**History of Sleep Medicine: Lessons Learned**

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**Speaker Disclosures**

• I have no relevant commercial relationships to disclose.
• Distinguished speaking faculty for Merck
• All conflicts of interest of any individuals who control the content of this CME activity, including faculty and members of the Continuing Medical Education Committee and the Continuing Medical Education Department, have been identified and resolved.

**Hippocrates 400 B.C.**

• “I know many persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason until they awaken.....”

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Common Sleep Disorders
- Insomnia
- Sleep Apnea (Obstructive and Central)
- Periodic Limb Movements
- Restless Leg Syndrome
- Narcolepsy, Hypersomnolence
- Parasomnias
- Circadian Rhythm Disorders

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Lessons Learned
- Multiple sleep disorders often occur concomitantly,
- each mimicking and exacerbating one another.
- Important to address each.

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Multiple Sleep Disorders Often Occur Concomitantly
- Sleep Apnea + Insomnia
- Sleep Apnea + Narcolepsy
- Sleep Apnea + RLS
- Sleep Apnea + REM Sleep Behavior Disorder
- “Overlap Syndrome” (RBD + parasomnia)
- OSA+RLS+Insomnia+Narcolepsy+RBD

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Aristotle 350 B.C.

• “...almost all other animals are clearly observed to partake in sleep, whether they are aquatic, aerial, or terrestrial,...”

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What do these mammals have in common... with birds?

Dolphin, Manatee, Fur Seal, Pilot Whales

Birds (crucial for migration)

Lesson Learned

Phylogeny: evolutionary development and history of a species

Unihemispheric sleep
(with either diminished REM or lack of REM)

- Dolphin, Manatee, Fur Seal, Pilot Whales
- Birds (crucial for migration)
William Shakespeare
Lady Macbeth Sleepwalking 1603

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1603 Shakespeare’s *Macbeth*

- “Gentlewoman. . . . have seen her rise from her bed, throw her nightgown upon her, unlock her closet, take forth paper, fold it, write upon’t, read, afterwards seal it, and again return to bed; *yet all this while in a most fast sleep*”.

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Lessons Learned
The boundaries between wake and sleep are not discrete

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Sexsomnia Pearls
arousal disorder subtype (SW parasomnia).

• Atypical Sexual Behavior / Aggression During Sleep.

• Can also be associated with sleep walking and sleep related eating disorders.

31 year old woman
The “good news/bad news” case
Timothy L. Grant, 31 year old woman

The “good news/bad news” case

Episodes of dream enactment characterized by:
- Reaching out and grabbing her boyfriend.
- Fondling herself with no recollection of doing so.
- Pulling his hair.
- Calling out the names of other men in her sleep.

Sir Thomas Willis
1672

• “Wherefore to some, when being in bed they betake themselves to sleep... Leaping and contractions of the tendons and so great ........that the diseased are no more able to sleep, than if they were in the place of the greatest torture!...”

Professor Karl-Axel Ekbom
1944

• “Restless Leg Syndrome”
RLS Lessons Learned

• Look for low Ferritin, < 50
• PLM’s on PSG, need not always be treated
• Treat the patient, not just the bed partner
• Look for treatable OSA
• Pharmacotherapy
  – Gabapentin (less augmentation and rebound)
  – Dopamine agonist
  – FeSO4
  – Opioids

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Sir Thomas Willis  Karl-Axel Ekbom

?????

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Charles Dickens

• 1836 Charles Dickens’ fat, sleepy servant boy named Joe, a comic caricature who survived in medical lore as a classic case of sleep apnea, "the Pickwickian Syndrome."

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Joe, the fat boy, “in a state of somnolency”, The Posthumous Papers of the Pickwick Club, Charles Dickens, 1836

Joe—damn that boy, he's gone to sleep again!

Eduard Grützner - Falstaff ...

- Falstaff, who appears in three Shakespeare plays, was obese, snored, and fell asleep at inappropriate times.
- AKA Sleep Apnea

Sleep Apnea Milestones

- 1816 William Wadd, “corpulence, obesity” associated with “sleepiness”.
- 1818 John Cheyne, “a case of apoplexy…breathing would cease.”
- 1934 W.R. Harrison describes Cheyne Stokes breathing and CHF.
- 1937 Annie Spitz describes 3 clear cases of OSA, CHF, CSR, and sleepiness.
- 1956 Sydney Burwell describes Pickwickian syndrome.

Kryger MH, Atlas of Clinical Sleep Medicine, Saunders 2010

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Sleep Apnea Milestones, cont.

