SLEEP MEDICINE

Dr mansour deylami

Circadian rhythms

- Circadian rhythms affect almost every aspect of the body function including activity and rest patterns , cognitive function (learning and memory) , cardiovascular and endocrine physiology (heart rate ,metabolism , hormone secretion) , and gene expression (15% of the genes in the human body show daily rhythms)

Virtually all species (bacteria , plants , animals , humans ,) show circadian rhythms that regulate periodic changes in behavioral and physiologic parameters within a period of approximately 24 hours .

These rhythms synchronize our activity to the external light – dark cycle in the majority of living creatures and helps them stay in tune with the environmental light – dark cycles

- What are the 4 circadian rhythms?
- **Each type of biological rhythm has a certain name to show how long it lasts:**

  1 – Diurnal (night and day)

  2 – Circadian (24 hours)

  3 – Ultradian (less than 24 hours)

  4 - Infradian/Circalunar (1 month)

  5 – Circannual (1 year)

- Chronotype = our sleep timing preference
- Is a manifestation of our internal biological clock
- Variation in chronotype has been linked to sleep disorders , cognitive and physical performance , and chronic diseases (diabetes – HTN – depression)

biological clock

- Biological clocks are organisms' natural timing devices, regulating the cycle of circadian rhythms.
- They're composed specific molecules (proteins) that interact with cells throughout the body.
- every tissue and organ contains biological clocks.
- Researchers have identified similar genes in people, fruit , flies, mice, plants, fungi, and several other organisms that make the clocks' molecular components.

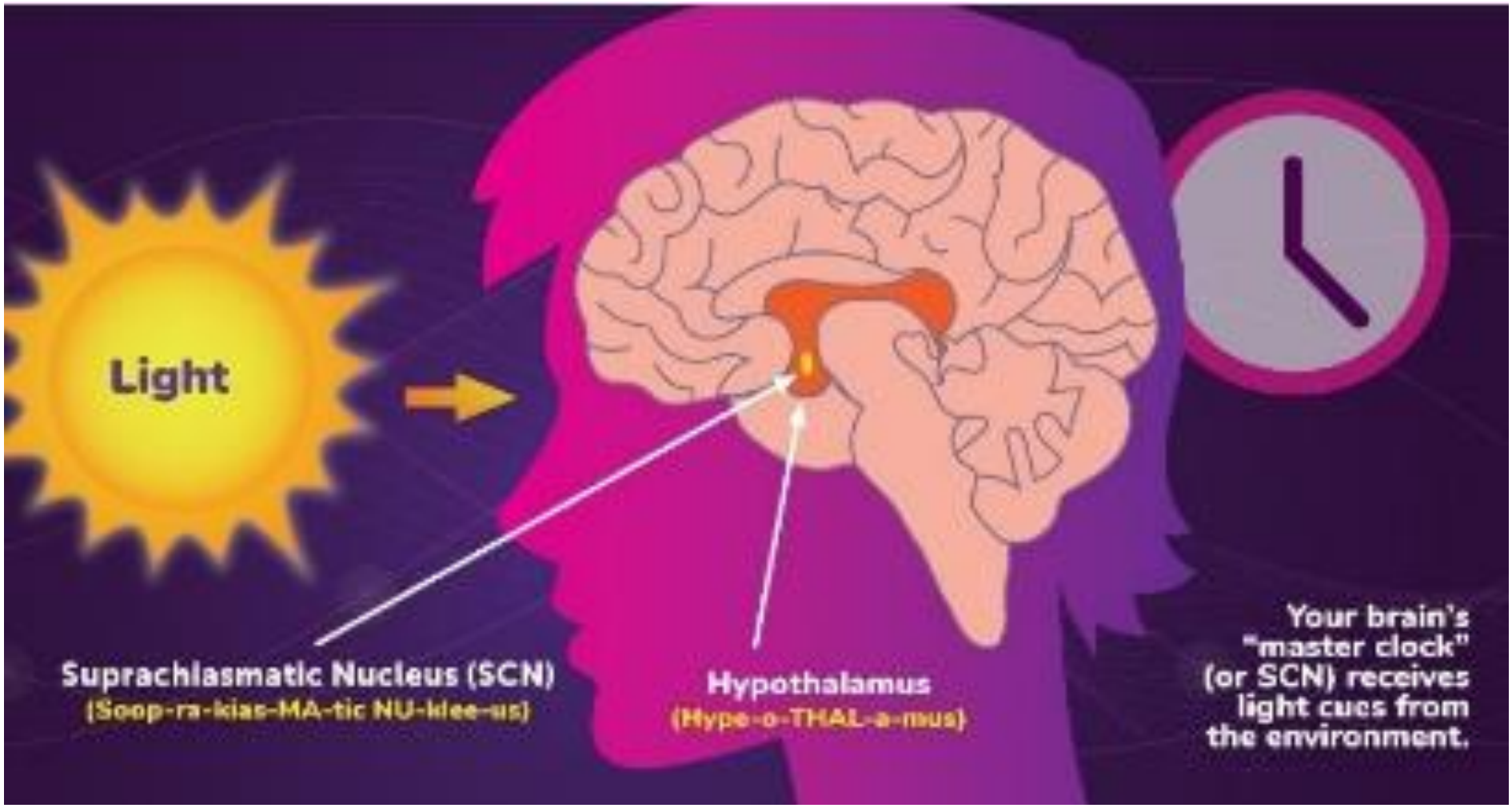
- Clock genes generate endogenous clock pulses in most cells of the body , synchronized by regulatory pathways across the body to a superior rhythm generator (a so – called master clock)
- Desynchronization of tese rhythms seems to be involved in the pathogenesis of metabolic , psychiatric , and other disorders

