Melatonin

Indication
Side effects

(review articles)

Laily Alizadeh MD.
Resident of Geriatric Medicine
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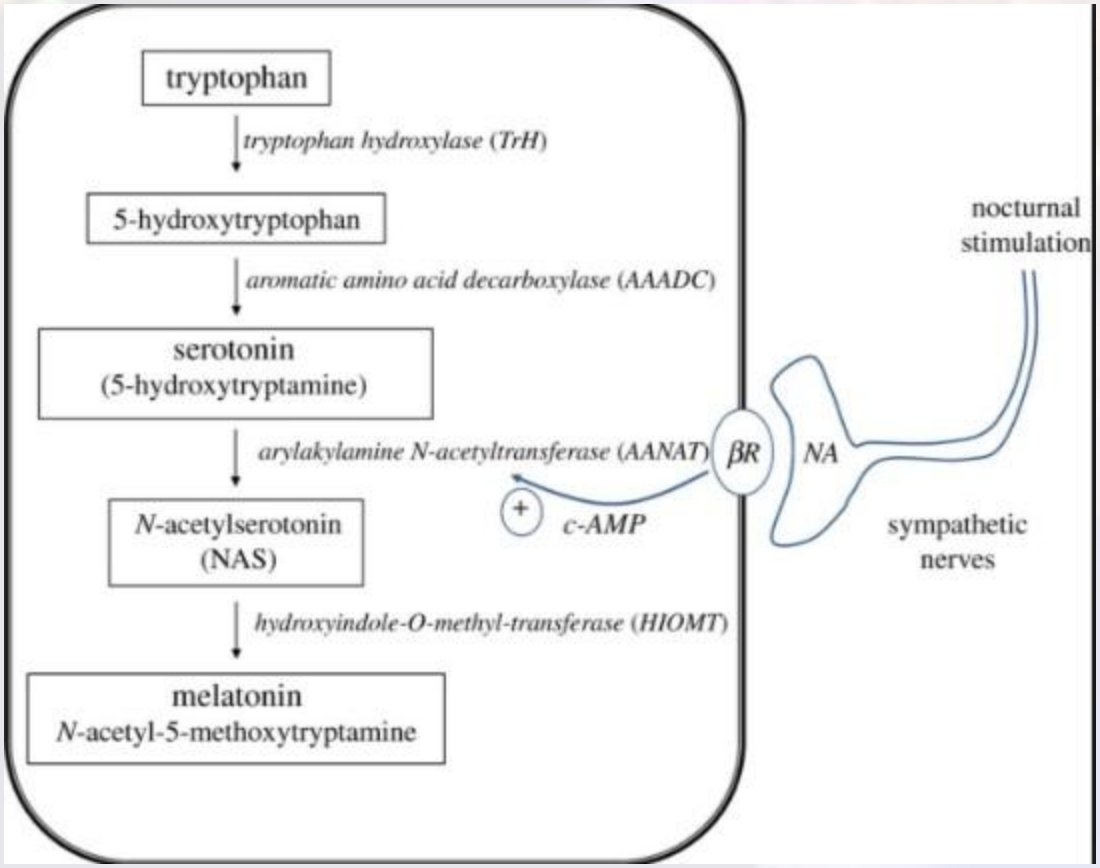
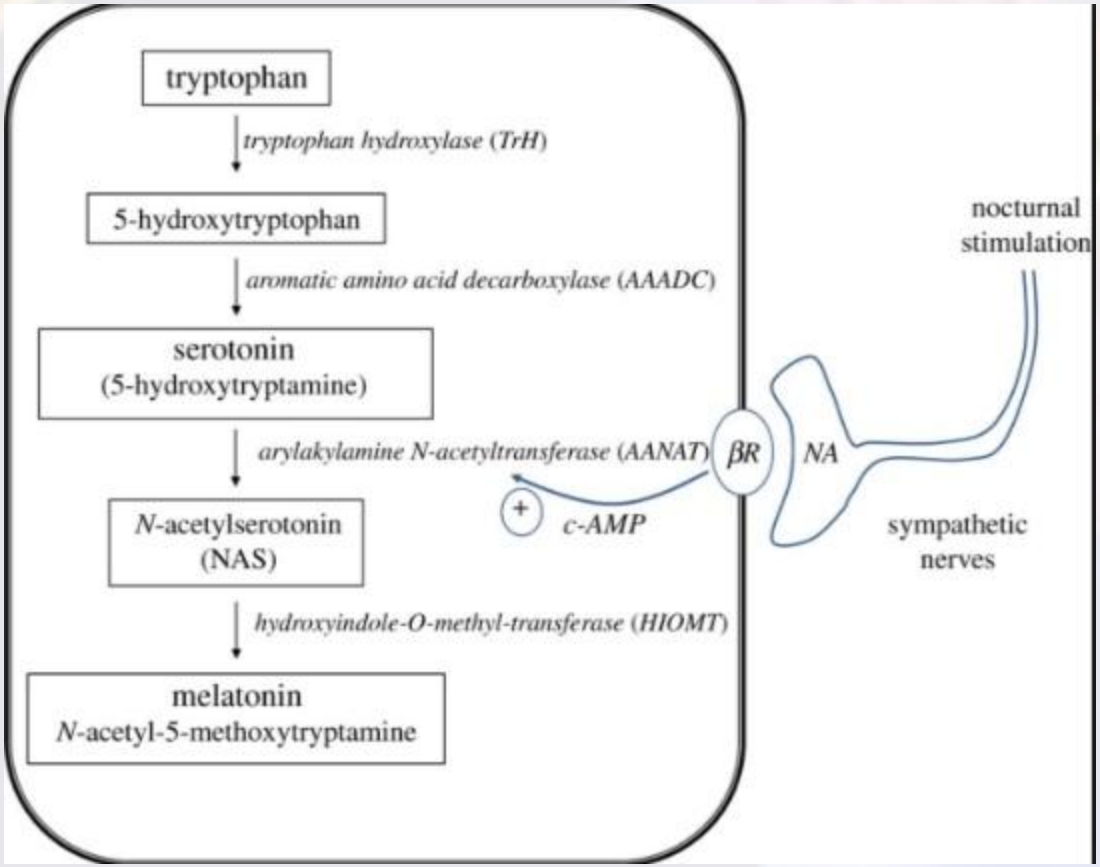
- **Melatonin hormone** is produced in the **pineal gland**
- from the amino acid **tryptophan**
- secreted into the blood and cerebrospinal fluid.
- **Regulate sleep** and **circadian rhythms.**
- **nocturnal plasma melatonin concentrations** are at least 10-fold higher than daytime concentrations

