Avoid Lack of Sleep: Research suggests that the restorative function of sleep may be due to increased neurogenesis and the enhanced removal of neurotoxic waste products, such as metal laden AB protein from the brain. This occurs by three mechanisms:

- Increased convective exchange of cerebrospinal fluid with the interstitial fluid
- Increased BDNF production that stimulates neurogenesis
- Increased neprilysin activity that degrades AB protein in the brain

REM sleep increases P-CREB production that in turn increases somatostatin production. Somatostatin increases neprilysin activity and BNDF production, both of which may be responsible for the observed memory consolidation during REM sleep.

AD is associated with dysregulation of the orexinergic system causing a lack of sleep resulting in higher levels of AB peptides in the brain and less memory consolidation. Exposure to normal solar lighting is recommended to stimulate melanopsin production during the day. This helps to maintain circadian rhythms and a good night's sleep. Daytime lighting with a strong blue spectral component results in AD patients having better quality sleep, but can't be recommended routinely due to blue light induced retinal damage.

Avoid Lack of Sleep

Enhance AB protein and aluminum clearance: Sleep does more than relieve the feeling of sleepiness. It has been found that both natural sleep and anesthesia induced sleep are associated with a 60% increase in the interstitial space in the brain. The interstitial space is the space between neurons. It is filled with interstitial fluid. This increased space results in a significant increase in convective exchange of cerebrospinal fluid with the interstitial fluid. This convective flux has been shown to increase the rate of beta-amyloid (AB) protein clearance during sleep as compared to the rate of AB clearance while awake[517].

AB protein as oligomers and plaque in the brain is complexed with metal ions including aluminum. Purging these metal laden AB protein complexes from the brain is an excellent way to lower levels of accumulated aluminum in the brain[137]. Factors that slow the rate of clearance of beta-amyloid (AB) from the brain account for its' build- up over time. Enhancing the rate of clearance will postpone the onset of AD and possibly prevent AD.

Consolidate Memories: Sleep has also been implicated in the off-line reprocessing of recently acquired memory. This process is called memory consolidation. The neurochemical mechanism for memory consolidation in mice has been found to involve a molecular cascade ending in the production of a molecule named P-CREB, that increases the transcription of genes responsible for brain derived neurotrophic factor (BDNF) production [179,180,518,519]. Rapid eye movement (REM) sleep has been found to speed up this molecular cascade in the mouse brain increasing P-CREB production[520] and improving long term memory, brain plasticity, and learning[181,182].

Lower AB Peptide and Plaque Levels: By increasing P-CREB production, REM sleep also increases the transcription of genes responsible for somatostatin production[179,180,518,519]. There is an inverse relationship between P-CREB levels and AB peptide in mouse brain. This is probably due to P-CREB increasing somatostatin levels that thereby increasing neprilysin activity that in turn lowers AB peptide and plaque levels. Therefore, REM sleep can postpone the onset of AD by increasing both P-CREB and somatostatin levels in hippocampal neurons[103].

The beneficial effects of REM sleep can be negated by aluminum accumulating in the brain. It has been found that aluminum chloride in the diet of neonatal and postnatal rats inhibits P-CREB production by modifying the calcium/calmodulin complex[520]. This in turn lowers both hippocampal BDNF and somatostatin production resulting in long term memory impairment, spatial learning impairment, and AB peptide accumulation[101,102].

Sleep Better with Daytime Solar or Blue Lighting: Orexin (a.k.a. hypocretin) is a neurotransmitter produced in the hypothalamus by 10,000 to 20,000 orexin neurons that extend over the entire brain and spinal cord. Orexin promotes wakefulness and regulates arousal, wakefulness, and appetite. Circadian rhythms are controlled by high levels of orexin during the

day and low levels at night. In AD, dysregulation of the orexinergic system results in too much orexin in the cerebrospinal fluid[521]. In mild and moderate AD this dysregulation causes more awakenings and less REM sleep during the night resulting in greater than normal daytime sleepiness. This condition is correlated with cognitive impairment in AD[146] possibly due to more AB protein accumulation and less AB clearance at night[521].

Melanopsin, like orexin, promotes wakefulness and is involved in neuronal communication with the brain's clock. The brain's clock controls circadian rhythms and is called the suprachiasmatic nucleus. Melanopsin, one of the three light-sensitive retinal opsin proteins in the human eye, is found in neurons in the retina called intrinsically photosensitive retinal ganglion cells (ipRGCs). Blue light photostimulates melanopsin in ipRGCs linked neuronally to the brain's clock. The solar spectrum reaching the earth has a strong blue component. Therefore, exposure to solar lighting during daytime hours is recommended to photostimulate melanopsin maintaining daytime wakefulness. This daytime wakefulness helps to maintain circadian rhythms and a good night's sleep resulting in less AB protein accumulation and more AB clearance.

AB oligomers complexed with aluminum compared with other metals are less prone to aggregate and are sufficiently small to scatter blue light[522]. The percentage of blue light being scattered to total blue light entering the eye increases as AB oligomer concentration rises in the retina[523]. Also ipRGC degeneration has been recently observed in AD patients[524]. Therefore, some patients with AD need to see more blue light to compensate for both scattering and degeneration in order to maintain circadian rhythm. Thus it is not surprising that using lights with enhanced output in the blue spectral region during the day allows some elderly patients with AD to sleep better at night[525]. Moderation is called for as long-term blue light exposure can cause retinal damage. Mixing exposure to both solar and blue lighting during the day is a good compromise.

Sleep and Stroke Risk: Moderation may also be called for in the case of sleep. Recently 9,692 people's average nightly duration of sleep over a 9.5 year period was evaluated for correlation with risk of stroke. The participants were 41 to 82 years of age. During this time period there were 346 participants who had a stroke. It was found that people who routinely slept longer than 8 hours per night were 46% more likely to get a stroke as compared with those who routinely

slept less than 8 hours per night[526]. The correlation was strongest for people 63 and over having an increased risk of hemorrhagic stroke by persistently sleeping for more than 8 hours.

A meta-analysis was performed on six studies including 559,252 people in 7 countries. Over the 7 to 34 year periods of these studies the participants had 11,695 stroke events. This meta-analysis came to the same conclusion that people who sleep longer than 8 hours are 45% more likely to have a stroke[526].

Sleep may be an indicator of increased stroke risk and not be a cause of stroke. For instance, the duration of sleep has also been correlated with both carotid artery atherosclerosis, as measured by artery wall thickness, and atrial fibrillation[527,528]. This makes sense as the heart must pump harder with atherosclerosis and a-Fib, which requires more sleep for the heart's daily recovery. As discussed in Chapter 2, atherosclerosis and a-Fib are increased risk factors for stroke.