

# Pharmacological and Biological Circadian Therapy in Alzheimer's Disease

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## INTRODUCTION

Alzheimer's disease markedly affects the quality and quantity of both rapid eye movement (REM) and slow wave sleep (SWS).<sup>1</sup> The disease is a multi-factorial condition that also affects cognitive, behavioral and neurophysiological function. Accordingly, effective pharmacological treatment of Alzheimer's sleep related disorders focuses on achieving a balance in which the therapeutic benefits of improved sleep quality outweigh the adverse side effects.<sup>1</sup> Currently, no single pharmacological target has been implicated in the pathology in Alzheimer's type dementia (ATD) sleep disorders.<sup>2</sup> As the etiology of Alzheimer's disease (AD) still eludes science, pharmacologists are choosing to target the sleep-wake circadian cycle directly.<sup>3</sup>

Alzheimer's disease is a neurodegenerative process affecting pyramidal neurons with concurrent formation of "plaques and tangles" resulting from abnormal  $\beta$ -amyloid protein production. Particularly affected are the cholinergic neurons found in the basal nucleus of Meynert and their extensive projections.<sup>4</sup> The characteristic "forgetfulness" (anterograde amnesia) is derived from a decrease in hippocampal function.<sup>5</sup> Because the disease develops differently from person to person, researchers believe that there may be more than one pathologic process that leads to the same outcome.<sup>6</sup>

There are two main areas of the brain involved in sleep and both undergo degeneration in AD (Figure 1):

1- The Brainstem: Serotonergic and noradrenergic systems are active during the wakeful state and their activity declines markedly during REM sleep. Cholinergic neurons are active during REM sleep.

2- The Suprachiasmatic nucleus: receives direct input from the optic nerve and pineal gland.<sup>7</sup>

Acetylcholine (ACh) release from the basal ganglia oscillates daily and plays an essential regulatory role in the sleep-wake cycle. Furthermore, it acts as the main neurotransmitter in attention and learning. Because these neurons degenerate in AD, normal ACh levels regulating the sleep-wake cycle are theoretically vulnerable to cholinomimetic drugs. ACh release measured with the use of neostigmine changes significantly across the sleep cycle in cortex and hippocampus, substantia innominata, thalamus and medullary

reticular formation.<sup>8</sup> Since ACh evidently plays an integral role in many brain processes, isolation of the cholinergic system with regards to sleep is a challenging prospect. Treatment of AD requires a pharmacological agent that targets only the degenerative cholinergic neurons; likewise, AD related sleep medications should only target the neurons pertinent to the sleep-wake cycle.

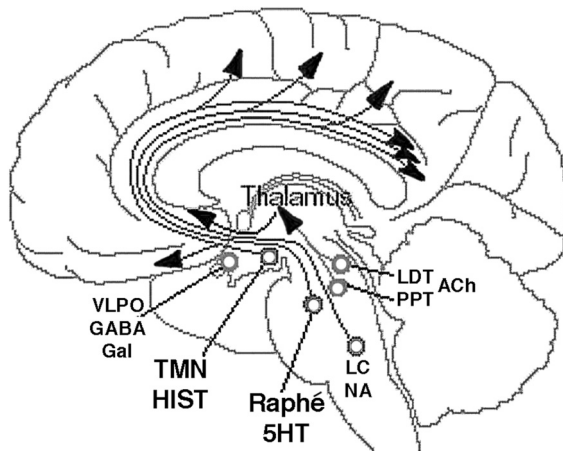


Figure 1. The ascending arousal system sends projections from the brainstem and posterior hypothalamus throughout the forebrain. Neurons of the laterodorsal tegmental nuclei and pedunculopontine tegmental nuclei (LDT and PDT) send cholinergic fibers (ACh) to many forebrain targets, including the thalamus, which then regulate cortical activity. Aminergic nuclei [remaining circles] diffusely project throughout most of the forebrain, regulating the activity of cortical and hypothalamic targets directly. Neurons of the tuberomammillary nucleus (TMN) contain histamine (HIST), neurons of the raphe nuclei contain 5-HT and neurons of the locus coeruleus (LC) contain noradrenaline (NA). Sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO) contain GABA and galanin (Gal).

Histamine blood levels have been shown to oscillate in AD patients. Levels correlate positively with delta activity (a measure of slow wave sleep) in central, temporal and parietal areas in the right hemisphere. Increasing histamine levels in AD progression seem to be of peripheral origin but active within the CNS.<sup>9</sup> It appears that a very subtle dysfunction in brain histamine might contribute as a secondary event to the aetiopathogenesis of AD related sleep disorders.<sup>1</sup> Therefore, pharmacological targeting of central histaminergic receptors may prove useful in the treatment of AD related sleep disorders.

