170
ANXIETY	20	(1.1)	0.065	19	(1.2)	0.179
COUGH	41	(2.2)	0.134	20	(1.3)	0.189
PHARYNGOLARYNGEAL PAIN	29	(1.6)	0.095	14	(0.9)	0.132
RHINITIS	21	(1.1)	0.069	15	(1.0)	0.141
RASH	18	(1.0)	0.059	9	(0.6)	0.085
Any Event	922	(49.8)	3.013	609	(38.7)	5.743

** Total patients in Body System with AE (including those having less than 1% occurrence)*
EPAR, Assessment report for Circadin. Procedure No.EMEA/H/C/695 updated 2009

Melatonin and Neurological Sleep disorders

CIRCADIAN RHYTHM SLEEP DISORDERS: EXOGENOUS CAUSES ASSOCIATED WITH ALTERED MELATONIN SECRETION PATTERN

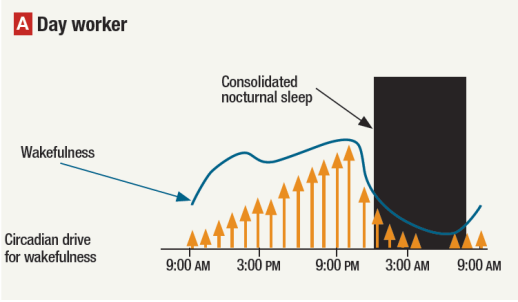
- Disruption of the physiologic circadian rhythm due to changes in environmental conditions e.g.
  - **Shift work**
  - **Sleep deprivation**
  - Exposure to light during the night, or trans- meridian flights

Results in clinical symptoms in parallel with alteration of melatonin secretion

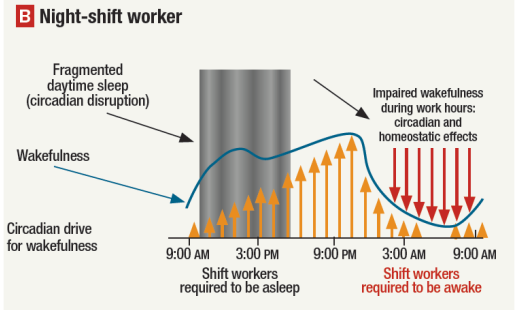
Shift Work and Shift Work Sleep Disorder

- Working in the dark period normally devoted to sleep
- Major cause of desynchronization of biological rhythms
- Multiple adverse clinical consequences including
  - behavioral changes, sleep disorders, safety problems at work, altered hormonal and metabolic regulation, and susceptibility to hormone-dependent cancers

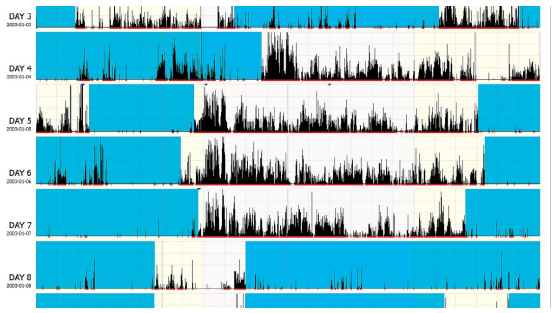
Shift Work Disorder (SWD)



Shift Work Disorder (SWD)



Shift Work Disorder (SWD)



Transmeridian Flights and Jet Lag Disorder

- Rapid passage across multiple time zones in long- distance transmeridian air travel results in desynchronization of internal circadian rhythm from the day–night status at destination
- Sudden disruption of the rest–activity cycle leads to
  - Insomnia
  - Premature awakening
  - Diurnal sleepiness
  - Loss of efficiency known as the jet lag disorder

Transmeridian Flights and Jet Lag Disorder

- Intensity of the disorder varies according to duration and intensity of flight, number of time zones crossed (usually seven or more) and individual tolerance
- East- ward flights, which provoke a marked phase advance, most distressing
- Besides unpleasant consequences for air flight passengers, jet lag problematic for airplane crew, risk of altered vigilance and reactivity

Transmeridian Flights and Jet Lag Disorder

- Various protocols involving timed bright-light exposure or melatonin administration, or both
- Phase advance circadian rhythm of travelers planning eastward flights crossing nine or more time zones, including
  - 1-hour earlier wakeup time and bedtime every day for the 3 consecutive days preceding the flight,
  - 30 minutes of bright light on awakening
  - Melatonin in the afternoon
  - Melatonin (either 0.3 or 3 mg) induced a significantly larger phase advance

