NAMS REGIONAL SYMPOSIUM ON SLEEP MEDICINE

PHARMACOLOGY OF SLEEP

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Introduction

- Sleep is a global process regulated by most regions of the brain.
- These regions utilize multiple neurochemical systems which interact with each other to generate wakefulness and two states of sleep.
- Wakefulness is promoted by neurons in the basal forebrain, pons, midbrain, and posterior hypothalamus that constitute ascending reticular arousal system (ARAS) and act through neurotransmitters: acetylcholine, norepinephrine, dopamine, serotonin, histamine, GABA, glutamate, neuropeptide-S and orexins/hypocretins.
- However, none of these neurotransmitters appears to be absolutely essential for maintaining the wakefulness.
- Most of these ARAS neurons produce **l**ow-**v**oltage, **f**ast (high) frequency **a**ctivity (LVFA) in the EEG (and increased muscle tone in EMG) and diffusely activate the cortex and other forebrain targets.

Introduction, Contd….

- NREM sleep is mainly driven by neurons in the preoptic area that inhibit the ARAS neurons (mainly through the inhibitory neurotransmitters: largely by GABA and to some extent by neuropeptides- enkephalins and galanin), which produce high-amplitude, low- frequency EEG oscillations (and decreased muscle tone in EMG).

Introduction, Contd….

- REM sleep is regulated primarily by neurons in the pons, with additional influence arising in the lateral hypothalamus by using neurotransmitters: acetylcholine, monoamines, GABA and melanin-concentrating hormone (MCH), which interact with glutamate or GABA in neurons of sublaterodorsal nucleus (SLD; also called subcoeruleus, or LCα), which project to the ventromedial medulla and ventral horn of the spinal cord, providing pathways through which they may inhibit motor neurons.
- Activation of the SLD region elicits atonia and REM sleep-like EEG activity.
- The REM sleep is characterized by LVFA coupled with rapid eye movements and complete loss of muscle tone (called REM sleep muscle atonia) .

Introduction, Contd….

- Mutual inhibition between these wake- and sleep-regulating regions likely helps generate full wakefulness and sleep with rapid transitions between these states.
- Some homeostatic sleep factors, called somnogens (to name a few: adenosine, cytokines: IL-1β, TNF- α, prostaglandin: PGD2, and nitric oxide) mainly produced during prolonged wakeful states and inflammatory morbid conditions also affect and modify the NREM and REM sleep states .

Pharmacology of Drugs Used in Sleep Disorders

- A broad understanding of all neurotransmitter mechanisms involved in wake-sleep cycle allow clinicians and researchers to better understand the effects of drugs, lesions, and neurologic diseases of sleep and wakefulness and consequently their use to rationalize the pharmacotherapy of sleep disorders.

Pharmacology of Drugs Used in Sleep Disorders, Contd….

- Clinical pharmacology of sleep medicine can be loosely classified into drugs aimed at treating:-
  - Sleepiness (Hypersomnias) - excessive day-time sleepiness, narcolepsy/cataplexy, shift-work disorder, jet-lag;
  - Sleeplessness, (Insomnias);
  - Sleep-related movement disturbances;
  - Obstructive sleep apnea.
- Although most of the drugs are available by prescription - only, the stimulant: caffeine and the antihistamine: diphenhydramine are common over-the-counter options for sleepiness and sleeplessness, respectively.

Excessive Sleepiness (Hypersomnias)

- The primary hypersomnias are uncommon compared to disorders that include sleepiness as a secondary symptom to sleep disruption.
- When the patient reports sleepiness, it is critical to investigate potential primary causes, such as sleep apnea or insomnia.
- Pain syndromes, mood disorders, and general medical problems may be comorbid with sleep apnea and/or disrupted sleep.
- However, residual day-time symptoms persist in some patients despite optimized management of potential primary causes, leading to consideration of stimulant agents in the appropriate clinical setting.

Narcolepsy/Cataplexy

- Narcolepsy is a rare disabling disorder affecting about 25 over 100 000 persons and characterized by:
  - excessive daytime sleepiness and
  - abnormal rapid eye movement (REM) sleep manifestations, including cataplexy (sudden loss of muscle tone triggered by strong emotions),
  - direct transition from wakefulness to REM sleep (DREMs) periods,
  - sleep paralysis (inability to move following awakening from REM sleep), and
  -hypnagogic hallucinations.

Narcolepsy/Cataplexy, Contd….