In an attempt to compensate for lost SWS and REM overnight sleep, individuals with AD

frequently nap during the day. However, because AD naps rarely reach REM stage, they poorly atone for lost hours.<sup>1</sup> In fact, an increase in nap frequency and duration is often used to diagnose the progression of mild/moderate AD to severe AD. Prominent hypersomnolence or severe insomnia is typically only found in later stages of the disease.<sup>2</sup> A recent study suggests that daytime napping might be a risk factor for mortality, perhaps because it is a marker for significant nocturnal sleep disturbance or because blood pressure declines as it does during sleep at night. This increases the risk of cardiovascular or cerebrovascular accidents.<sup>5</sup> Severe AD patients may spend as much as 40% of their time awake in bed often in a confused state, thus increasing the need for daytime sleep.<sup>10</sup>

AD sleep disorders may also be manifestations of psychological issues in a patient who suffers from the disease. For example, AD in its progressive forms may cause agitation, depression, anxiety, anger, hallucinations and delusions.<sup>10</sup> Because depression and mania cause insomnia in non-demented patients, AD sleep disorders may be easily treatable by targeting these behavioral mechanisms. Currently, anti-depressants are widely prescribed in treatment of AD sleep related disorders, a remedy which leads many physicians to believe erroneously that behavioral pathologies are the only causes of AD related sleep disorders.

Current treatments for improving sleep in AD fall into three broad categories: pharmacological, cognitive-behavioral or psycho-educational strategies and biological/circadian therapies.<sup>10</sup> This paper will concentrate on pharmacological and biological/circadian therapies. Behavioral approaches will be dealt with from a pharmacological viewpoint, but this should not diminish the importance of cognitive therapy. Biological/circadian therapies are currently the treatment of choice as pharmacological therapies that specifically target AD sleep disorders are still in their infancy. Sleep disturbance is sometimes a side effect of the cholinomimetic drugs as cholinergic neurons in the brainstem are particularly active in the wakeful state. Evidence of sleep disturbance as a reaction to these drugs is well documented in the young but results are less conclusive in the elderly.<sup>3</sup> Apart from anti-depressants, benzodiazepines and other hypnotics are widely prescribed as pharmacological intervention. These have been clinically shown to be habit forming and are less than ideal. Thus, the treatment benefits of sedating medications in persons with a progressive dementing illness may not outweigh the potential risks of their continued use for sleep

and night-time agitation.

Treatment of AD sleep related disorders is not just necessary for the improvement of patient lifestyle. It has been demonstrated that there is a significant correlation between quality of diurnal sleep and better cognitive performance.<sup>3</sup> Effective treatment may theoretically delay or even reverse the progression of dementia. As a greater understanding of the pathophysiological processes in AD are elucidated, pharmacological intervention is emerging as a hopeful treatment strategy in treating a critical component of AD progression.

### DRUGS AFFECTING SLEEP/WAKE CYCLE IN ALZHEIMER'S DISEASE

Pharmacological interventions involve tricyclic anti-depressants, benzodiazepines, non-benzodiazepines, classical antipsychotics, atypical antipsychotics and antihistamines (table 1).

Table 1. Drugs affecting the sleep/wake cycle in Alzheimer's Disease.<sup>3</sup>

Drug	Recommended Dose (mg/day)	Potential Side Effects
<b>Tricyclic Antidepressants</b>		
Nortriptyline	10-75	Anticholinergic Effects Orthostatic Hypotension
Trazodone	25-75	
<b>Benzodiazepines</b>		
Lorazepam	0.5-2	Lethargy, Confusion, ataxia Dependence
Oxazepam	10-30	
Triazolam	0.0625-0.125	
<b>Non-Benzodiazepines</b>		
Zolpidem	5-10	
Zaleplon	5-10	
<b>Classical Antipsychotics</b>		
Chlorpromazine	10-100	Sedation, anticholinergic Extrapyramidal symptoms Sedation, anticholinergic
Haloperidol	0.5-1	
Thioridazine	10-100	
<b>Atypical Antipsychotics</b>		
Clozapine	25-100	Sedation, agranulocytosis Orthostatic hypotension
Risperidone	1-6	

These classes of medications target a wide spectrum of sleep disorders and therefore fail to target AD night-time agitation *per se*. Furthermore, clinical case studies of these drugs that pertain specifically to AD are sparse.