The superior rhythm generator or master clock

- A master clock in the brain coordinates all the biological clocks in a living thing, keeping the clocks in sync.
- In vertebrate animals, including humans, the master clock is a group of about20,000 nerve cells (neurons) that form a structure called the suprachiasmatic nucleus, or SCN.
- The SCN is in a part of the brain called the hypothalamus and receives direct input from the eyes.

- The SCN receives external inputs about light and darkness from the retinal cells and synchronizes inputs of melatonin levels .

- Note :
- Research suggests the ideal time to go to sleep for human is **10 p.m.**


Light
Suprachiasmatic Nucleus (SCN)
(Soop-ra-kias-MA-tic NU-klee-us)
Hypothalamus
(Hype-o-THAL-a-nus)
Your brain's "master clock" (or SCN) receives light cues from the environment.

How do circadian rhythms affect health?

- Circadian rhythms can influence important functions in our bodies, such as:
- 1 - Hormone release
- 2 - Eating habits and digestion
- 3 - Body temperature

- However, most people notice the effect of circadian rhythms on their sleep patterns.
- The SCN controls the production of melatonin, a hormone that makes you sleepy. It receives information about incoming light from the optic nerves, which relay information from the eyes to the brain. When there is less light—for example, at night—the SCN tells the brain to make more melatonin so you get drowsy.

- Changes in our body and environmental factors can cause our circadian rhythms and the natural light-dark cycle to be out of sync.
- 1 - Mutations or changes in certain genes can affect our biological clocks.
- 2 - Jet lag or shift work causes changes in the light-dark cycle.
- 3 - Light from electronic devices at night can confuse our biological clocks.
- These changes can cause sleep disorders, and may lead to other chronic health conditions, such as obesity, diabetes, depression, bipolar disorder, and seasonal affective disorder.

- What is the healthiest circadian rhythm ?
- **An ideal routine :**

1 – Sleep : Aim to spend eight hours in bed each night to allow at least seven hours of sleep. ...

2 – Diet : Eat within an 8- to 10-hour window of time each day. ...

3 – Light : Spend at least 30 minutes outdoors during daylight hours to reduce depression, increase alertness and improve mood.

- The sleep cycle is regulated by the circadian rhythm, which is driven by the suprachiasmatic nucleus (SCN) of the hypothalamus.
- Transitions between sleep and wake states are orchestrated by multiple brain structures, which include:

1 - Hypothalamus: controls onset of sleep

2 - Hippocampus: memory region active during dreaming

3 - Amygdala: emotion center active during dreaming

4 - Thalamus: prevents sensory signals from reaching the cortex

5 - Reticular formation: regulates the transition between sleep and wakefulness

6 - Pons: helps initiate REM sleep.