CIRCADIAN RHYTHM SLEEP DISORDERS: ENDOGENOUS ORIGIN

- Characterized by complaints of insomnia or daily sleepiness primarily result from alterations in the internal circadian timing system or misalignment between normal timing of sleep and 24-hour social and physical environment
- Two main types of primary circadian rhythm sleep disorders include
  - Advanced sleep phase syndrome (ASPS)
  - Delayed sleep phase syndrome (DSPS)

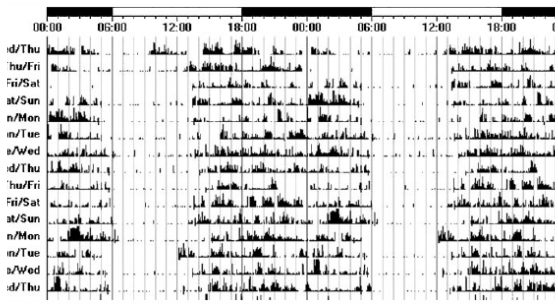
Advanced Sleep Phase Syndrome

- In ASPS, most evening activity preempted by early bedtime with waking up at 3 am or earlier
- This pattern is often observed among older people
- Advanced rhythm of body core temperature and melatonin secretion peak resulting from endogenous alteration of biological clock
- Melatonin 0.3 to 5 mg had no demonstrable effects in nonelderly adults. However, sleep quality was restored in elderly

Delayed Sleep Phase Syndrome

- Delayed sheep phase syndrome (DSPS) defined by abnormally late sleep and wake time with difficulty arising in time to fulfill morning obligations
- Often observed in younger people with few rigidly scheduled work or social commitments (e.g., students or the unemployed); also common in night people (owls)
- Melatonin peak secretion spontaneously delayed
- Exogenous melatonin (5 mg daily) given 5 hours before the patient's normal bedtime induced onset of sleep 90 minutes earlier

Delayed Sleep Phase Disorder (DSPD)



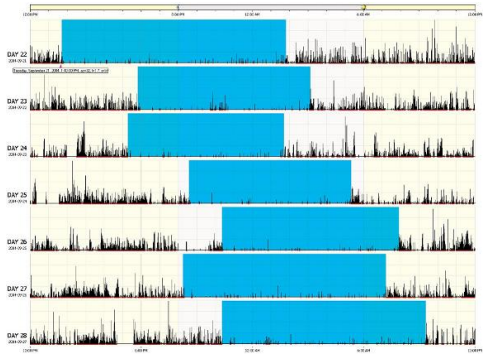
Delayed Sleep Phase Syndrome

- In children with severe neurodevelopmental diseases with and without epilepsy, who often suffer from disorganized circadian rhythms and DSPS
  - Slow-release melatonin (5 mg) improved sleep latency and total sleep time
- Melatonin used in children with attention-deficit/hyperactivity disorder (ADHD) with sleep-onset insomnia
  - Melatonin advanced circadian sleep–wake rhythms and endogenous melatonin secretion, with enhanced total time asleep

Blindness

- Blind persons who are totally deprived of light perception have desynchronization of their biological rhythm to free running
- Daily administration of melatonin in evening is efficient to restore a normal rest–activity cycle
- Effectiveness of melatonin therapy depends upon its time of administration relative to timing of patient's circadian clock

Free Running Disorder (FRD)



Normal Aging

- Aging is associated with alterations of sleep–wake timing, body core temperature, heart rate, blood pressure, and hormone secretion and higher incidence of type 2 diabetes or cancer
- Many potential causes may be involved, including
  - Primary sleep disorder, depression, medical illness, or medications
- However, age-related alteration of the biological clock and of circadian regulations appear to be the major causes of rest activity dysregulation associated with insomnia in elderly subjects

Normal Aging

- 2-mg tablet taken 2 hours before bedtime showed significant improvement in sleep quality and morning alertness, shortened sleep latency, and absence of withdrawal effect at drug discontinuation
- Patients aged > 55 years, with lower excretion of melatonin had higher response to melatonin replacement therapy