- REM-like symptoms of hypnagogic hallucinations occurr around sleep onset or awakening and sleep paralysis
- Narcolepsy is caused by deficient neurotransmission by orexins, excitatory peptides which are released by neurons from the lateral hypothalamus with widespread projections, namely to aminergic neurons known to be involved in the control of wakefulness, for example, histaminergic or noradrenergic neurons.
- Histaminergic neurons seem even necessary to the waking action of orexins, and reduced levels of histamine in the cerebrospinal fluid (CSF) of narcoleptic patients were recently reported.

Excessive Sleepiness (Hypersomnias), Contd….

Primary hypersomnias such as narcolepsy –cataplexy syndrome and idiopathic hypersomnia are treated primarily with the use of wake-promoting medications:

- Stimulants acting on noradrenergic and dopaminergic systems to alleviate excessive daytime sleepiness:

- Amphetamines –dextroamphetamine; methamphetamine: Used for excessive sleepiness, such as narcolepsy and phase-shift disorder.
- Methylphenidate; dexmethylphenidate : Used for excessive sleepiness, such as narcolepsy, phase-shift disorder, sleepiness secondary to other conditions or illnesses.
- Modafinil; armodafinil : Approved to treat excessive daytime sleepiness associated with narcolepsy, shift-work sleep, disorder, and obstructive sleep apnea
  - In narcolepsy, modafinil decreased daytime-sleepiness without affecting nighttime sleepiness and when used for shift-work sleep disorder, it increased sleep latency during nighttime shifts.
  - Modafinil showed less need for recovery sleep after sleep deprivation and fewer sleep disturbances with no REM sleep deficit.
- Caffeine: The drug non the prevent the actions of adenosine on other elements of the sleep regulatory system, such as histamine, orexin, and the GABAergic neurons (in VLPO)

Excessive Sleepiness (Hypersomnias), Contd….

Primary hypersomnias such as narcolepsy –cataplexy syndrome and idiopathic hypersomnia are treated primarily with the use of wake-promoting medications:

- Antidepressants; especially those promoting increased noradrenergic tone: amitriptyline, protriptyline [with or without gamma-Hydroxybutyrate (GHB, sodium oxybate) is used to improve night-time sleep in narcoleptics].

  GHB is a metabolite of GABA that modulates sleep via activation of $GABA_B$ receptors.

Excessive Sleepiness (Hypersomnias), Contd….

Primary hypersomnias such as narcolepsy –cataplexy syndrome and idiopathic hypersomnia are treated primarily with the use of wake-promoting medications:

- Newer Therapies: include pharmacological agonists of the:
- Orexin receptors antagonists: Almorextant, MK-4305, and
- Transplantation of orexin neurons and orexin gene therapy

- Histamine H_3 receptor antagonists/inverse agonists: Ciproxifan or Tiprolisant, Pitolisant are under development for the treatment of excessive daytime sleepiness disorders, narcolepsy, diurnal somnolence seen in parkinson's disease and other degenrative CNS diseases.
  These histamine H_3 receptor antagonists/inverse agonists promote wakefulness and EEG desynchrony and improve the excessive daytime sleepiness observed with narcolepsy. This wake-promoting effect is likely mediated by increased HA tone as the response to an H_3 antagonist is absent in mice lacking H_1 receptors

Excessive Sleeplessness (Insomnia)

- Insomnia, defined as insufficient quantity or quality of sleep, is the most prevalent sleep disorder.
- Approximately 50% of adults complain of occasional insomnia, and 10-15% of chronic insomnia, persisting for at least 1 month.
- Insomnia can involve difficulty falling asleep, staying asleep, or poor quality of sleep.
- Insomnia can be considered a constellation of symptoms with variety of underlying causes.
- As a symptom, it can be secondary to disorders of mood, pain, or a variety of other neurological and general medical disorders.
- Insomnia is classified into two types: comorbid, with other psychological and/or physical pathologies; and primary, existing independent of other identifiable causes conditions.
- Consequences of insomnia include: daytime sleepiness, lack of energy, and cognitive impairment.
- Insomnia may even precipitate or accompany the development of psychiatric disorders.

Excessive Sleeplessness (Insomnia), Contd….

- One of the most intriguing, yet poorly understood aspects of insomnia is the misperception phenotype, in which patients underestimate their sleep times compared to objective measurements.
- Insomnia can also be the presenting feature of circadian phase disorders – most commonly delayed circadian phase.
- The primary challenge with regards to the diagnosis and treatment of insomnia is that both depend entirely on the clinical history, with no basis in objective testing.

Excessive Sleeplessness (Insomnia), Contd….