The extraocular movements that occur during REM are due to the activity of PPRF (paramedian pontine reticular formation/conjugate gaze center).

Sleep architecture

- Sleep occurs in five stages: wake, N1, N2, N3, and REM.
- Stages N1 to N3 are considered non-rapid eye movement (NREM) sleep, with each stage a progressively deeper sleep.
- Approximately 75% of sleep is spent in the NREM stages, with the majority spent in the N2 stage.
- A typical night's sleep consists of 4 to 5 sleep cycles, with the progression of sleep stages in the following order: N1, N2, N3, N2, REM.

- A complete sleep cycle takes roughly 90 to 110 minutes.
- The first REM period is short, and, as the night progresses, longer periods of REM and decreased time in deep sleep (NREM) occur.
- When the dominate wave in EEG are alpha and beta it is called the brain is activated and when the dominate wave became theta and delta the brain called depressed

Wake stage / alert

- EEG recording : beta waves - highest frequency, lowest amplitude (alpha waves are seen during quiet/relaxed wakefulness)
- The first stage is the wake stage or stage W, which further depends on whether the eyes are open or closed.

1 - beta waves predominante : During attention and cortical activation as eye-open wakefulness . (F = 16 - 30)

2 - alpha waves predominante : As individuals become relax , drowsy (reduced attention) and close their eyes .(F=8 – 13) the individuals do not sleep , and a full level of cognitive function can be estabished easily even without a strong sensory stimulus

N1 (STAGE 1) = light sleep

- Transition from wakefulness to N1 sleep stage
- EEG recording: theta waves (F = 5- 8) – this is the lightest stage of sleep .
- This transition from alpha to theta activity is widely accepted as the EEG of sleep onset .
- HR and heat production decrease .{decrease temp}
- Muscle tone is present in the skeletal muscle, and respiration is regular and deep .
- This stage lasts around 1 to 5 minutes, consisting of 3% of total sleep time.

N2 (stage 2) = deeper sleep

- EEG recording : teta wave + intermittent sleep spindles and k – complexes .
- Sleep spindles = play an important role in memory consolidation , specifically procedural and declarative memory
- K – complexes = represents an activation of brainstem and subcortical brain area during sleep for selective processing of unexpected sensory inputs (e.g. sounds) that might require complete arousal and restoration of consciousness to address a potential threat .

- In comatose patients with brain injury , the presence of k- complexes in response to an acoustic stimulus during coma is a marker of a better outcome compared with comatose patients with no evoked k- complexes .
- K –complexes have been shown to function in maintaining sleep and memory consolidation .
- In N2 our body process memory and regulate his metabolism .
- N2 is necessary for removal of soul fatigue .

- Stage N2 sleep lasts around 25 minutes in the first cycle and lengthens with each successive cycle .
- eventually N2 consisting of about 50% of total sleep.
- This stage of sleep is when bruxism (teeth grinding) occurs.

N3 (stage 3) deepest NON – REM sleep

- EEG recording: delta waves - lowest frequency, highest amplitude
- N3 is also known as slow-wave sleep (SWS).
- This is considered the deepest stage of sleep and is characterized by signals with much lower frequencies and higher amplitudes, known as delta waves.
- This stage is the most difficult to awaken from, and, for some people, even loud noises (> 100 decibels) will not awaken them.
- As people age, they tend to spend less time in this slow, delta wave sleep and more time in stage N2 sleep.

- Although this stage has the greatest arousal threshold, if someone is awoken during this stage, they will have a transient phase of mental fogginess, known as sleep inertia.
- Cognitive testing shows that individuals awakened during this stage tend to have moderately impaired mental performance for 30 minutes to an hour.
- This is the stage when the fatigue is relieved and body repairs and regrows tissues, builds bone and muscle and strengthens the immune system.
- This is also the stage when sleep walking, night terrors, and bed wetting occurs.