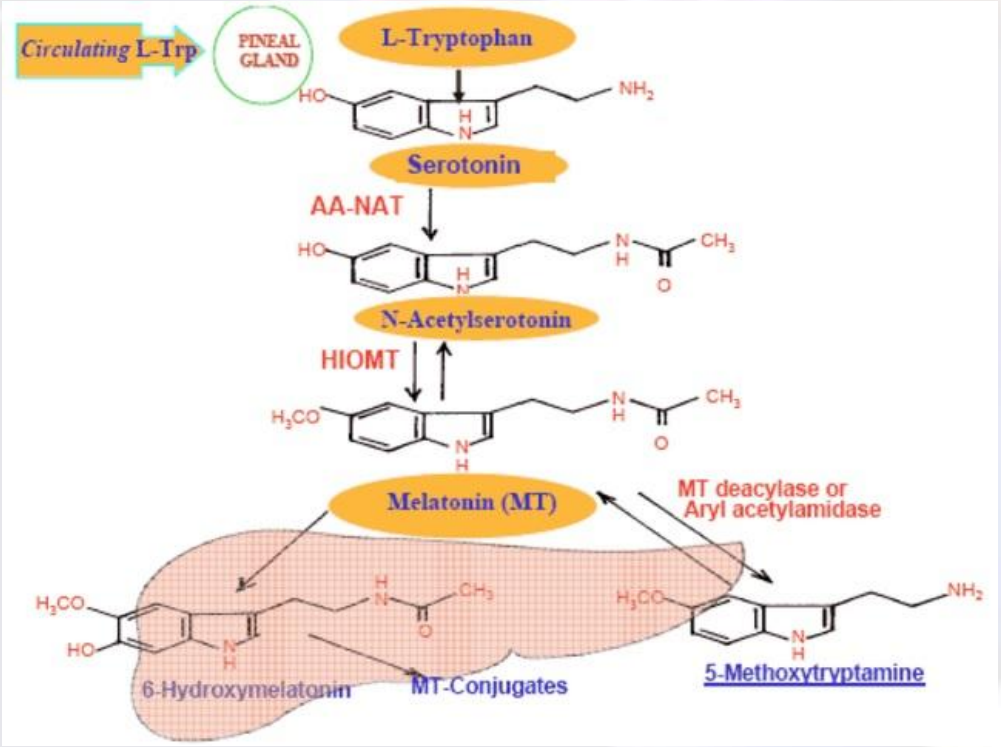
Tryptophan is first 5-hydroxylated by the enzyme tryptophan hydroxylase and then decarboxylated by the enzyme aromatic L-amino acid decarboxylase to form 5-hydroxytryptamine, or serotonin.



