SLEEP: A Practical Discussion

Teodoro V. Santiago Jr., UPCM 1967

Rise in Drug Use for Sleep, Anxiety Worries Doctors

People turn to prescription medications as virus affects mental health

Health concerns, social isolation and the stress of job losses are taking a toll on people's well-being. More than a third of Americans say the pandemic is having a "serious impact" on their mental health, according to a survey released March 25 by the American Psychiatric Association. Among parents with chil-

The most popular anti-anxiety medications are benzodiazepines that include Valium, Xanax, Ativan and Klonopin. These drugs enhance the activity of the central nervous system's main inhibitory neurotransmitter, GABA (gamma-aminobutyric acid). GABA's primary function is to reduce the ac-

the short-term treatment of acute anxiety. Dr. Potash advises patients to limit their use to weeks, not months. The problem, he says, is that people can quickly develop a tolerance to their effects—sometimes in as little as two weeks—which can lead patients to increase the dose. This is especially the case with the shorter-acting drugs

What is an experience that we have all spent a third of our lives doing? The answer of course is sleeping, as we are normally in bed 7-8 hours of each day. We know that a good night's sleep is essential to maintaining our good health. Unfortunately, current times have challenged that. As evidence, the *Wall Street Journal* on 5/26/20 carried an article on the rise of sleep medicine prescriptions during the current COVID-19 lockdown. While expressing the concern that most of these medications were habit forming, it conceded that chronic sleeplessness was equally problematic. As physicians, we have sacrificed many nights for the good of our patients. Could these have long-term consequences? I don't know for sure but in my last few years at Rutgers, I took care of two surgical colleagues who were quite busy during their heyday and who both suffered from significant insomnia after they retired. I couldn't help but think that all of those sleepless nights messed up their circadian rhythm. I imagined that the obstetricians, anesthesiologists and surgeons among us might be at the forefront of possibly having sleep related problems. Furthermore, advancing age by itself also presents its own set of issues. I thought, at the risk of being presumptuous, that some of us might find a discussion on "Sleep" to be welcome. So before my aging neurons permanently wither, here is a last hurrah from me on this subject. Former medical students, residents and fellows who rotated in the Rutgers Sleep Clinic would find what is written here, quite familiar to them, that is if what I said registered in their minds.

How does a pulmonary physician get to deal with sleep disorders, one might ask. The answer lies in the condition called sleep apnea. Anything related to breathing is a pulmonary specialist's concern. The fact that the apnea only occurs during sleep and not while awake meant that we had to understand sleep. And once we learned sleep medicine, it did not take long for pulmonary specialists to deal with other sleep disorders as well. I thought that I would divide this "treatise" into two parts: Part I will deal with *Normal Sleep*, and Part II will deal with *Sleep in the Elderly.*

Part I. Normal Sleep

The sleep-wakefulness cycle is controlled by the *suprachiasmatic nucleus* (SCN) in the hypothalamus. As its name implies, it is located just superior to the optic chiasma. How do we know that the SCN is the circadian pacemaker? If ablated in animals, they lose all patterns of a sleep-wake cycle. If destroyed by disease in humans (strokes or degenerative conditions like Alzheimer's Disease), the individual would be alternately asleep or awake round the clock. We see these most often in residents of nursing homes. The SCN is responsive to exogenous (light) and

endogenous (melatonin from the pineal gland) influences. The SCN cycle is close to but not identical to our planet's spinning on its axis, as it measures 24 hours and 11 minutes (1). This carries several implications. If we allow the SCN to *free run*, it will phase delay by close to 11 minutes daily so that if we remove all light and time cues from our environment e.g. as in experiments where volunteers stayed in a cave devoid of time cues and continuously lit for their total duration of stay, their bedtime hour at the end of a month, unbeknownst to them, occurred at 3:00 AM. An analogous situation occurs in persons perpetually in the dark, i.e. blind people, who have to rely on alarm clocks or companions, to *entrain* themselves into the day-night cycle. If a blind person complains of sleep difficulties, the first area of investigation is circadian rhythm problems.

The other common situations for such problems are new college graduates who may suffer from a phase-delayed pacemaker. This is because they regularly stayed up late while in college, *presumably* studying during weeknights and *definitely* partying during weekends. They can compensate for their phase-delayed pacemaker by sleeping late in the mornings and taking later classes. However, once gainfully employed with a 9:00 am to 5:00 pm job, they find it difficult to initiate sleep before 12:00 midnight but now no longer have the luxury of waking up late. They suffer from insufficient sleep due to phase-delayed insomnia and taking sleeping pills for a few nights will not correct this. Therapy necessitates phase advancing the SCN, which can be accomplished by exposure to bright lights (5000 lux) upon arousal each morning, for at least 30 minutes. Now you know why I wondered if a lifetime of irregular sleep-wake schedules as in my surgical colleagues could have permanently affected their circadian pacemaker.

Finally, for those of us who visit the Philippines where there is a 12 hour time difference with the USA, the most adjustment that the SCN can do with the influence of daytime light is about an hour a day, so that if you are only staying for a week, you should just accept having a messed up day and night for the duration of your stay. And if you are wondering why the timing of your other habits are messed up as well, e.g. daily bowel movements, these are under the influence of the circadian pacemaker too.