REM SLEEP (PARADOXICAL SLEEP)- 25%

- EEG recording: beta waves - similar to an awake individual and brain metabolism increase .
- REM is associated with an alteration of hemostatic regulation such as increased HR variability , irregular respiration and impaired body temperature control .
- REM is associated with dreaming and is not considered a restful sleep stage.
- the skeletal muscles are atonic and without movement, except for the extraocular and diaphragmatic breathing muscles, which remain active.

- The REM sleep usually starts 90 minutes after you fall asleep, with each of your REM cycles getting longer throughout the night.
- The first period typically lasts 10 minutes, with the final one lasting up to an hour.
- REM is when dreaming, nightmares, and penile/clitoral tumescence occur.
- Dreaming is a typical experience during REM sleep , but can also happen during NREM sleep.

- Important characteristics of REM :
- 1 - Associated with dreaming and irregular muscle movements as well as rapid movements of the eyes
- 2 - A person is more difficult to arouse by sensory stimuli than during SWS
- 3 - People tend to awaken spontaneously in the morning during an episode of REM sleep
- 4 - Loss of motor tone, increased brain O2 use, increased and variable pulse and blood pressure
- 5 - The brain is highly active throughout REM sleep, increasing brain metabolism by up to 20%

SDB (Sleep-disordered breathing)

- **Sleep apnea**
- Individuals with sleep apnea experience airway collapse in deeper sleep states, causing them to experience reduced time in stage N3 and REM sleep. This leads to excessive daytime drowsiness as proper, efficient sleep is not obtained throughout the night. There are two types of sleep apnea:
- 1 - Central sleep apnea = occurs when the brain fails to properly signal respiratory muscles during sleep.
- 2 - obstructive sleep apnea = is a mechanical problem in which there is a partial or complete blockage of the upper airway.

- The severity of SDB is usually quantified by the number of respiratory events per hour of sleep .
- This is necessary because a low number of short apneas and hypopneas can occur up to about 5 times per hour in healthy subjects .
- 2 measures can be used for this purpose :

    1- AHI (apnea hypopnea index)

    2 – RDI (respiratory disturbance index)

These are used to quantify (evaluate)the severity of OSA and treatment outcome .

-- in apnea your breathing is completely impaired for 10 seconds or longer

- The apnea-hypopnea index (AHI) is the combined average number of apneas + hypopneas that occur per hour of sleep.
- The respiratory disturbance index (RDI)is the average number of apneas + hypopneas + arousal (in EEG) associated respiratory event per hour of sleep.
- According to the American Academy of Sleep Medicine (AASM) the OSA is categorized into

  A - mild (5-15 events/hr)

  B - moderate (15-30 events/hr)

  C - severe (> 30 events/hr)

An AHI score of less than 5 per hour indicate normal , healthy breathing

OSA

- OSA is the most common type of SDB and is diagnosed in patients with more than 15 obstructive events per hours of sleep or
- With fewer respiratory events (5- 15 /h)if daytime symptoms (sleepiness) or comorbidities such as HTN or atrial fibrilation are present .
- Predisposing factors for OSA : obesity (major risk factor)- age - male sex - factor leading to swelling of the upper airway (smoking)- allergic rhinitis - respiratory depressant (they decrease muscle tone of upper airway dilator muscles)

- The rate of OSA in patients following surgery is between 45% and 75% .
- The incidence of OSA in patients undergoing bariatric surgery is as high as 78% .
- In women undergoing gynecologic oncology surgery the incidence of OSA is 50% .
- OSA is associated with serious medical consequences such as :
- HTN – MI – stroke –diabetes – diabetic neuropathy – cognitive disfunction resulting in occupational difficulties .
- OSA is associated with POST.OP delirium

- Typical daily signs and symptoms of OSA :

  1 – waking with dry mouth or headache

  2 – daytime sleepiness

  3 – falling asleep during monotonus situations such as watching TV

  4 – impairment of cognitive function

- Night time symptoms :