With the onset of **darkness, postganglionic sympathetic outflow** to the pineal increases, and the consequent release of norepinephrine onto pinealocytes causes stored serotonin to become accessible for intracellular metabolism. At the same time, the norepinephrine activates the enzymes that convert serotonin to melatonin, especially serotonin-N-acetyltransferase (SNAT) but also hydroxyindole-O-methyltransferase (HIOMT).



- Most of the melatonin is inactivated in the **liver,**
- where it is **first oxidized** to 6-OH-melatonin by a P450-dependent microsomal oxidase and then largely **conjugated** to sulfate or glucuronide before being excreted into the **urine or feces** . About 2 to 3 percent of the circulating melatonin is **excreted unchanged** into the urine or the saliva
- Salivary melatonin levels apparently correspond to those of the 25 to 30 percent of blood melatonin that is not bound to albumin
- Salivary melatonin measurements are not widely used.



Three probable melatonin receptors:

1. within the **suprachiasmatic nucleus (SCN) of the hypothalamus**, the **pars tuberalis of the pituitary**, and **cardiac blood vessels (MT1)**
2. the **retina and hippocampus (MT2)**
3. **kidney**, **brain**, and various **peripheral organs (MT3).**

Their affinities for melatonin are enhanced in the presence of several **G-proteins.**

Melatonin's MT1 and MT2 receptors are highly susceptible to **"desensitization,"** their activity decreasing markedly after exposure to supranormal concentrations of the hormone, particularly among older adults with insomnia who might inadvertently purchase excessively large doses of the hormone.

Circadian rhythm :

In all mammals melatonin secretion manifests a similar circadian rhythm,

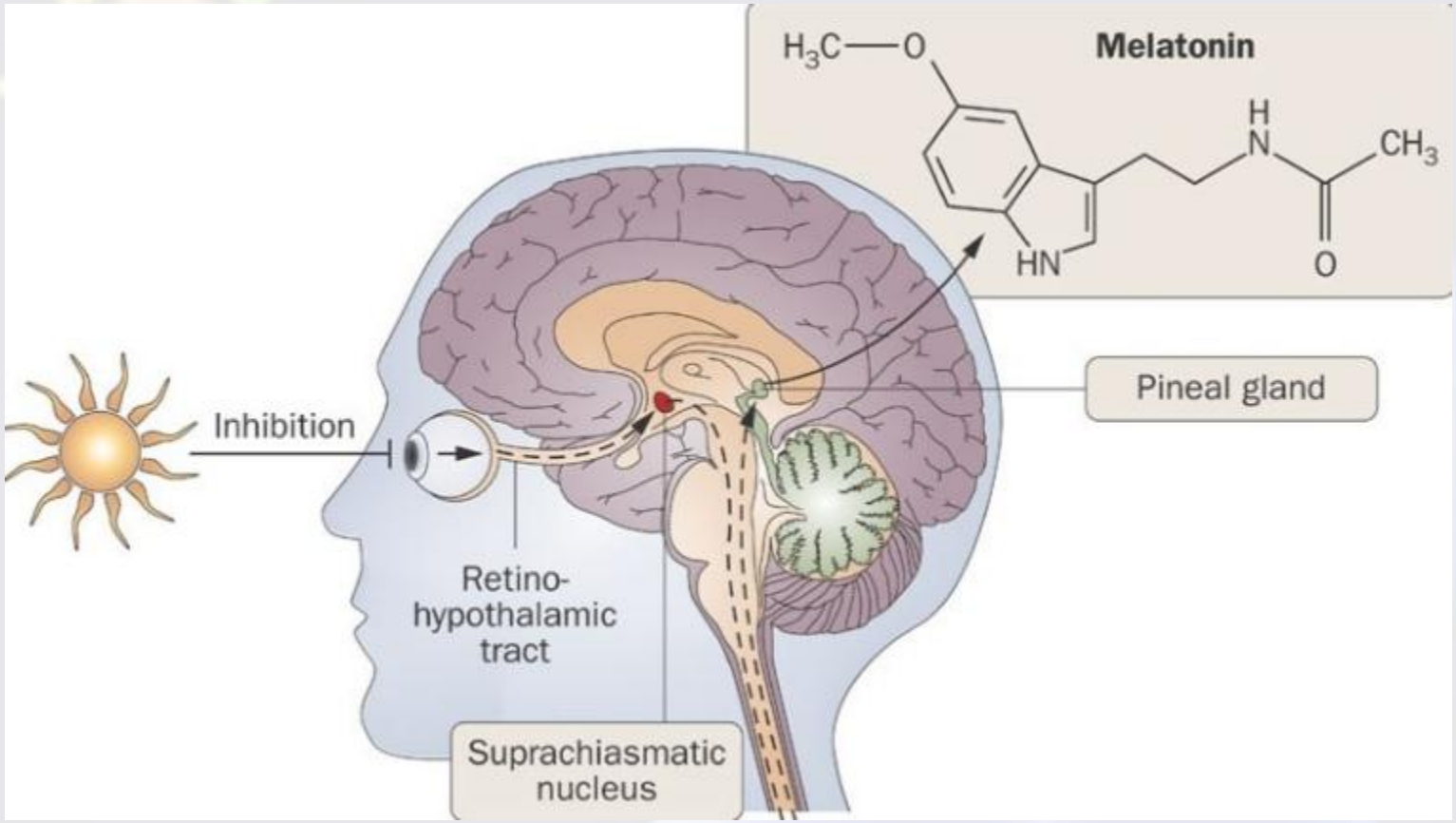
With plasma and urine concentrations low during daylight,