- Pharmacological treatment of insomnia usually involves sleep aids and of sleep promoting medications, e.g.:

1. Benzodiazepines (BZDs) and Nonbenzodiazepine Drugs acting as agonists of the α1 subunit of the GABA receptors and potentiate the action of sleep-promoting GABA-ergic neurons. These drugs are as:

   BZDs- alprazolam diazepam, flunitrazepam, nitrazepam, lorazepam, temazepam, and

   nonbenzodiazepines or "Z" drugs- (zaleplon, zopiclone, eszopiclone, zolpidem)
2. Antihistamine: diphenhydramine, pheniramine, chlorpheniramine, triprolidine,
3. Melatonin and melatonin receptor (MT_1, MT_2) agonist: melatonin;ramelteon (3-16 times more effective than melatonin).
4. Ritanserin, an antagonist of both 5-HT_{2A} and 5-HT_{2C-} receptors and

Excessive Sleeplessness (Insomnia), Contd….

- Pharmacological treatment of insomnia usually involves sleep aids and of sleep promoting medications, e.g.:

5. Antidepressants, such as:
   - Tricyclic antidepressants: amitriptyline, nortriptyline, clomipramine, desipramine,
   - Selective serotonin reuptake inhibitors (SSRIs): fluoxetine, fluvoxamine, citalopram, trazadone (aSSRI with antagonism also at $5HT_{1A}$, $5HT_{2A}$ and $\alpha 1$ adrenergic receptors), and
   - agomelatine, a unique compound that acts as both melatonin receptor agonist and serotonergic $5\text{-}HT_{2C}$ R antagonist.
6. A variety of other compounds used to treat insomnia antagonize histaminergic and orexinergic wake-promoting nuclei (almorexant, MK-4305), were shown to enhance both NREM and REM sleep and reduce wakefulness in animals, healthy humans, and insomnia patients.

Drugs for Sleep-related Movement Disorders

- Restless leg syndrome (RLS) and periodic limb movements (PLM) of sleep are the most common movement disorders resulting in sleep disturbance.
- The former is a strictly clinical diagnosis, while the latter is a polysomnographic finding.
- PLM may also be seen in narcolepsy, sleep apnea and RBD.
- Both are treated similarly, often beginning with the investigation for iron stores (serum ferritin) and oral repletion when needed,

  followed by dopaminergic medications (pramipexole, ropinirole), as well as off-label use of other classes of agents.
- REM behavior disorder (RBD) is most commonly treated with hypnotic benzodiazepines (clonazepam, first choice) or melatonin treatment prior to bedtime.

REM Sleep Behavior Disorder (RBD)

- RBD involves uncontrolled movements and muscular expression of dream sequences leading to sleep fragmentation and injury to patients and their sleeping bed partners.
- In the sleep laboratory such activity is correlated with enhanced EMG activity during sleep, whereas other aspects of REM sleep are normal.
- It is more common in people aged over 50 years old and affects more men than women.
- Acute RBD can be induced by various medications (e.g., antidepressants acting to increase serotonergic or noradrenergic tone), whereas the cause of the chronic form is unknown.
- Importantly, RBD has been shown to precede and predict the later development of neurodegenerative diseases known as synucleinopathies including parkinson's disease, dementia with lewy bodies disease, and multiple system atrophy.
- This suggests that a neurodegenerative process in the generation of idiopathic RBD, presumably occurring in the brainstem REM muscle atonia generation zones in the dorsolateral pons and medulla.
- RBD may be an important marker allowing early-stage preventative treatments of synucleinopathies since RBD often occurs many years earlier than the other conditions.
- The acute form of RBD is managed by withdrawal of the offending medication, whereas the chronic form can be well managed symptomatically by benzodiazepines (clonazepam first choice) or melatonin treatment prior to bedtime.

Drugs for Treatment of Obstructive Sleep Apnea (OSA)

- In sleep apnea, the patient stops breathing (the apneic moment) during sleep, leading to blood oxygen desaturation (hypoxia), as well as an elevation of carbon dioxide levels (hypercarbia/hypercapnia). Sleep apneas are divided into three categories: central, obstructive, and complex (a combination of obstructive and central sleep apneas).
- Central sleep apnea involves dysfunction of the central respiratory control centers in the brain. OSA affects nearly 7% of the general population and is characterized by episodic cessation in breathing during sleep due to closure of the airway, of at least 10 s in length, and usually accompanied by hypoxia and hypercarbia.
- The apneic moment is usually terminated by a slight arousal, as well as an increase in sympathetic tone, as airway patency is reestablished. OSA diagnostic criteria include a rate of 5 or more apneic episodes per hour, and the most severe cases may experience upwards of 70-80 moments per hour.
- The sleep profile of an OSA patient includes sleep fragmentation and decreased prevalence of both deep stage NREM and REM sleep.

Drugs for Treatment of Obstructive Sleep Apnea (OSA) Contd….