CNS DISORDERS ASSOCIATED WITH ALTERATION OF MELATONIN SECRETION PATTERNS: Pinealectomy

- Pinealectomy performed for pinealomas (3% to 8% of brain tumors in children) followed by dramatically reduced or abolished melatonin secretion
  - In some cases, melatonin replacement therapy improves insomnia or hypersomnia
- Replacement therapy with slow-release melatonin (2 mg daily) at 9 pm showed improvement in sleep quality and reduction of fatigue, normalization of sleep–wake cycles, and an improvement of educational performance

CNS DISORDERS ASSOCIATED WITH ALTERATION OF MELATONIN SECRETION PATTERNS: Mood Disorders

- Abnormalities in circadian rhythms associated with mood disorders such as major depressive disorder, bipolar disorder, and seasonal affective disorder
- Melatonin has been proposed as a combined marker for susceptibility to develop affective disorders

CLINICAL APPLICATIONS: Jet Lag

- Melatonin for the treatment of jet lag has been extensively studied in controlled studies and proven to be remarkably successful in reducing jet lag symptoms
- Using the melatonin had less overall jet lag symptoms at day 10
- Melatonin group experienced a better adaptation pattern in terms of sleep pattern, daytime tiredness, and normal energy levels than the placebo group

CLINICAL APPLICATIONS: Acute insomnia

- Estimated that 50 to 70 million American adults have difficulty sleeping
- One of the numerous options available is melatonin, both in healthy adults as an acute remedy for insomnia and in elderly with chronic insomnia
- Acute use of melatonin in healthy adults without insomnia at doses of 0.3 to 1 mg at 8:00 or 9:00 pm significantly
  - Reduces sleep-onset latency and latency to stage 2 sleep
  - Melatonin does not produce any "sleep hangover" symptoms

CLINICAL APPLICATIONS: Insomnia in Elderly

- Most elderly sleeping average of 7 hours a night
- Although total amount of sleep time does not change, but alterations in sleep architecture are common includes
  - Decrease in deep sleep (stages 3) and rapid eye movement (REM) sleep, as well as an increase in stage 1
- Elderly have reduction endogenous melatonin production (due to deterioration in neuronal functioning of SCN), disrupts normal wake/sleep cycle

CLINICAL APPLICATIONS: Insomnia in Elderly

- Although melatonin did not improve sleep efficiency in normal subjects, but those with chronic insomnia had significant improvements in sleep efficiency, with the 0.3 mg dose triggering the strongest effect
- Physiologic dose acted primarily in middle of the night and raised plasma melatonin levels to normal
- 3 mg of melatonin significantly raised plasma levels throughout a portion of the day and triggered reductions in core body temperature after ingestion of hormone

CLINICAL APPLICATIONS: Prolonged Release Melatonin in the Elderly

- Elderly with primary insomnia receive 2 mg of a prolonged release (PR) melatonin for two weeks
- Able to restorative value of sleep
- Melatonin users did not experience any rebound insomnia or withdrawal symptoms
- Administration of PR melatonin in older adults with primary insomnia may delay the production of nighttime cortisol, with subsequent improvements in both sleep quality and morning alertness

CLINICAL APPLICATIONS: Insomnia in Perimenopausal Women

- Perimenopausal women (45 to 52 years) with insomnia were treated with 2 mg of melatonin improved
  - Sleep latency scores
  - Pittsburg Sleep Quality Index (PSQI)
  - Quality of life significantly

CLINICAL APPLICATIONS: Chronic Sleep Onset Insomnia in Children

- Pediatric insomnia is estimated affect 1% to 6% of children
- However, significantly elevated to 50% to 75% if there are other associated psychiatric or neurodevelopmental issues such as attention deficit hyperactivity disorder (ADHD), autistic spectrum disorders (ASDs), and epilepsy
- Children who used melatonin had better outcomes of eating, sleeping, response to attention, fatigue, illness, and overall health
- Melatonin users had advancement in sleep onset, a reduction in sleep latency

CLINICAL APPLICATIONS: Fibromyalgia

- Fibromyalgia (FM) challenging condition with characteristic symptoms include widespread and variable chronic pain, fatigue, stiffness, cognitive disturbances, depres- sion, and insomnia
- Although alterations secretion of melatonin observed in FM patients, whether phenomenon contributes to pathophysiology remains controversial
- Melatonin significant reduction from baseline in musculoskeletal tender, severity of pain, and sleep disturbances (−67.2%)
- Although fatigue, depression, and anxiety did not show improvement