Ascending after the onset of darkness**,**

Peaking in the middle of the night between 11 pm and 3 am, and then falling sharply before the time of light onset .

While this rhythm normally is environmental light cycle, it does persist when people are placed for a few days in a dark room and, as described above, does not immediately phase-shift when the light schedule is altered , indicating that it is not simply generated by the light-dark cycle but also by cyclic endogenous signals, probably **arising in the SCN**.

Signals originating in the retina or the SCN reach the pineal via a retinohypothalamic tract, the superior cervical ganglia, and postganglionic sympathetic fibers that re-enter the cranial cavity . In contrast, light has no known direct effects on pineal melatonin synthesis in humans and other mammals.


Melatonin
H_3C—O
H
N
CH_3
HN
O
Pineal gland
Inhibition
Retino-
hypothalamic
tract
Suprachiasmatic
nucleus

Exogenous melatonin : synchronize and to shift the phases of various human circadian rhythms

- In studies of healthy volunteers, 0.5 mg of pure melatonin or 0.05 mg of melatonin in corn oil (which causes earlier peaks in, and the more rapid disappearance of, elevated plasma melatonin concentrations)
- **Melatonin was able to shift the core body temperature rhythm;** significant effect was found only with doses ≥0.5 mg.
- These doses increased plasma melatonin concentrations well above the upper limits of normal (>1327 pg/mL [5712 pmol/L]), may not be a physiologic effect.

Plasma concentrations :

- The amount secreted by the pineal gland
- The influx of melatonin into tissues when its plasma concentrations are high and efflux from them when plasma concentrations are low
- Its destruction in the liver
- Its secretion into such body fluids as urine and saliva

Foods contain melatonin (wine, tomatoes), there is no evidence using specific assay techniques that food is a source of melatonin or that food sources increase plasma melatonin concentrations.

Principal factor affecting plasma melatonin concentration is its rate of secretion, which **varies with the circadian rhythm and with age.** Diet does not affect melatonin concentrations.

- Bioavailability : 9-33%
- Melatonin : **oral** and **sublingual pills** and short half-life
- Two studies with high dose of melatonin (3 mg and 4 mg) found their levels were maintained above 50 pg/ml for more than 10 hours than in the low dose group (0.3 mg and 0.4 mg) .
- Higher dose carries the risk of prolongation of supraphysiological levels in older adults the next day. This might cause problems with side effects like **drowsiness, somnolence, or unsteady feeling** when waking up, despite melatonin's low toxicity.
- With **higher doses and prolongation of supra-physiological levels, loses its effectiveness on sleep parameters**
- Lowest possible dose of **immediate release melatonin (range from 0.3-1 mg) preferably 1 hour before bedtime** probably mimics the normal physiological circadian rhythm and can avoid prolonged supraphysiological levels.

Surgery and use of **opioids** : decrease serum melatonin levels

Changes in **hepatic, renal clearance, and body composition**, especially in patients with chronic medical conditions alter melatonin levels

So, melatonin circadian rhythm secretion **varies** with:

- age
- acute illnesses
- underlying chronic concomitant disease
- some of the medications:

- ❑ interfere with the transmission of neurotransmitter signals to pineal cells (like propranolol, a beta-blocking agent)
- ❑ those that inhibit melatonin's metabolism (like 8-methoxypsoralen)
- ❑ few drugs that lack clear links to melatonin's synthesis or metabolism (eg, caffeine, ethanol)
- ❑ The antidepressant fluvoxamine increase the effect of plasma melatonin by inhibiting serotonin uptake through the CYP1A2 mechanism.