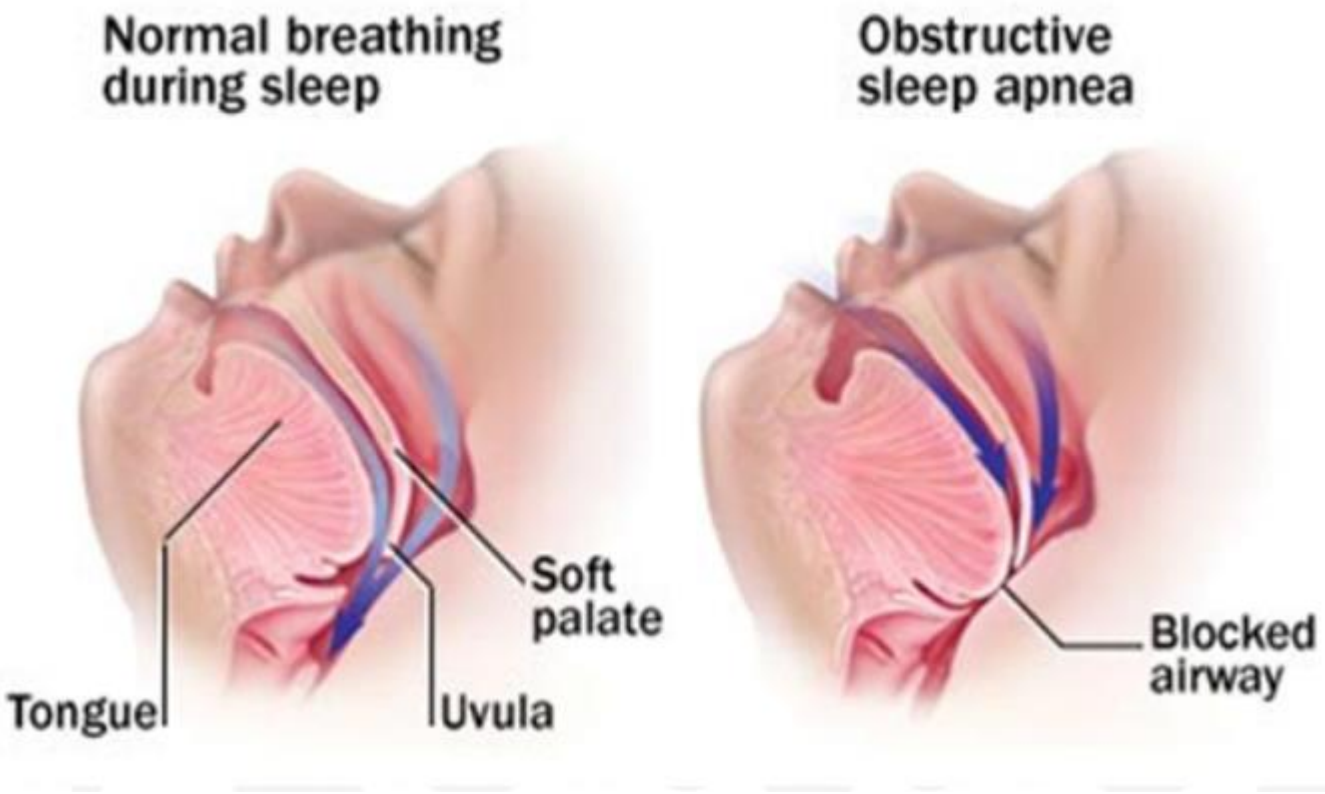
  1 – pseudo-nocturia (frequent awakening during the night

  2 – awaking from own snoring with choking sensation

  3 – tachycardia

  4 – sleep that is not restorative

- Obstructive sleep apnea **occurs when the muscles that support the soft tissues in your throat, such as your tongue and soft palate, temporarily relax**.
- When these muscles relax, your airway is narrowed or closed, and breathing is momentarily cut off.
- Upper airway dilator muscles (genioglossus and tensor palatini)counterbalance the negative inspiratory pressure generated by the pump muscle to permit airflow during inspiration


Normal breathing during sleep
Obstructive sleep apnea
Soft palate
Tongue
Uvula
Blocked airway

- Treatment of OSA :
- 1 - CPAP (the most effecting)
- 2 – oral appliances include mandibular repositioning appliance and tongue- retaining devices = in mild to moderate OSA who do not tolerate CPAP therapy

Note :

- O2 is currently not recommended a primary treatment of OSA .
- Weight loss lead to reduction of severity of OSA.
- The effectiveness of most nasopharyngeal surgical approaches for OSA remain unclear . However tonsillectomy is beneficial in adults and children if tonsillar hypertrophy exist .