### **Benzodiazepines**

Seven diagnosed AD males were placed on the standard geriatric dose (0.125mg) of the short acting benzodiazepine, triazolam. Exclusion criteria for the experiment were previous sleep disorders and/or use of a drug with prominent cholinergic or anti-cholinergic effects. Because the leading AD medications are cholinomimetic drugs, the study did not monitor drug-drug interactions between the two classes of drugs in AD patients. The patients were monitored for alteration in sleep activity and memory function. Group data failed to reveal any significant effect of triazolam on total sleep time at night, latency to sleep onset, number of nocturnal awakenings,

total sleep time during the day or mean level of activity during night or day in the six subjects with complete actigraph data.<sup>11</sup> Furthermore, typical benzodiazepine side effects such as psychomotor and memory impairment, rebound insomnia and dependence were reported. This study was significant in that it was the first study to monitor the effects of a sleep hypnotic in AD that had been proven effective in normal geriatric patients. The researchers concluded that the disrupted sleep of typical AD patients might not be comparable to conditions that cause insomnia and/or chronic sleep deprivation in normal patients. Benzodiazepines also have minimal effects on sundowning i.e. a deterioration of AD symptoms after sunset.<sup>3</sup> Thus, the side effects of prescribed benzodiazepine sleep agents may in fact prove to be detrimental to AD patients rather than therapeutic.

### Cholinomimetic Drugs

Acetylcholine release within the basal forebrain changes significantly as a function of sleep and wakefulness.<sup>9</sup> Anticholinesterases are the drugs of choice in slowing the degenerative symptoms in AD. Their effects on sleep are variable but more research is needed to examine the effects of these drugs on sleep in AD patients.<sup>10</sup> No extensive research has been conducted on the anticholinesterase Tacrine in relation to sleep and AD. Rivastigmine, an acetylcholinesterase inhibitor, has been shown to reduce REM sleep in younger adults but in older adults had no negative affect on REM duration, sleep efficiency, sleep latency, number of awakenings or time awake.<sup>3</sup> Another anticholinesterase inhibitor, Donepezil, was shown to improve cognitive performance in AD patients but over 40% of the patients had insomnia as a side effect.<sup>12</sup>

As was seen in the triazolam study, cholinomimetic drugs are often excluded due to possible drug-drug interactions.<sup>3</sup> This, coupled with the sparse knowledge underlying AD sleep-related disorders, means that the effects of anticholinesterases and pharmacological hypnotic agents are still largely unknown. The fact that many AD pathological symptoms overlap those associated with sleep deprivation further complicates treatment as differentiation between the two is largely speculative. Future pharmacological agents that symptomatically target AD sleep related disorders must harmonise with those pharmacological agents that target the disease *per se*.

### Histaminergic Drugs

Histamine is involved in the control of vigilance, sleep and wakefulness, as well as in the

modulation of circadian rhythmicity. This H<sub>1</sub>-mediated arousal response has also been demonstrated by EEG studies. Blood histamine levels increase as AD progresses but the extent to which this affects the CNS is a topic of hot debate. Laboratory experiments by Novoa *et al* indicate that the histaminergic system seems to be involved in pathological states relating to the neurodegeneration as seen in AD. Histamine levels increase as AD progresses; concurrently, the severity of sleep disorders in AD also increases as the disease progresses (Figure 2).<sup>9</sup>