- The night-time symptoms of OSA are snoring and fragmented sleep with excessive daytime sleepiness accompanied by cognitive and attention deficits, which affects the individual's quality of life.
- In addition, OSA is an independent risk factor for hypertension, diabetes, stroke and cardiac rhythm disturbances.
- The effects on the bed partner from marital discord related to lost sleep from snoring in the OSA patient, along with the higher risk of occupational injury and lost work productivity, is often under-appreciated.
- OSA impacts both the individual and society and should be classified as a modern public health issue, thus making therapeutic treatment options for OSA patients of high importance.

Drugs for Treatment of Obstructive Sleep Apnea (OSA) Contd….

- Effective treatments for apnea include: the CPAP (continuous positive airway pressure) device, dental devices, weight loss, and bariatric surgery.

- Pharmacological interventions to treat OSA increase the activity of the upper airway dilator muscles, as well as the ventilator drive, e.g., noradrenergic (protriptyline) and serotonergic agents (fluoxetine,paroxetine), progestogens, and bronchodilators (salbutamol).
- Some patients experience the majority of apneic moments during REM sleep.
- Therefore, treatment with serotonergic agents that suppress REM sleep may be useful.
- The stimulant modafinil has been prescribed to address the daytime hypersomnia experienced by the OSA patient.

Drugs for Treatment of Posttraumatic Stress Disorder (PTSD)

- The diagnostic criteria for PTSD include hyperarousal and disturbed sleep including sleep-onset insomnia, inability to stay asleep, excessive daytime sleepiness, and traumatic nightmares.
- Approximately 8% of the adult population suffers from PTSD caused by exposure to either emotional or physical trauma.

Medication for PTSD

Numerous medications have been prescribed to decrease the hyperarousal associated with PTSD, with varying degrees of improvement of sleep disturbances.

Treatments include:

1. Benzodiazepines
2. Selective serotonin reuptake inhibitors (fluoxetine, citalopram)
3. Atypical antidepressants (nefazadone and trazodone)
4. Beta blockers (propranolol), and
5. α-Adrenergic antagonists (prazosin)

Table: Effects of Commonly Used Drugs on Sleep and Waking Disorders

Drug Type	Examples	Pharmacologic Effect	Neurobiologic Mechanism	Clinical Effects
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Fluvoxamine Citalopram	Increase extracellular levels of 5-HT	5-HT inhibits REM sleep-producing cells	Decreased REM sleep
Tricyclic antidepressants	Amitriptyline Nortriptyline Clomipramine Desipramine	Increase extra extracellular levels of 5-HT and NE	5-HT and NE inhibit REM sleep-producing cells	Decreased REM sleep
Traditional, amphetamine-like stimulants	Amphetamine Dextroamphetamine Methylphenidate	Increase extracellular levels of DA and NE	Increased DAA and NE signaling	Increased wakefulness
Wake-promoting, non-traditional stimulants	Modafinil Armodafinil	Increase extracellular levels of DA	Increased DA signaling	Increased wakefulness
Benzodiazepines	Alprazolam Diazepam Clonazepam Lorazepam Nitrazepam	Enhance GABA signaling via $GABA_A$ receptors	GABA inhibits the arousal systems	Increased sleep
Non-benzodiazepine sedative hypnotics	Zaleplon Zopiclone Zolpidem	Enhance GABA signaling via $GABA_A$ receptors	GABA inhibits the arousal systems	Increased sleep
Classic antihistamines	Diphenhydramine Triprolidine	Block HA H_1receptors	Reduced HA signaling	Increased sleep
Typical antipsychotics	Haloperidol Chlorpromazine	Block DA receptors	Reduced DA signaling	Increased sleep

Thank You

Narcolepsy/Cataplexy

- Narcolepsy is defined by a tetrad of symptoms:
  -excessive daytime sleepiness,
  -cataplexy,
  -hypnagogic hallucinations, and
  -sleep paralysis.
- Narcolepsy affects all the three stages of sleep and wakefulness, with a prevalence of 1 in 2, 000 individuals and an onset in early adulthood.
- In this disorder there is a pronounced fragmentation of wakefulness, disrupted night-time sleep and intrusion of REM signs into wakefulness.
- Particularly striking and disabling are involuntary sleep attacks and episodes of (REM-like) muscle atonia induced by emotional arousal (cataplexy) with preservation of consciousness resulting from both abnormal control of REM regulatory mechanisms and alterations in emotional processing.
- Additional REM-like symptoms are hypnagogic hallucinations (hallucinations occurring around sleep onset or awakening) and sleep paralysis (inability to move following awakening from REM sleep).