CLINICAL APPLICATIONS: Chronic Fatigue Syndrome

- Chronic fatigue syndrome (CFS) associated with number of symptoms, including intense and disabling fatigue not improve with rest
- One factors contributing to fatigue and sleep disturbances in CFS is disruption in hypothalamic-pituitary-adrenal axis
- Certain subset of CFS patients may respond to therapeutic use of melatonin

CLINICAL APPLICATIONS: Children with Epilepsy

- Children using the additional melatonin had a significantly greater average percentage reduction in their total sleep scores
- Median reduction in the parasomnia who took melatonin
- No adverse effects noted

CLINICAL APPLICATIONS: Autism/Fragile X Syndrome

- Children with ASDs not only have a higher incidence of sleep-associated problems
- Melatonin use led to significant improvements in sleep duration and sleep-onset latency

CLINICAL APPLICATIONS: Children with Insomnia and Attention Deficit Hyperactivity Disorder

- Children with ASDs not only have a higher incidence of sleep-associated problems
- Melatonin use led to significant improvements in sleep duration and sleep-onset latency
- Melatonin help advancements in sleep onset and significant increase in total sleep time
- No changes were noted in behavior and cognition

CLINICAL APPLICATIONS: Children with Migraine/Tension-Type Headaches

- Annual prevalence for migraine and tension-type headaches can vary between 3%-11% and a 10%-24% occurrence, respectively
- 3 mg of melatonin at bedtime for 90 days
  - Frequency and number of attacks per month and duration of attacks (hours) decreased
  - 2/3 had >50% reduction in headache attacks
  - Some had complete resolution of headaches

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CLINICAL APPLICATIONS: Depression

- Melatonin did not show significant improvement in major depressive disorder symptoms
- some individuals may benefit from melatonin use such as those with
  - Depression and delayed sleep phase syndrome
  - Women during perimenopause or menopause

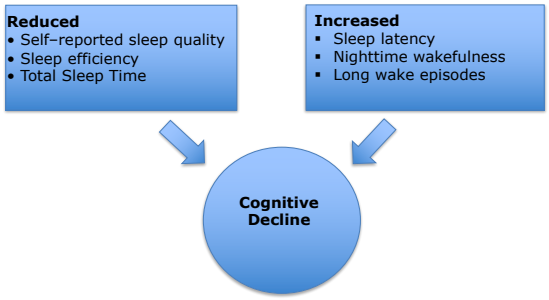
CLINICAL APPLICATIONS: Alzheimer's Disease

- Estimated that 24.3 million people worldwide with dementia in 2001, and would rise to 81.1 million by the year 2040, AD expected to increase 13 million by the year 2050
- In addition to a deterioration in memory, day-to-day functioning, sundowning syndrome or nocturnal delirium is common behavior found 2.4% to 25% of those diagnosed with AD
- Sundowning can occur typically 3:00 pm and 7:00 pm and associated with a heightened degree of agitation, irritation, and confusion

CLINICAL APPLICATIONS: Sundowning Phenomenon in Alzheimer's Disease

- AD received 9 mg melatonin daily at bedtime for 22 to 35 months
- Melatonin use significantly improved their sleep quality but no changed of neuropsychiatric test parameters
- However, the condition of sundowning was no longer clinically detectable in 80% of patients

Poor sleep leads to cognitive decline line in healthy cognitively impaired and demented



Risk factor for Alzheimer's dementia

- Age
- Family history and genetics
- Gender
- MCI (Mild Cognitive Impairment)
- **Poor sleep quality**
- Lack of exercise
- High blood pressure
- Smoking

Marcello et al. Eur J Pharmacol. 2008; Nimmrich & Ebert, Rev Neurosci. 2009; Selkoe, Nat Med. 2011; Osorio J Am Geriatr Soc. 2011

Prevalence of insomnia in AD

- 55% of adults 65 years and older have at least one chronic sleep complaint.
- Sleep disturbances in AD affecting up to 45% of the patients. These disturbances are similar in nature to adults without AD
- Nighttime awakenings are common in AD, affecting caregivers quality of life and can lead to nursing home placement
- Acetyl-cholinesterase (AChE) inhibitors cause sleep disturbances in 14% of patients and daytime fatigue in 5% of patients
- **Altogether 1 out of 2 AD patients suffers from insomnia**