• 1967 Weisbaden, Gastaut, Lugaresi describes Pickwick Syndrome (AKA sleep apnea syndrome).
• 1974 Kryger, Sleep apnea Rx’d with tracheostomy.
• 1975 Sleep Apnea term introduced by Christian Guilleminault’s team.
• 1976 Sleep Apnea Syndrome is published
• 1981 Colin Sullivan describes use of CPAP in Lancet

Kryger MH. Atlas of Clinical Sleep Medicine, Saunders 2010

How to keep the burning embers of romance alive

OSA Lessons Learned

1) Consequences of OSA related to both arousals and hypoxia.
2) Arousals provoke increased sympathetic tone.
3) OSA may exist without snoring.
4) 1/3 may not be obese, more subtle in women, increased post menopause.
5) With difficult to control HTN and atrial fibrillation, look for occult OSA.
Rationale for Treating Sleep Apnea (cont.)

Prevention of:

- Hypertension
- Cardiovascular Disease
- Cerebrovascular Disease
- Diabetes
- Depression
- Nocturia
- Sexual Dysfunction
- Morning Headaches
- GERD
- Cognitive Impairment
- Glaucoma
- Cancer

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65 yo international attorney
The “Could I Please Borrow a Cup of Sugar” case.

- 12 year history of OSA.
- Stopped using CPAP 5 years ago when unit broke.
- Nocturnal episode of “running naked in the middle of the night to the next door neighbor’s house and knocking on their door”
- No further episodes with just renewed CPAP alone.

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65 yo international attorney

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OSA Lessons Learned

- Multiple sleep disorders can occur concomitantly.

- Arousals related to underlying SDB can trigger parasomnias.

- **Usually best to first treat the SDB.**

William Hammond 1869 describes insomnia

- Civil War military physician/neurologist.
- Uses the phrase “persistent wakefulness”.
- Sleep state misperception, AKA paradoxical insomnia.

Starry Night

Vincent Van Gogh
Vincent Van Gogh
1853-1890

- “What is to be feared most is insomnia, and the doctor has not spoken about it to me, nor have I spoken of it to him either. But I am fighting it myself. I fight this insomnia by a very, very strong dose of camphor in my pillow and mattress, and if ever you can’t sleep, I recommend this to you.”

Letter to his brother

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Hypnotics

- 1831 Samuel Guthrie discovery of chloroform for anesthesia
- 1832 Justus von Liebig discovers choral hydrate ‘first used and abused sedative hypnotic’.
- 1864 Adolf von Baeyer discovers barbituric acid
- 1902 Fischer and Mering synthesize Veronal, the first widely used barbiturate.
- 1956 Leo Stigemback discovers benzodiazepine Librium
- 1986 Arbilla and Langer describe zolpidem, the first nonbenzodiazepine.
- 2014 Suvorexant/orexin antagonist introduced.

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Lessons Learned

Insomnia treatment considerations

- Look for concomitant sleep disorders, – i.e. OSA, RLS, etc.
- Look for other complicating etiologies, – i.e. medications, medical illnesses, medications.

Best Rx:
- Medications (if any) + CBT (Cognitive Behavioral Therapy).

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**Milestones in Sleep Architecture**

Ushering in the “modern age” of sleep medicine

- 1929 Hans Berger first to record EEG.
- 1935 Alfred Lomis describes NREM.
- 1953 Nathaniel Kleitman and Eugene Aserinsky used eye movements to document REM associated with dream recall.
- 1957 William Dement describes REM sleep in cat.

**Typical Progression of Sleep Over the Course of the Night**

![Diagram of sleep stages](image)
EEG States of Being

Lessons Learned
Sleep Architecture

First part of the night
- More slow wave sleep
- More NREM parasomnias (i.e. confusional arousals, sleep terrors, sleep walking) w/o recall
- More parasympathetic tone
- More hemodynamically stable

Lessons Learned
Sleep Architecture

Latter part of the night
- More REM sleep (sleep apnea is worse)
- More REM parasomnias (i.e. REM sleep behavior ds, nightmares, sleep paralysis) w/ recall
- More sympathetic tone
- More hemodynamically unstable
Sleep and His Half-brother Death
by John William Waterhouse 1874

Sleep was previously perceived as a passive process.

• “Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension”.

Robert MacNish, The Philosophy of Sleep, 1834

Literature, Art, and Sleep through the ages

• Throughout literature, a close relationship between sleep and death has been perceived.
Lessons Learned

The brain is quite active in sleep

- Blood flow increases up to 80% during REM Sleep
- Overall, up 25% in sleep as c/w wakefulness
- Increased O2 consumption in REM.
- CSF cleansing occurs during sleep.

Circadian Rhythm Milestones

- 1729 Jean-Jacques d'Ortrous De Mairan
  - Mimosa plant in box able to "tell time" even w/o sunlight.
- 1972 Robert Moore SCN importance in circadian physiology.
- 1976 Fred Turek and Michael Menaker melatonin can alter sparrow circadian clock.