Prolonged use of **portable light-emitting devices** (laptops, tablets, smartphones) before bedtime can have a **negative impact on melatonin secretion, circadian rhythms, and sleep**. These observations suggest that **evening use of light-emitting devices may contribute to phase-delays in the circadian clock and difficulty initiating sleep**.

Age :

- Melatonin secretion varies with age.
- Melatonin **secretion starts** during the **third or fourth months of life**
- It then increases rapidly**, peak at ages one to three years**
- decline slightly to a plateau that persists throughout early adulthood .
- In 70-year-olds being only a quarter or less of what they are in young adults
- This decline may reflect the progressive, age-related **calcification of the pineal gland**
- **One strategy in using supplemental melatonin is to administer it to older adults with age-associated insomnia in doses just sufficient to compensate for this age-related decline.**

Patients with nocturnal hypertension :

- While ***sleeping at night***, the **blood pressure normally falls by approximately 15 percent from daytime values**.
- Patients in whom this reduction does not occur are considered to have nocturnal hypertension, which has been associated with an **excess risk of cardiovascular disease**.

Two observations suggest that melatonin plays a role in nocturnal blood pressure regulation:

- The normal nighttime surge in serum melatonin concentration may be blunted in patients with nocturnal hypertension .
- Melatonin administration appears to lower blood pressure, particularly at night .

Although **exogenous melatonin may have a modest effect on nocturnal blood pressure**, is not currently recommend its use for this indication since there are no data showing improved outcomes.

MELATONIN PREPARATIONS

- In the United States, melatonin is considered a "dietary supplement," without a prescription.
- Exogenous melatonin administration have two effects like physiologically with nocturnal melatonin secretion:
  - The **promotion of sleep onset and maintenance**
  - **The phase-shifting of circadian rhythms**.(ie, 0.1 to 0.3 mg ***for sleep*** and 0.3 to 0.5 mg ***for phase-shifting***
- **Be suggest the use of lower, more physiologic doses of melatonin, particularly in older adults** . When preparations providing 0.3 to 0.5 mg are *unavailable*, the user can purchase 1.0 mg pills and *cut them in half*.
- Although melatonin is relatively nontoxic, some marketed doses (1 to 10 mg) can elevate plasma concentrations to 3 to 60 times their normal peak values .Supraphysiologic concentrations of melatonin produce numerous biological effects, including **daytime sleepiness, impaired mental and physical performance , hypothermia , and hyperprolactinemia** .

Melatonin agonists such as:

- **ramelteon,**
- **agomelatine,**
- **circadin,**
- **TIK-301 and**
- **tasimelteon**

In conclusion, melatonin and related drugs is a new and promising era for medicine. Melatonin receptors and melatonin drugs will take attention with greater interest day by day in the future.

SUBLINGUAL MUCOSA AS A ROUTE FOR SYSTEMIC DRUG DELIVERY

Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route.

- Sublingual route : **rapid onset** of action, with **better** patient **compliance** than orally ingested
- tablets
- In terms of permeability, the sublingual area of the oral cavity > buccal area> palatal area
- The portion of drug absorbed through the sublingual blood vessels **bypasses the hepatic first-pass metabolic** processes giving **acceptable bioavailability**.

Adverse effects :

Despite used in excessive doses, there does not appear to be a major pattern of side effects.

One report described a search over 35 years , Of the nine studies reporting adverse effects, pharmacologic doses were used (1 to 36 mg), **headache, confusion, and fragmented sleep were among the side effects reported. Dizziness, somnolence, nausea**, and headache have been reported with the melatonin agonist ramelteon.

Health care professionals should caution patients who are taking melatonin with other medications to discuss with the pharmacist about the possibility of interactions which may either enhance risk or reduce efficacy.

Sleep medication side effects

Medications used to promote sleep can cause side effects in geriatric patients.

- **Benzodiazepine: falls or contribute to delirium**
- **Non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone :similar risk**
- Medications containing **diphenhydramine : deliriogenic effects via their anticholinergic properties**
- **Tricyclic antidepressants:** delirium secondary to anticholinergic effects, orthostatic hypotension, falls from [alpha]-1blockade, and cardiac arrhythmias
- **Atypical antipsychotics** sometimes are used off-label to help initiate sleep, but they carry a "black-box" warning regarding **sudden death from cardiovascular events in geriatric patient** switch dementia.
- **Hydroxyzine** and **trazodone** also are associated with side effects such as **orthostatic hypotension and daytime sedation**, and are not always effective.