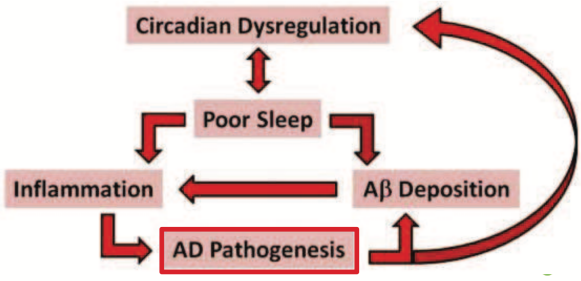
Foley et al. Sleep. 1995; Landry & Liu-Ambrose Front. Aging Neurosci. 2014; Osorio et al J Am Geriatr Soc. 2011

Insomnia in AD patients

- There is a strong association between objective and subjective measurements of sleep and subsequent cognitive decline
- Poor sleep and specifically the inability to sustain extended periods of both sleep and wakefulness exacerbate 'age-related' cognitive decline.
- A significant correlation between disrupted SWS and increased plasma levels of amyloid-beta was demonstrated-suggesting causality between poor sleep and the subsequent cognitive decline

Diekelmann & Born, Nat Rev Neurosci 2010; Swearer et al. J Am Geriatr Soc., 1988; Altena et al. Prog Brain Res., 2010; Chavant et al. Br J Clin Pharmacol., 2011; Spira et al. JAMA Neurology, 2013; Pollak et al. J Geriatr Psychiatry Neurol. 1991

Causal relationship between insomnia and AD



Landry & Liu-Ambrose Front. Aging Neurosci. 2014

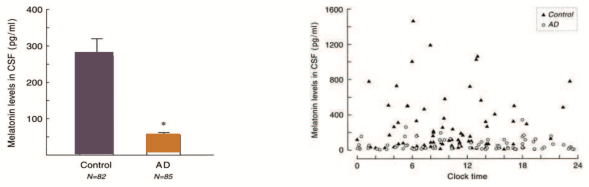
CENTRAL NERVOUS SYSTEM DISORDERS ASSOCIATED WITH ALTERATION OF MELATONIN SECRETION PATTERNS:

Alzheimer's Disease

- Circadian rhythm disturbances observed in patients with Alzheimer's disease
- Rest–activity rhythm disturbances manifest as fragmentation of the rhythm, and high levels of activity during the night
- Melatonin secretion rhythm impaired by both age and cognitive impairment, with reduced nocturnal melatonin levels
- These rest–activity disturbances can be improved by increasing environmental lighting and daytime activity

Melatonin deficiency is common among AD patients

Early Neuro-pathological changes in Alzheimer's Dementia are accompanied



Zhou et al, J Pineal Res., 2003; Liu et al. J Clin Endocrinol Metab, 1999; Cecon et al FASEB J 2015

Why should we treat insomnia in AD patients?

- Among community-dwelling older adults, reports of shorter sleep duration and poorer sleep quality are associated with greater Aβ burden
- Amyloid is produced while brain activity is increased; excess is cleared away by the glymphatic system when asleep
- Poor sleep may promote Aβ deposition and exacerbate loss of cognitive function
- Decrease in brain activity during night sleep is essential for amyloid clearance in AD related areas such as the precuneus
- The precuneus is most sensitive to poor quality of sleep

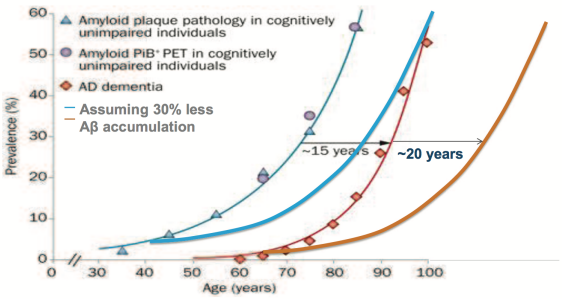
Osorio J Am Geriatr Soc. 2011; Blackwell et al. Sleep 2014; Carpenter et al., Clin. Gerontologist 1996, McCurry et al., J Geriatr Psychiatry Neurol,1999 Lucey et al. Neurobiology of Aging, 2014; Dissel et al Current Biology , 2015

Sleep disorders in AD are misperceived !