Some have opined that sleep is simply the withdrawal of consciousness. However, it is obviously a different state than coma or general anesthesia where most brain activity is depressed. During sleep, some neurons especially in the pons and amygdala are more active than during wakefulness. Sleep duration varies like a bell-shaped curve among individuals, with majority of adults needing 7-8 hours. Some do well with 3-4 hours while others need more than 10 hours of sleep. The indicator that one gets an adequate amount of sleep is *absence of daytime sleepiness*.

Normal sleep is divided into non-rapid eye movement sleep (NREM) and rapid eye movement (REM) sleep. These are recognized electrometrically with leads placed in the scalp (EEG), chin (EMG) and laterally near the eyes (EOG). NREM sleep has 3 stages reflecting depth of sleep, called N1 (light sleep), N2 and N3 (deep sleep). Most of our sleep is spent in stage N2. REM sleep has an EEG resembling the awake state but is distinguished by paralysis of the skeletal muscles and bursts of rapid eye movements. Now you know why we monitor chin muscle tone (EMG)

and eye movements (EOG) in the laboratory. We do our dreaming during REM sleep and nature, by paralyzing us, helps prevent us from *acting out our dreams*. Obviously at least one important skeletal muscle had to be spared by this paralysis or man (and other mammals) would not have evolved as a species, and that is the diaphragm (cardiac muscles are smooth muscles, so the heart was never in jeopardy). It is postulated that this spinal motoneuron inhibition by REM sleep is spindle density influenced, and respiratory muscles have a lot less muscle spindles than postural muscles (2). The other skeletal muscles that are spared paralysis are innervated by cranial nerves (the eye muscles) and if nothing else, these aid sleep physicians in recognizing REM sleep electrometrically.

The normal sleep sequence is to first enter NREM sleep prior to going into REM sleep. In a normal night, REM sleep usually occurs ~90 minutes after NREM sleep onset. This is shortened in a sleep-deprived individual. This sleep sequence *ensure*s that we are safely in bed prior to the onset of REM-induced paralysis, and dreaming. To go from wakefulness directly into REM sleep can obviously be problematic. Does it ever occur? It most certainly does in a condition called Narcolepsy that has as primary symptoms excessive daytime sleepiness, *hypnagogic* hallucinations and cataplexy. The sleep attacks in Narcolepsy are REM sleep events and its diagnosis in the Sleep Laboratory entails demonstrating sleep-onset REM periods after an uneventful night's sleep. Narcolepsy's other symptoms are easy to understand if we recall the other physiologic accompaniments of REM sleep. The term *hypnagogic* means "at sleep onset." Hypnagogic hallucinations are the dreams of REM sleep except that they occur in an individual who may still be partially awake. Thus, they present like hallucinations. Similarly, cataplexy is the skeletal muscle paralysis of REM sleep and when occurring in an upright individual, may cause them to lose muscle tone and fall to the ground. I had to actively prevent CPR from being performed in one of my patients who experienced a cataplectic attack while on her way to her outpatient room. Recent research indicates that Narcolepsy is caused in part by a deficiency in hypocretin (also called orexin) (3), giving hope to these patients that they could soon be treated specifically for a deficiency and not with stimulants and REM suppressants.

One final interesting thought. There seems to be a correlation between REM sleep and endogenous depression. Patients with endogenous depression enter REM sleep from NREM sleep quicker (e.g. 40 minutes) than non-depressed patients (~ 90 minutes). Most anti-depressant drugs e.g. tricyclics, Prozac, Paxil, MAO inhibitors, significantly decrease REM sleep. That this side effect may be part of their therapeutic action is illustrated by an experiment where depressed subjects were monitored in the sleep laboratory for several nights undergoing *selective but total REM sleep deprivation*, i.e. they were awakened each time they entered REM sleep. After about a week, their depression got better! One wishes that the same type of experiment could be done to patients suffering from post-traumatic stress syndrome, where recurrent frightful dreams are thought to be part of the process perpetuating the PTSD (*Classmate Dr. Josie Olympia, are you reading this?).*
In a given night, a normal adult spends about 15 percent of time in bed awake, 5 percent in N1, 45 percent in N2, 15 percent in N3 and 20 percent in REM sleep. Infants spend 50 percent of their sleep time in REM sleep while adolescents have a greater proportion of stage N3 sleep. Acute sleep deprivation causes an increase in N3 sleep the following evening while chronic sleep deprivation causes a REM sleep rebound. Unfortunately, sleep also has an amnesic effect so that anything within 5 minutes of sleep onset, one usually forgets. Think back to all of those Gross Anatomy minutiae that you tried to memorize each night that you couldn't recall during the exams. Your hippocampus wouldn't have failed you if you stayed up a little longer after putting Morris'

textbook down. So while understanding sleep might make us marvel at how well the human species has been put together, I hope that you did not read this presentation in bed and fallen asleep shortly thereafter! You might have difficulty understanding our forthcoming sequel on Sleep in the Elderly.

References:

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About the Author: *Dr. Santiago is Professor Emeritus of Medicine and former Chief of Pulmonary and Critical Care Medicine at Rutgers-Robert Wood Johnson Medical School in New Brunswick, New Jersey. He has published several papers on the ventilatory and cerebrovascular responses during sleep. This discussion on sleep was originally published serially for his classmates, in the UPCM Class 1967 newsletter "Tidbits, Nos 22-24", and has been slightly revised for the UPMASA audience.*