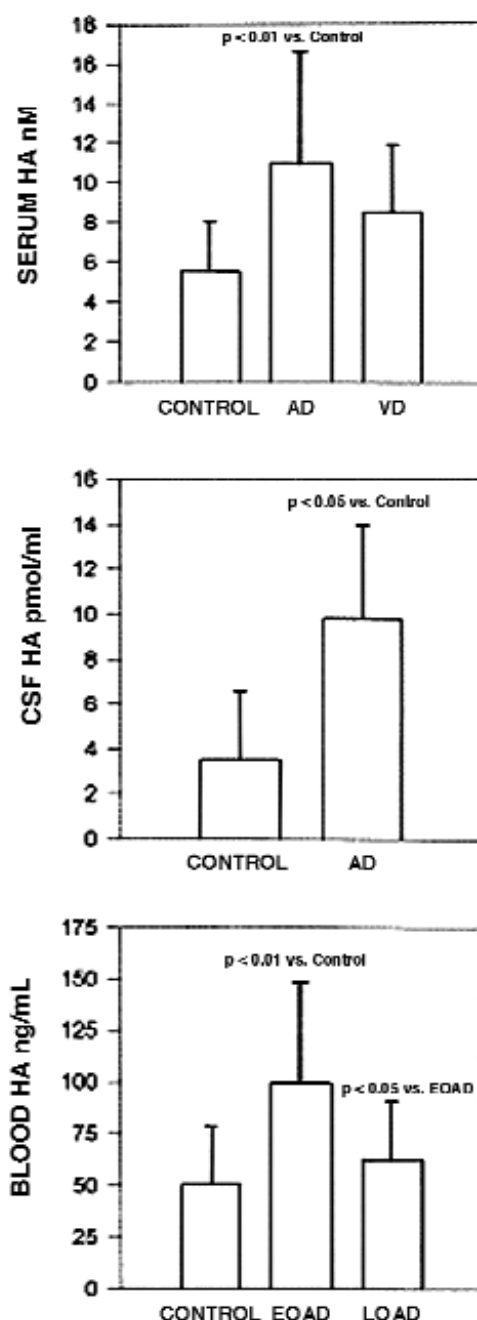


Figure 2. Histamine (HA) levels in serum of Alzheimer's disease (AD) and vascular dementia (VD) patients with respect to control subjects; histamine levels (HA) in cerebrospinal fluid (CSF) of Alzheimer's disease (AD) compared to control subjects; whole blood histamine levels in early-onset (EOAD) and late-onset (LOAD) AD patients with respect to control subjects. Results are expressed as mean  $\pm$  SD.

The fact that first generation H<sub>1</sub> receptor anti-histamines induce drowsiness further supports the argument that histamine plays an integral role in arousal. Considering that the histaminergic system acts as a regulatory center for brain activity, its malfunctioning can alter important pathways implicated in motivated behaviours, behavioural disorders, control of waking state, neuroendocrine and cardiovascular regulation.<sup>9</sup> When the role of histamine in arousal is coupled with our relatively good understanding of histaminergic receptors, a key pharmacological target arises that could help provide effective AD sleep related treatment.

### Melatonin

Melatonin is a peptide hormone produced by the pineal gland that influences sleep-wake cycles and other circadian rhythms. It has a sedative effect and is currently used to treat sleep disorders and jet lag.<sup>13</sup> The most extensive research regarding AD sleep related disorders have focused on the circadian affect of exogenous melatonin in the neurodegenerative model. Across all studies researchers concluded that melatonin secretion is altered in AD, but post-mortem examination failed to show the classic pathological finding of  $\beta$ /A<sub>4</sub> deposition in pinealocytes.<sup>12</sup> However, a deficiency of CSF melatonin is postulated to be critical for the development of AD.<sup>14,15</sup> AD patients simultaneously showed significantly reduced amplitude, larger variation of peak times and diminished amount of total secretion in the melatonin secretion rhythm compared with their non-demented counterparts (figure 3).<sup>15</sup> Hypotheses for this include:

- 1- Organic deterioration of the circadian time-keeping system including the suprachiasmatic nucleus and its afferent and efferent projections.<sup>8</sup>
- 2- Decreased social interaction, encounter with the sun and general external sensory stimulus due to environmental factors commonly found with individuals with AD.<sup>12</sup>
- 3- Studies have found that melatonin levels are increased in AD patients during daytime and that these patients do not react equally to bright light as their non-demented counterparts.<sup>13</sup>

Preliminary reports suggest that melatonin decreases sundowning in AD patients. Furthermore, in vitro experiments found that melatonin functions as an anti-oxidant and neuroprotector in rat and primate brain tissue.<sup>13</sup> Inadequate melatonin in AD allows hydroxyl radicals produced by mitochondrial complex IV to damage mitochondria and initiate a cascade of oxygen radicals that causes the neuropathological changes in AD.<sup>12</sup> Thus, in addition to its

neuroprotective qualities, melatonin has been shown to help correct the aberrant retina-SCN-pineal axis required for normal sleep in AD patients.<sup>12</sup> Irrespective of the method of assessment, melatonin showed positive effects in insomniac patients in most studies.<sup>16</sup> Although it is imperfect, melatonin is currently accepted to be the most effective pharmacological therapy for correcting AD sleep related disorders.