Delirium and dementia are common disorders seen in older adults.

- Delirium is a condition where there is acute cognitive decline with abnormal sleep-wake cycle and psychomotor activity.
- Medication management of these conditions is not optimal at this point.
- The challenging and controversial areas in delirium and dementia pharmacotherapy are seen especially with behavioral management. Some of the medications like ***antipsychotics*** and ***benzodiazepines*** used can cause unwanted consequences, especially when these are used for long periods in high doses.
- So, there is a need for new treatments and the recent studies are showing melatonin and its agonists have some promise in these conditions.
- Melatonin has pleiotropic effects like antiapoptotic, anti-inflammatory, immunomodulative, and antioxidant effects.
- In recent years, there is emerging evidence pointing out that it prevents progression of neurodegenerative diseases .

Melatonin levels in delirium

- A study done plasma melatonin levels were measured **preoperatively** and **two days postoperatively**.
  - ✓ In patients who did not develop postoperative delirium, there was no change in melatonin levels.
  - ✓ Whereas, in patients who developed delirium without any complications, there was decrease in melatonin levels, but
  - ✓ in the group with complications (like sepsis) there was increase in melatonin levels.

- Another study on older subjects compared 6-SMT levels during delirium with recovery phase from delirium. Subjects with ***hyperactive delirium had decreased urinary 6-SMT levels***; ***hypoactive delirium had increased levels***, and ***mixed delirium had no change*** in the levels.

- A recent small study on elderly subjects showed melatonin levels measured at 12.00 during the time of acute delirium diagnosis were **higher than after delirium resolution** in non-demented subjects [18.5 pg/ml (13.8-27.5) vs. 12.9 pg/ml (9.8-17.08), $p<0.01$].

So, **delirious subjects may respond differently to melatonin treatment based on the type of delirium and the cause for delirium, as well as whether they have an underlying dementia or not.**

- Case report series showed melatonin usefulness in treating postoperative delirious subjects, unresponsive to antipsychotics or benzodiazepines .
- An RCT study on 300 subjects of hip arthroplasty under spinal anesthesia, where subjects took **5 mg melatonin** in the evening **prior to surgery** and also received the same dose 90 minutes preoperatively, showed a **significant decrease in postoperative delirium** when compared to controls (9% vs. 33%, p=0.003, NNT=5) .
- In RCT on older acutely medical ill subjects above the age of 65 years showed that ***0.5 mg of melatonin every night or until discharge*** resulted in a ***lowered risk of incident delirium***, compared to placebo (4% vs. 19%, p<0.02).
- A recent multicenter double-blind RCT on 378 hip surgery subjects who were on **3 mg of melatonin for 5 days starting within 24 hours on admission found no difference in the incidence of delirium**, but observed that subjects in the melatonin group **had lesser longer lasting episode of delirium** (2 or more days) (26% vs. 47%, p=0.02).

Ramelteon in Delirium

The findings of a number of case series showed ramelteon was beneficial in managing prevalent delirium.

- These studies showed not **only improvement in the sleep-wake cycle** but **also improvement in attention and cognitive function**. The dose of ramelteon used in these studies was **8 mg orally at night time**.
- A case report showed benefit even in switching from risperidone to ramelteon.
- A RCT on medically sick elderly subjects showed that ramelteon **8 mg orally daily** compared to placebo **reduced the risk of incident delirium** (3% vs. 32%) (p=0.003). This study showed ramelteon was useful in preventing delirium.

Melatonin and ramelteon as monotherapy seems to be effective in the prevention and treatment of delirium.

Melatonin in Alzheimer's Disease (AD)

- Studies had also shown that melatonin levels were lower in AD patients compared to age-matched controls .
- **CSF-melatonin levels were shown to be low in the preclinical stages of AD**.
- In cognitively impaired subjects, in addition to low melatonin level**, flattened diurnal curve as well as peak levels were also seen**.
- At this point, medications available for AD management help to improve symptoms but have no disease-modifying effects. In animal studies, it had been shown that melatonin counteracts the beta amyloid effects caused by increased oxidative stress, increased lipid peroxidation, and abnormal mitochondrial function. This neuroprotective effect can reduce AD neuropathology and eventually delay or prevent AD progression . Melatonin improved the learning and memory deficits in an APP695 *transgenic mouse* model of AD.

A decreased melatonin level and a disturbed sleep wake cycle were seen in AD.