- **Generally regarded as**
  - A normal signs of aging
  - At a later stage "sundowning" becomes a secondary symptom to the disease
- **Should be regarded as**
  - A major risk factor to AD
  - A comorbidity that ultimately brings about faster deterioration in cognition and function

Osorio J Am Geriatr Soc. 2011

Improving sleep: Buying time



Modified from Langbaum et al Nat Rev Neurol. 2013; Osorio J Am Geriatr Soc. 2011

Current insomnia treatment in AD patients

- No treatment specially to treat insomnia in this vulnerable population
- Behavioral techniques (specifically, sleep hygiene education, daily walking, and increased light exposure) can improve sleep, but not effective
- Sedating BZDs and tricyclic antidepressants are currently being used to treat insomnia in AD patients and can result in habituation, loss of efficacy, and drug-induced insomnia, without significant improvements in daytime function
- Neuroleptics and antipsychotic drugs are also used and can paradoxically induce circadian rest–activity disturbances in susceptible patients, increase risk for falls, cognitive impairment, sleep apnea, decrements in self-care, and higher medical costs

McCurry et al. J Am Geriat Soc, 2005; Deschenes & McCurry Curr Psychiatry Rep. 2009

Hypnotics should be avoided in the treatment of insomnia in AD patients

- The currently used hypnotics reduce REM sleep and SWS and thus cause further deterioration in skill acquisition and cognitive capabilities
- Administration of Zolpidem associated with residual impairments in driving, psychomotor performance and memory
- A recent study in the French Pharmacovigilance Database revealed that Zolpidem, Topiramate, Alprazolam and Bromazepam presented the most significant associations with memory disorders
- A study in Taiwan showed that long-term use of BZDs associated with increased risk for dementia

Leufkens et al. J. Sleep Res., 2009; Seibt et al. Sleep, 2008; Wu et al Am J Geriat Psychiatry, 2009; Chavant et al. Brit J Clin Pharmacol, 2011; Chung et al., PLoS One 2013, Diem et al., J Gerontol Geriatr Res 2014; Hall-Porter et al., Journal of Clinical Sleep Medicine 2014; Billiotl de Gage et al., BMJ. 2012 &2014; Yaffe and Boustani, BMJ 2014; Hsin-I. Shih et al Medicine 2015

Rationale for Circadin® treatment for sleep in AD

- Adults with moderate to severe AD have extreme disruption of the sleep-wake rhythm
- Disturbances in clock synchronization processes and sleep quality can exacerbate cognitive decline
- Melatonin concentrations in the cerebrospinal fluid have been found to be significantly decreased in patients with AD (one fifth of those in control patients)
- The loss in melatonin may be causally related to sleep disturbance and subsequent faster cognitive decline in AD.
- The loss in melatonin may exacerbate the disruption of the sleep-wake rhythm
- Exogenous Melatonin demonstrated beneficial effects in experimental models of AD

Tohgi et al. Neurosci Lett., 1992; Cheng et al. Mol Cell Biol,2006 Dissel et al Current Biology, 2015; Zhou et al, J Pineal Res., 2003; Liu et al. J Clin Endocrinol Metab, 1999; Cecon et al FASEB J 2015

CLINICAL APPLICATIONS: Alzheimer's Dementia

- 3 mg of melatonin demonstrated that melatonin users had increase in amount of mean evening sleep time
- Reduction in the night time activity counts
- No change in daytime sleep or activity
- Those utilizing melatonin had significantly improved ADAS cognition and non-cognition scores

SR but not IR melatonin tends to be beneficial in AD

Design: A multicenter, randomized, placebo-controlled clinical trial of 2 dose formulations of oral melatonin coordinated by the National Institute of Aging-funded Alzheimer's Disease Cooperative Study. Subjects with Alzheimer's disease and nighttime sleep disturbance were randomly assigned to 1 of 3 treatment groups: placebo, 2.5-mg slow-release melatonin, or 10-mg melatonin.

Measurements: Nocturnal total sleep time, sleep efficiency, wake-time after sleep onset, and day-night sleep ratio during 2- to 3-week baseline and 2-month treatment periods. Sleep was defined by an automated algorithmic analysis of wrist actigraph data.