Central sleep apnea

- CSA is defined as cessation of air flow without respiratory effort at night sleep .
- It is a disorder in which your breathing repeatedly stops and starts during sleep .
- In OSA the respiratory effort is maintained or even increased during an apnea
- CSA occurs because your brain does”t send proper signals to the muscles that control your breathing .
- This condition is different from OSA , in which you can not breathe normally because of upper airway obstruction .
- CSA is less common than OSA .

- CSA can be found in : older men or can result from other condition such as CHF , stroke , neurologic disorder (ALS) .
- NOTE = it was not found in : 1- younger men
- 2 – women
- another forms of central breathing disorders is altitude-induced breathing instability (sleeping at high altitude) and cheyene- stockes respiration (CSR) that can occur while awake but usually occur during sleep.

- Cheyene-stockes is commonly seen in patients with CHF and left ventricular systolic dysfunction(seen in 50% patients with CHF).
- CSR is defined as a crescendo-decrescendo pattern of hyperventilation between 20 and 30 seconds in duration followed by 10 to 40 seconds of hypopneas or apneas .
- It can also occur during exercise or wakefulness and is more common in men and worse in the supine body position .
- Apnea = decrease in respiratory flow of 90% or more from baseline for atleast 10 seconds .
- Hypopneas = 40% decrease in inspiratory flow with a decrease in SPO2 of only 3%

- Respiratory therapies of CSR :
- 1 – oxygen
- 2- respiratory stimulants (acetazolamide–theophilline)
- 3- NIV

- Note = the effectiveness of CPAP as therapy is controversial .
- CSR will often resolve with adequate treatment of CHF , so , optimization of medical therapy is the best treatment .

Obesity hypoventilation syndrome (OHS)

- OHS is defined as the combination of noctural and daytime hypoventilation that cause hypercapnea + obesity (BMI > 30)
- The hallmark is an alveolar hypoventilation leading to hypercapnia and the responsible mechanisms is central hypoventilation .
- 90% of patients with OHS also suffer from OSA .
- In severe obesity there is a compensatory mechanism that increase the respiratory drive and help maintaining eucapnia in the presence of the abnormal chest wall mechanics and high work of breathing , and in OHS this mechansm is abolished

- In OHS the body response to co2 is normal or reduced + increased alveolar Pco2 and serum bicarbonate .
- treatment : weight loss + NIV

Narcolepsy حمله خواب

- Narcolepsy is **a sleep disorder that makes people very drowsy during the day**.
- They fall asleep suddenly .
- People with narcolepsy find it hard to stay awake for long periods of time. This can cause serious problems in their daily routine.
- It affect both males and females equally . two peak time periods have been identified , 1 – around 15 y and 2- around 35 y
- Narcolepsy is caused by a lack of the brain chemical hypocretin (orexin) which is secreated from hypothalamus and regulates wakefulness . This lack is caused by the immune system mistakenly attacking the cells that produce it or the receptors that allow it to work .

- Narcolepsy is not rare ! But it is an under – recognized condition .
- Some well- known personalities who suffered from this condition include : - winston chirchil

- thomas edison

- louis braille

- A small dose of caffeine has positive effects on alterness in patients with narcolepsy .