Melatonin in MCI

- In a small study of 10 human subjects with MCI symptoms, 6 mg/day of melatonin **improved sleep, mood, and memory.**
- A retrospective case controlled study on 50 MCI subjects: Melatonin 3-9 mg/day doses were used for 9-18 months. Subjects who receive melatonin showed **better performance in MMSE** (1.6±0.16 vs. -0.7±0.21, $p<0.001$ and ADAS-Cog (cognitive subscale of Alzheimer's disease Assessment Scale) (-3.6±0.42 vs. 3.2±0.97, $p<0.001$) when compared to non-melatonin group.
- Another retrospective study by the same authors with higher doses of melatonin (3-24 mg orally daily) over longer period (15-60 months) showed similar benefit with cognition ($p<0.001$).

Even though few studies showed benefit in MCI subjects, larger randomized controlled trials are lacking .

Melatonin in AD

- A double blind placebo-controlled study on 20 AD subjects with a mean age of 79.2±6.4 years. 11 received **melatonin 3 mg/day for 4 weeks**. There was an **improvement in ADAS-Cog** (p=0.017), but **no significant improvement in MMSE**.
- A double blind RCT in 12 nursing homes, elderly subjects aged 85±5 years were randomly assigned to active treatment or placebo (light exposure). Study results showed **in combination with bright light, melatonin attenuated agitated behavior by 9%**. Most notably, melatonin reduced sleep onset latency by a relative 19%, increased total sleep duration by 6%, and increased the mean duration of uninterrupted sleep periodsby 25% in these dementia subjects. Furthermore**, in combination with bright light, melatonin improved sleep efficiency (3.5%), nocturnal restlessness (9%), and the average duration of brief nocturnal awakenings** (12%).
- But an RCT study in demented subjects at nursing homes in San Diego, USA found **no significant effects of melatonin on sleep or agitation**. In this study, melatonin (8.5 mg immediate release and 1.5 mg sustained release). The authors in this study concluded that **the lack of efficacy may be related to the absence of a true treatment effect or due to the supra physiologic dose of melatonin used**

Melatonin in Combination with Galantamine

- In *in vitro* studies, combination of melatonin and galantamine had synergistic neuroprotective effect .
- A Spanish animal study also showed similar evidence.
- A randomized, double-blind, parallel-group study was conducted in 80 subjects, ranging from 52-85 years with mild to moderate AD who were also receiving galantamine. Subjects treated with 2 mg melatonin as an add-on to galantamine for 24 weeks had significantly better cognitive performance than those treated with placebo, as measured by the ***MMSE and IADL***. This study showed that **melatonin may have a synergistic effect with galantamine on cognitive function** .

Melatonergic Drugs and Its Effect on Behavioral Disorders Associated with Dementia

- A systematic showed that in 2 out of 4 RCTs and 5 case series in demented subjects**, melatonin improved agitation and sundowning behaviors.**
- A case report showed **ramelteon 8 mg orally at bedtime improved refractory behavioral and psychological symptoms of dementia in severe AD** over 3 months period **.**
- Another case-series study on subjects with **Lewy Body dementia showed ramelteon 8 mg orally daily resulted in improvement of visual hallucinations and REM sleep disorder .**
- A recent case report showed the benefit of **combining ramelteon 8 mg with an atypical antipsychotic quetiapine for behavioral disorders** in a 75 year old man who had delirium on top of an underlying Alzheimer's dementia **.**

Evaluation of antioxidant activity and protective effect against amyloid β-induced damage.

- Oxidative stress has been recognized as a contributing factor in ageing and various diseases including **cancer** and **neuropathological disorders**.
- Indole derivatives such as the neurohormone melatonin (MLT) constitute an important class of therapeutic agent in medicinal chemistry**.**
- **MLT can scavenge different reactive oxygen species and can also stimulate the synthesis of antioxidant enzymes.**
- In conclusion, **MLT derivatives represent promising scaffolds for discovery of effective antioxidant and neuroprotective agents.**

The role of melatonin and melatonin agonists in counteracting antipsychotic-induced metabolic sideeffects

This systematic review aims to investigate whether melatonin or melatonin agonists significantly attenuate metabolic side effects among psychiatric populations treated with atypical antipsychotics.

- **Melatonin was beneficial in lowering blood pressure among bipolar disorder patients; this blood pressure-lowering effect was not prominent among schizophrenic patients.**
- Melatonin appeared to **improve lipid profiles and body composition and attenuated weight gain among both schizophrenic and bipolar disorder patients.**
- Ramelteon showed a significant efficacy in lowering total cholesterol level.