Table 5—Demographic and descriptive background variables and baseline, and 8-week change score by arm for the secondary outcome measures.

Variable	PLACEBO	ML 2.5SR	ML 10.0	OVERALL
Age, y	77.0 ± 8.5	78.4 ± 8.2	76.5 ± 10.1	77.4 ± 8.9
Duration AD	5.1 ± 2.9	4.6 ± 2.6	5.1 ± 3.4	4.9 ± 3.0
Education, y	12.5 ± 3.7	13.1 ± 4.1	12.4 ± 3.3	12.7 ± 3.7
MMSE at baseline	14.2 ± 9.0	12.8 ± 9.6	14.6 ± 8.5	13.9 ± 8.8
MMSE change	0.34 ± 2.7	-0.33 ± 2.8	-0.20 ± 3.4	0.16 ± 3.0
ADAS	38.0 ± 18.3	38.9 ± 19.1	38.8 ± 19.6	38.5 ± 18.9
ADAS change	1.4 ± 4.9	0.25 ± 5.4	0.97 ± 5.5	0.87 ± 5.3
ADL (23 item)	36.5 ± 23.5	30.5 ± 23.7	35.6 ± 23.2	34.1 ± 23.5
ADL change*	-0.98 ± 4.7	-0.65 ± 6.0	-0.49 ± 6.7	-0.71 ± 5.8
Hamilton	7.2 ± 3.4	7.8 ± 3.5	7.8 ± 3.7	7.6 ± 3.5
Hamilton change*	-1.7 ± 4.5	-1.2 ± 4.6	-1.9 ± 3.9	-1.6 ± 4.4
NPI	18.5 ± 17.1	24.9 ± 20.0†	15.5 ± 15.8	19.7 ± 18.1
NPI change*	-0.17 ± 14.1	-6.4 ± 15.1‡	0.46 ± 11.9	-2.1 ± 14.0
SDI (product of averages)	3.3 ± 1.8	3.7 ± 2.2	3.8 ± 2.4	3.6 ± 2.2
SDI change*	-1.6 ± 1.4	-1.9 ± 2.6	-2.3 ± 2.3	-1.9 ± 2.2
Sleep Quality Rating	3.0 ± 0.7	3.0 ± 0.7	3.2 ± 0.7	3.1 ± 0.7
Sleep Quality Rating Change	0.3 ± 0.6	0.41 ± 0.7§	0.2 ± 0.4	0.30 ± 0.6

*Negative score = improvement.
†Mann-Whitney test: unadjusted $P = .012$ for ML 2.5SR mg vs ML 10 mg.
‡Mann-Whitney test: unadjusted $P = .047$ for ML 2.5SR vs placebo.
§Unadjusted $P = .023$ for ML 2.5SR vs ML 10.
∥Adjusted $P = .03$ for ML 2.5SR without data from subject with free-running circadian rhythm vs placebo.
ML 2.5SR refers to treatment with 2.5 mg sustained-release melatonin; ML 10, treatment with 10 mg melatonin; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NPI, Neuropsychiatric Inventory; SDI, Sleep Disorders Inventory.

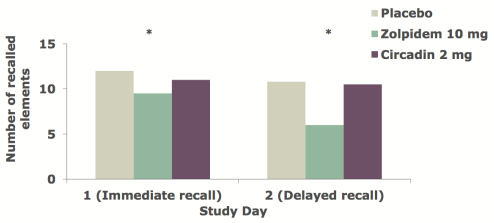
Singer et al. Sleep, 2003

Rationale for Circadin® as insomnia treatment in AD patients

- Slow-Wave Sleep (SWS) and REM sleep are important for memory consolidation
- Circadin improves physiological sleep without impairing memory
- The precuneus activity can be effectively attenuated with melatonin
- Melatonin has a neuroprotective and clock resetting action
- Supportive evidence from a trial of Circadin® vs placebo in AD patients

Luthringer et al Int Clin Psychopharmacol. 2009, Arbon et al. J Psychopharmacology 2015; Otmani et al. Hum Psychopharmacol, 2008; Gorfine & Zisapel Neuroimage 2006, Wade et al Wade et al. Clin Interv Aging, 2014 ; Joshi et al Mol Neurobiol. 2014 ; Zisapel Cell Mol Life Sci. 2007