- **Symptoms of narcolepsy :**

1 - Excessive daytime sleepiness. People with narcolepsy fall asleep without warning (involuntary) and have disturbed noctural sleep

2 – cataplexy : Sudden loss of muscle tone in awake individual

(catalepsy is when muscle become rigid and the person has a loss of sensationto painful stimuli-no response- loss of control)

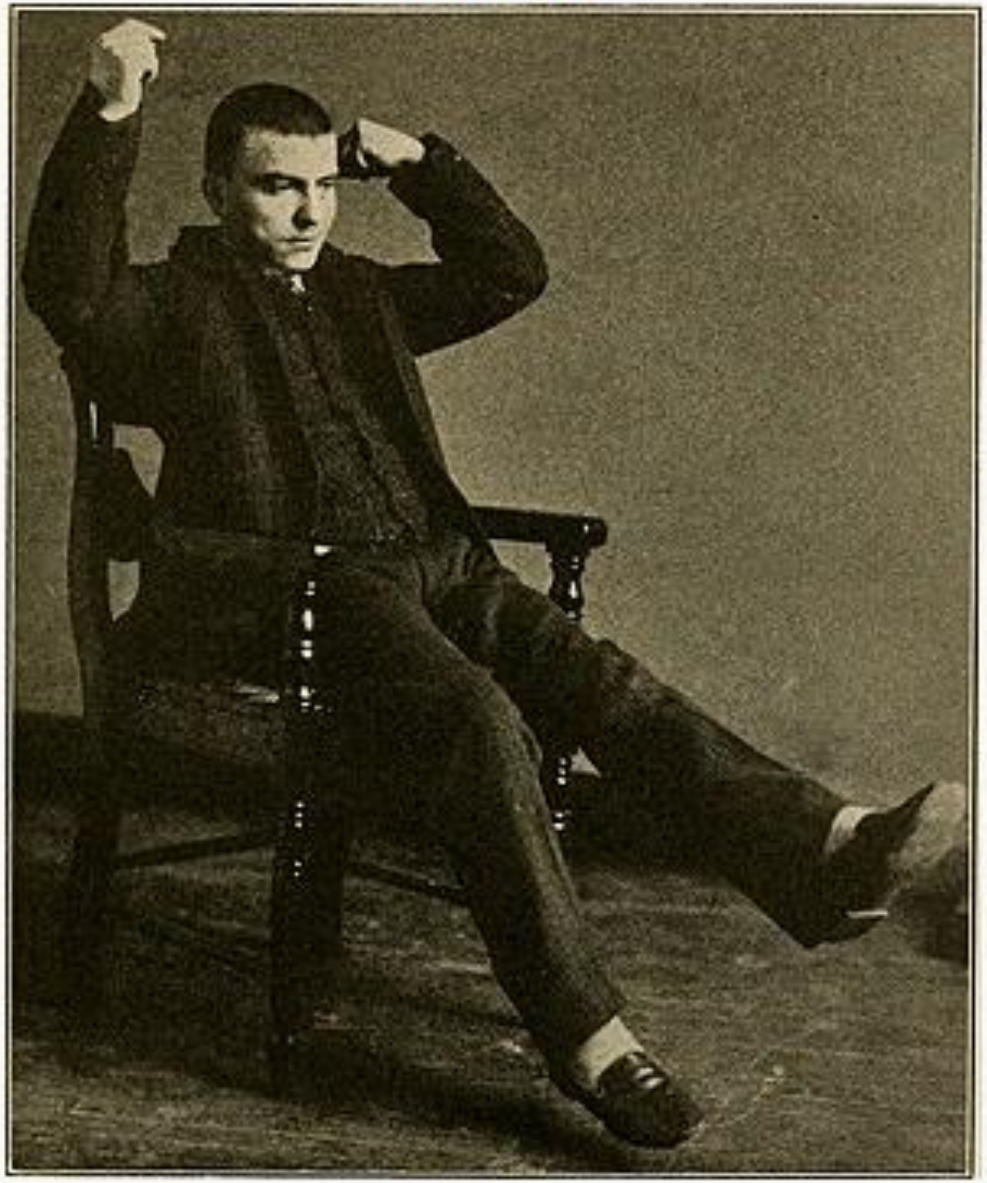
3 - Sleep paralysis. People with narcolepsy often experience sleep paralysis. ...

4 – Hallucination (hypnogogic and hypnopompic)

5 - Changes in rapid eye movement (REM) sleep.the patient suddenly enter REM sleep without going through NREM sleep .

- In addition to experiencing the typical symptoms , individuals also sleep for long periods each night (>10 h)

Catalepsy



Catalepsy

Specialty Neurology

Sleep paralysis بختک

this happen when you wake up suddenly from REM sleep stage , in this situation your brain is active and awake , but your body is still in REM mode and can not move , causing you to feel like you are paralized .