Increased Melatonin Signaling Is a Risk Factor for Type 2 Diabetes

- Type 2 diabetes (T2D) is a global pandemic. Genome-wide association studies (GWASs) have identified >100 genetic variants associated with the disease, including a common variant in the melatonin receptor 1 b gene (*MTNR1B*).
- Increased *MTNR1B* expression in human islets from risk G-allele carriers, which likely leads to a reduction in insulin release, increase T2D risk.
- Accordingly**, in insulin-secreting cells, melatonin reduced cAMP levels, and *MTNR1B* overexpression exaggerated the inhibition of insulin release exerted by melatonin**.
- **Enhanced melatonin signaling in islets reduces insulin secretion, lead to hyperglycemia and greater future risk of T2D**.
- The findings also imply that **melatonin physiologically serves to inhibit nocturnal insulin release.**

Daily Melatonin Administration Attenuates Age-Dependent Disturbances of Cardiovascular Rhythms

Increased blood pressure and reduced robustness of circadian rhythms are frequently reported in elderly subjects.

- 97 normotensive and hypertensive volunteers of both genders and 63 to 91 years old participated.
- The experiment lasted for three weeks.
- After one control week, part of the group (n=63) **received 1.5 mg melatonin** (MelaxenTM) each day at 22:30 h for **two weeks**. The other 34 subjects were placebo-treated.

Melatonin has a direct hypotensive effect. Also, it stabilizes the internal temporal order enhancing the circadian component and the synchronization between rhythms of different physiological functions.

NICE **Guidelines for the use of Melatonin**
January 2014

Recommendation:

The UK licensed product for the short-term monotherapy of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over is Circadin®.

In Worcestershire, melatonin is recommended to aid sleep in the following circumstances:

- **Treatment of children and adults with neurological and/or behavioural problems, including Attention Deficit Hyperactivity Disorder (ADHD) and autism.**
- **Treatment of older adults with dementia where alternative hypnotics have failed.**
- **Critical Care where use of first line hypnotics has failed.**
- **As part of the sleep Electroencephalography (EEG) procedure at Worcestershire Trusts.**

Advantages of melatonin over other hypnotic agents include:

- lack of hangover effect.
- no loss of effect or risk of tolerance with repeated dosing.
- no physical dependence (that being a state resulting from chronic use of a drug that has produced tolerance and where negative physical symptoms of withdrawal result from abrupt discontinuation or dosage reduction).
- low prevalence of unwanted effects

Prescribing should be limited to those people where sleep problems adversely affect quality of life and where other methods of management are ineffective or impractical.
Long-term effects on endocrine systems and the long term consequences of exogenous melatonin administration are unknown.

Circadin® is licensed in the UK for the treatment of primary insomnia in patients 55 years or older and limited to a fixed dose of 2mg daily for up to 13 weeks.

Mental Health and Older Adults:

Whilst attention to sleep hygiene processes and identification and treatment of co-morbid conditions remains paramount there is evidence to show that melatonin can improve the agitated and unsettled time that frequently occurs later in the day – commonly referred to as 'sundowning'. Prescription hypnotics within license remain first line pharmacology but melatonin has been found to be both safe and effective in doses of up to 10mg daily. Benefit is usually reached by 6mg daily. As with use in other patient groups there appears to be little early morning unwanted sleepiness, and tolerance and dependence with chronic dosing is not apparent.

Adverse effects

Melatonin is generally well tolerated. Reported adverse effects include: headache, dizziness, nausea and drowsiness. Further controlled trials are required to assess both short and long term side effects.

Cautions in use

- Some reports suggest melatonin improves seizure control when used in patients with epilepsy; others indicate that it may worsen seizure control. When used in patients with epilepsy, it is important to closely monitor the effect of melatonin on seizure frequency.
- The manufacturer of Circadin® advises caution in patients with renal disorders and not to use melatonin in patients with liver disorders.
- The manufacturer of Circadin® advises melatonin should not be used in patients with autoimmune and some rare hereditary glucose tolerance disorders.
- Interactions with fluvoxamine, psoralen, cimetidine, quinolones and estrogens are listed.
- Avoid alcohol and other sedatives.
- No evidence of safety in pregnancy or breastfeeding.
- Adults should be warned of the potential for melatonin to affect ability to drive or operate machinery.

Prescribing Points

- **Melatonin should be prescribed as a regular treatment taken up to 2 hours before bedtime.**
- **It has no role as a daytime PRN (when required) sedative.**
- Doses employed in older adults range from 2mg to 10mg daily.
- Benefit should be apparent soon after commencing treatment.
- Initial Dose: 2mg once daily.
- Titrate upwards (2mg increments) to a maximum of 10 mg daily, depending on observed response.
- If no effect has been experienced after 7-14 days then the medicine should be stopped.
- Melatonin should initially be prescribed for a 2-4 week period and be used in conjunction with behavioural advice.