Miguel De Cervantes

1547-1616 1605
Miguel de Cervantes Saavedra,
The Ingenious Hidalgo Don Quixote of La Mancha, 1605

• *And in his right hand he held his unsheathed sword, with which he was slashing about on all sides, uttering exclamations as if he were actually fighting some giant;* and the best of it was his eyes were not open, *for he was fast asleep, and dreaming that he was doing battle with the giant.*  

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REM Sleep Behavior Disorder
1986

Carlos Schenck  
Mark Mahowald

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Review of Lessons Learned

• RBD can be seen as a pseudo phenomenon as related to medications (SSRI’s, TCAD’s, *not* Bupropion), secondary to arousals as related to underlying OSA.

• RBD may be a precursor to synucleinopathies/neurodegenerative disease.

• Clonazepam and/or melatonin effective Rx.

• REM w/o atonia may persists even after effective Rx.

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Herman Melville
1819-1891  
Moby-Dick

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Melville’s Moby Dick 1851
Ishmael’s sleep paralysis

- “... and slowly waking from it-
  half steeped in dreams- I opened my eyes ...

- For what seemed ages piled on ages, I lay there, frozen ...
  yet ever thinking that if I could but stir it one single inch, the horrid spell would be broken”.

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Hypocretin / Orexin
Narcolepsy

- 1934 Luman Daniels links sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis.
- 1960 Gerry Vogel SOREM's
- 1999 Emmanuel Mignot reports defect in canine narcolepsy.
- 2000 Jerome Siegel
  Hypocretin-1/Orexin A undetectable in the CSF of most narcoleptics w cataplexy.

Emmanuel Mignot

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Lessons Learned
Narcolepsy

- Cataplexy
  - In children, may not be triggered by emotion, more like "tics".
  - Deep tendon reflexes absent during cataplexy.

- 30% of general population has MLTS on MSLT < 8 min

Sleep onset REM episode on preceding PSG
- now counted for narcolepsy scoring (REM latency < 20 min
- (i.e. add up PSG SOREM + MSLT SOREM'S)

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Lessons Learned
Narcolepsy

- Narcolepsy often occurs concomitantly with other sleep disorders.

- Modafinil/Armodafinil may affect oral contraceptives and anticoagulants.
  Stevens Johnson’s syndrome reported.

- Xyrem/sodium oxybate is a potential respiratory suppressant. May need to recheck OSA for desats.

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Sleep Medicine Milestones

- 1961 Sleep Research Society, becomes APSS.
- 1969 Rechtschaffen and Kales scoring manual
- 1970 William Dement founded Stanford Sleep Disorders Center
- 1976 American Sleep Disorders Association becomes AASM
- 1982 NIH consensus symposium on insomnia
- 1990 Michael Thorpy spearheads ICSD
- 1990 National Sleep Foundation
- 2008 CDC establishes sleep as area of interest

Kryger MH, Atlas of Clinical Sleep Medicine, Saunders 2010
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Sleep: An Active Process

• “More has been learned about sleep in the past 60 years than in the preceding 6,000”

• “In this short period of time, researchers have discovered that sleep is a dynamic behavior. Not simply the absence of waking, sleep is a special activity of the brain, controlled by elaborate and precise mechanisms”

J. Allan Hobson. Sleep. 1989

55 yo retired police officer
The “I’ll Be There With Bells On” case

• Long standing SI and SM insomnia
• Snoring with apneas
• 15 month history of bizarre nocturnal activity w and wo dream content

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55 yo retired police officer

• Episodes so severe her husband has resorted to “tying bells to a belt around her waist, fastened with a rope to a large table in the dining room”.

Timothy L. Grant, MD, FAASM
55 yo retired police officer

Bizarre nocturnal behavior:

- “Taking showers with clothes on”
- “Taking clothes off”
- “Drinking citrus cleaning fluid”
- “Moving silverware into refrigerator”
- “Sneaking while asleep”
- “Making Christmas decorations”
- “Sleep eating”
- “Sleep cooking”
- “Swears and becomes agitated, if awakened.”
- “Getting up with a knife or scissors during the night”

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Diagnosed with:

- Sleep walking
- Confusional arousals
- Sleep related eating disorder
- Sexsomnia (“taking off clothes”)
- REM Sleep Behavior Disorder
- Poor sleep hygiene
- Insomnia
- Obstructive sleep apnea

Rx: responds with CPAP, benzo, melatonin, and CBT

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~Miguel de Cervantes, Don Quixote, 1605

- "blessings light on him that first invented sleep!
- "It sets the king and the shepherd, the fool and the wise man, even"
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