Episodes of sleep paralysis last from a few seconds to 2 minutes .

- Narcolepsy patients experience longer , more negative , and more vivid dream than others and nightmares are a frequent symptoms in them .
- Vitamin B12 deficiency is independently associated with narcolepsy .
- About 50% of patients with the narcolepsy-cataplexy syndrome suffer from memory problems .
- These patients are suseptible to delayed emergence from anesthesia , postsurgical hypersomnia , and apneic episodes

- Treatment of narcolepsy :
- 1 – behavioral treatment = periodic and regular sleep times and scheduled daytime naps are recommended.
- 2 – pharmacologic =amphetamine– modafinil - methylphenidate – selegiline (MAOI) .
- Medical treatment should be maintained during the PERIOP period .
- The most commonly used treatment of daytime sleepness is modafinil which acts via dopaminergic pathways and accelerates emergence from anesthesia .
- Cataleptic events can also occur during regional anesthesia

Sleep and sedation in ICU

- Impaired sleep is common in patients in ICU .
- Contributing factors = noise – light – pain – anxitey – inflammation – administration of fluids and nutrition
- ICUs are among the most noisy areas in hospital .
- Sleep fragmentation occurs consistently during sedation and mechanical ventilation .
- Changes in light exposure alter sleep patterns .
- Circadian rhythms and the duration of deep NREM and REM sleep are severly reduced or abolished in icu patients .
- 50% of sleep occur during daytime hours .

- Melatonin is a natural hormone that is produced by the pineal gland (located in the brain). It **helps control the sleep cycle**.
- The body produces melatonin just after it gets dark, peaking in the early hours of the morning and reducing during daylight hours.
- Melatonin acts on receptors in the body to encourage sleep.
- Impaired rhythmicity in melatonin secretion pattern is seen in critically ill patients .

- Melatonin levels decrease with increasing age , making older ICU patients more sensitive to circadian rhythm disruptions .
- Drugs that increase melatonin levels throughout the 24- hour period :
- 1 – opioids
- 2 – B-agonists (B- blocker decrease)
- 3 – vasopressors
- 4 – positive inotropes
- 5 – albuterol aerosolized
- 6 – endogenous catecholamines

- Both NIV and ventilation via breathing tube impair sleep architecture and quality .
- All weaning procedures during the daytime combined with assist control ventilation during the nighttime improve sleep .
- BZD have conflicting effects on melatonine .
- GABA receptor agonist such as propofol , BZD , opioids , reduce REM sleep and worsen sleep disorders .
- Melatonin has been selected as sleep-promoting medication for ICU patients in some countries .

- In the USA melatonin is considered a dietary supplement but in several other countries it is availableonly with a prescription and is considered a drug .
- Melatonin side- effects = dizziness –nausea – headache – HOTN .
- Do not use melatonin in : pregnant – breastfeeding – autoimmune disorder – seizure-depression .
- Melatonin is fast-acting (typically begin in between 20 minutes)and can last up to 5 hours , with a typical half-life of 40 – 60 minutes .

- Suvorexant ：
- The orexin receptor antagonist is approved for the treatment of insomnia in ICU

- Consequences of sleep disturbance in ICU :

1 – increased susceptibility for infection (decreased phagocytic activity of lymphocyte and natural killer cells .

2 – insulin resistance and imaired glucose tolerance .

3 – induce the onset of a catabolic state .

4 – change in the activity of the hypothalamo-pituitary-adrenal axis with altered plasma levels of cortisol and thyrotropin .

Restless legs syndrome (Ekborn syndrome)

- Is a neurologic disorder by 4 cardinal features :
- 1 – the urge to move the limbs , usually associated with paresthesia or dysesthesia
- 2 – aggravating effect on rest
- 3 – ameliorating effects on physical activity
- 4 – symptoms worsen during the course of day
- Patients with RLS usually also complain about sensory symptoms in the legs
- First line treatment is dopamine agonists in the evening (ropinirole – pramipexole)
- Other : gabapantine – levodopa -opioid