Circadin® does not impair memory



Otmani et al. Hum Psychopharmacol, 2008

CLINICAL APPLICATIONS: Migraine

- Individuals with chronic migraines have decreased levels of urinary 6-sulphatoxymelatonin levels, supporting melatonin's role in the pathophysiology of migraine
- Melatonin use decreased headache frequency, intensity, and duration
- Complete resolution of the migraine seen in 25% of patients

CLINICAL APPLICATIONS: Cluster Headache

- 10 mg of melatonin had significant reduction in daily attacks, and observed decrease in daily analgesic
- Headache frequency was reduced in both the first and second week of melatonin treatment
- Melatonin could act by
  - Modulating 5HT2 receptors
  - Inhibit the synthesis of prostaglandin E2
  - Increase the activation threshold level of aminobutyric acid pain pathway

CLINICAL APPLICATIONS: Tinnitus

- A perception of ringing or roaring or humming sound within ears without any acoustic stimulation is known as tinnitus
- Melatonin could assist in reduction of tinnitus symptoms by reducing labyrinth pressure
- 3 mg of melatonin 1 to 2 hours before bedtime
- Patients with higher initial tinnitus scores more likely to respond to melatonin use

Melatonin: DOSAGE

- Melatonin has been used at a variety of different dosages
- Most popular use to enhance sleep quality typical dosage 3 mg

CONDITION	DOSE
Alzheimer's dementia (+ sundowning symptoms)	3-9 mg in the evening
Acute insomnia	0.3-1 mg at bedtime
Cancer (solid tumors: breast, lung, prostate)	20 mg in the evening
Cachexia	20 mg in the evening
Taxane-related neuropathy	21 mg at bedtime
CFS and insomnia	5 mg at bedtime
Chronic insomnia	0.3-3 mg 30 minutes before bedtime
Children and insomnia	5 mg at 7 PM
Depression	
Delayed Sleep Phase Syndrome	5 mg at 7 to 9 PM
Perimenopausal/Menopausal	3 mg at 10 to 11 PM
Epilepsy and insomnia	6 mg for those less than 9 years of age and less than 30 kg in the evening; 9 mg for those greater than 9 years of age and greater than 30 kg
ASD and insomnia	3 mg before bedtime
ADHD and insomnia	3 mg for those less than 30 kg and 6 mg for those greater than 30 kg at 7 PM
Fibromyalgia	3 mg 30 minutes before bedtime
Functional dyspepsia	5 mg in the evening
GERD	3 to 6 mg in the evening
Headache	
Children: migraine prevention	3 mg at bedtime
Adults: migraine	3 mg at bedtime
Adults: cluster headache	10 mg at bedtime
IBS	3 mg in the evening
Infertility in women with IVF	3 mg in the evening
Jet lag	
Eastbound	5 mg 3 times daily, 3 days before and 3 days after, in the evening local time
Westbound	0.5 mg in the evening
Nicotine withdrawal symptoms	0.3 mg in the evening
Tinnitus	3 mg in the evening

ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; CFS, chronic fatigue syndrome; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IVF, in vitro fertilization; TID, three times daily.

Side Effects and Contraindications

- Common side effects of high dosage melatonin use include
  - Headaches, dizziness, nausea, and drowsiness
- it seems unlikely that chronic ingestion of moderate melatonin doses will have a profound impact on reproductive function in humans
- However, without further clinical evidence of safety, melatonin should not be employed in pregnancy and lactation

Conclusion

- The SCN is master clock that governs circadian rhythms of biological processes
- Melatonin key player regulation of SCN in re-entraining its rhythmicity
- Deleterious consequences of disruption of circadian rhythms, provoked by
  - Environmental conditions such as shift work, jet lag, or stress
  - Endogenous origin e.g. age, dementia, neurological disorders
- Disrupted biological rhythms associated with circadian rhythm sleep disorders, mood disorders, hypertension, obesity, type 2 diabetes, and cancer, all pathologic conditions

Conclusion

- Melatonin deficiency and disrupted circadian rhythm are common among neurological disorders
- Circadin® is the only insomnia treatment that preserves natural sleep architecture and does not impair memory
  - Effective, safe and beneficial treatment for insomnia in Neurological disorders e.q. Alzheimer's dementia