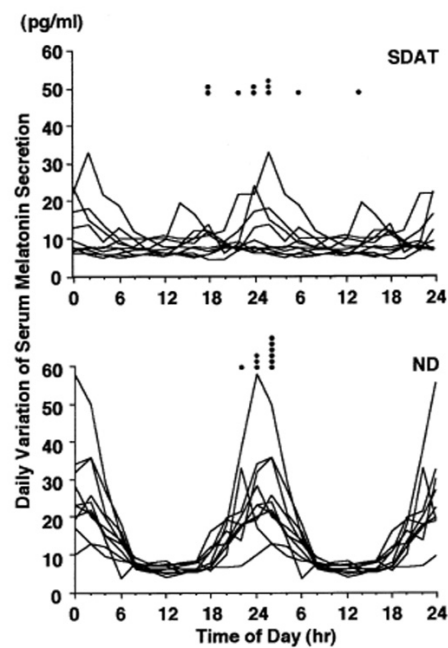


Figure 3. Raw data plots of daily variation of serum melatonin concentrations in the SDAT and ND groups. The ND group formed regular circadian patterns of melatonin secretion with nocturnal increase and sufficient daytime suppression. In contrast, the SDAT group showed irregular patterns of melatonin secretion with reduced peak secretion levels and large variations in peak secretion time indicated as small black points. Three patients in the SDAT group showed peak secretion times during the daytime, whereas none in the ND group did.<sup>15</sup>

### BRIGHT LIGHT THERAPY (BLT)

Natural sunlight regulates the body's natural daily arousal system, the circadian rhythm, via a direct neural pathway from the retina to the pineal gland. Light suppresses the release of melatonin which can stimulate ML<sub>1A</sub> and ML<sub>1B</sub> receptors. Because AD patients have altered circadian activity, artificial stimulation of their pineal gland may effectively normalise their circadian rhythm. In a study conducted by Nippon Medical School in Tokyo, AD patients were treated with bright light therapy (3000 lux; 1 lux equals a light intensity equivalent to 1 lumen/m<sup>2</sup>) daily from 9-11am. Treatment did not slow the cognitive degeneration as defined by the Clinical

Dementia Rating in severe AD patients. However, it did significantly decrease the percentage of nap time during the day and increase the percentage of night-time sleep in all 27 patients.<sup>17</sup> The therapeutic benefit was more pronounced in mildly demented patients and less marked in severely demented patients. Furthermore, in the treatment of AD with BLT, it was shown that short wavelength light is more effective at suppressing melatonin than long wavelength light.<sup>13</sup> These findings are clinically relevant for two main reasons:

1- BLT is a safe, non-pharmacological alternative to drugs that react poorly with patients with AD sleep related disorders.

2- The adaptations observed in circadian neuronal systems of aged individuals evidence neuronal plasticity even in severely demented patients.

Because community dwelling AD patients are exposed to light greater than 1000-lux less than 40 minutes per day on average, BLT may provide a safe, affordable solution to many AD related circadian abnormalities.

#### **Vitamin B<sub>12</sub>/Cobalamin**

The effects of vitamin B<sub>12</sub> and BLT on 28 AD patients were monitored to determine their effects on the sleep-wake cycle.<sup>18</sup> It is theorised that the methylation of homocysteine to methionine decreases levels of free homocysteine in the CNS, thereby reducing the neurotoxic effect of elevated homocysteine levels on melatonin suppressing neurons. Thus, increased levels of vitamin should further suppress melatonin during BLT and thus have a positive psychotropic alerting affect.<sup>18</sup> Patients with early-stage AD showed improved vigilance and decreased duration of daytime naps while receiving vitamin B<sub>12</sub> and BLT in comparison to BLT alone.<sup>18</sup> Those patients who received vitamin B<sub>12</sub> exclusively

failed to show an improvement. No difference was detected in severely demented individuals. Thus, the study concluded that vitamin B<sub>12</sub> increased the sensitivity of BLT rather than having a direct pharmacological effect.

#### **CONCLUSION**

The pathogenic processes underlying AD severely impair quality and quantity of sleep as the disease progresses. Currently, this aspect of AD remains largely untreated as the exact pathology in AD sleep disorders continues to elude researchers. A myriad of neurotransmitters and hormones contribute to the regulation of the sleep-wake cycle. These have been shown to be present in increasingly defective proportions as AD becomes more severe. The use of pharmacological agents in treatment carries some risk as side effects may outweigh therapeutic benefit. Consequently, biological and circadian therapy is currently the most effective treatment in AD sleep disorders. Because the pathogenicity in AD sleep disorders mirrors much of pathogenicity in AD memory disorders, elucidation of the neurophysiological processes in AD sleep disorders may provide valuable information in treatment of memory loss in AD.

AD related sleep disorders are an integral and pervasive aspect of the disease and can cause widespread perceptual and emotional disturbances. Consequently, immense strain is placed on family members, caregivers and the patient. Both pharmacological and non-pharmacological agents have been used to confront this aspect of the disease yet neither has proved an adequate solution. As more of the pathophysiological processes are revealed, pharmacological intervention is emerging as a hopeful therapeutic strategy in treating this critical component of AD.

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