

## Commentary

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# Treatment of Alzheimer's Disease: Trazodone, Sleep, Serotonin, Norepinephrine, and Future Directions

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Accepted 18 December 2018

**Abstract.** In this issue, an article by La et al. provides evidence that trazodone delayed cognitive decline in 25 participants with Alzheimer's disease (AD), mild cognitive impairment, or normal cognition. For participants considered to have AD pathology, trazodone non-users declined at a rate 2.4 times greater than those taking trazodone for sleep over a 4-year period. In the analysis of sleep complaints, the relationship between trazodone, a widely used medication for sleep problems in the elderly, and cognition was associated with subjective improvement of sleep disruption. Due to the design of the study, it was not possible to prove that the benefit of slowing cognitive decline was due specifically to the improvement in sleep. However, trazodone uniquely improves the deeper phases of slow-wave sleep. Other sedative medications are generally associated with worse cognitive function over time, and they do not improve sleep characteristics as does trazodone. Trazodone has a variety of effects on several monoaminergic mechanisms: a potent serotonin 5-HT<sub>2A</sub> and  $\alpha$ 1-adrenergic receptor antagonist, a weak serotonin reuptake inhibitor, and a weak antihistamine or histamine H<sub>1</sub> receptor inverse agonist. Because of the potential importance of this finding, further discussion is provided on the roles that trazodone may play in the modulation of monoamines, cognition, and the development of AD. If trazodone really does provide such a dramatic slowing in the development of dementia associated with AD, a great deal more research on trazodone is needed, including environmental and behavioral factors related to improvement of sleep, energy management, and neuroplasticity.

**Keywords:** Alzheimer's disease, energy, neuroplasticity, norepinephrine, serotonin, sleep, trazodone, treatment

In this issue, La et al. [1] show that trazodone has a positive effect on dementia associated with Alzheimer's disease (AD) by slowing the rate of cognitive decline. The authors suggest that the beneficial effect of trazodone could be mediated through its effect on augmenting slow-wave sleep (SWS). A drug to slow cognitive deterioration in AD has been the object of extensive searches for decades. Accordingly, there should be some additional attention given

to what trazodone is and how it might slow the rate of progression of AD and/or other dementias.

## TRAZODONE HISTORY

Trazodone, a triazolopyridine derivative and a phenylpiperazine, was developed in Italy in the 1960s by Angelini Research Laboratories. Trazodone was approved for medical use in December 1981 in the US by the FDA as an anti-depressant medication, Desyrel. However, trazodone is a less effective anti-depressant than many other agents. Further, the drug had already had extensive use outside of the US,

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so there was a relatively short patent-life, and the drug became generic in 1986. Thus, there was a lack of pharmaceutical industry support for extensive research on this drug.

In spite of the commercial difficulties for trazodone, clinical experiences soon showed that this drug has several beneficial effects. Trazodone is unique in its effects on sleep, increasing the deeper stages of SWS early in the sleep cycle and delaying REM onset [2–4]. There are an extensive number of studies that have supported the use of trazodone for insomnia [5]. Trazodone is one of the top two drugs used for off-label prescribing, usually for insomnia [6]. Trazodone is also beneficial and widely-used for anxiety, and it is arguably the most effective drug for post-traumatic stress disorder (PTSD), likely because of its effects on sleep [7]. Trazodone was tested for a potential benefit for agitation in AD, but the complex, multi-center study design did not show a statistically significant benefit for trazodone relative to other interventions [8], in spite of its reported usefulness in the management of agitation in dementia and PTSD [9]. In 2015, 27.6 million prescriptions for trazodone were filled in the US, twice the number of 2007 (<http://www.statistica.com> – accessed 11/11/2018). So, a finding that trazodone has a benefit for slowing AD progression is of considerable interest.

### **TRAZODONE MECHANISMS: MONOAMINES AND SLEEP**

Trazodone has relatively unique effects on several monoaminergic mechanisms. It is a potent serotonin 5-HT<sub>2A</sub> antagonist, a weak serotonin reuptake inhibitor (SRI) and also an antagonist at several other monoaminergic receptors including 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, adrenergic ( $\alpha$ <sub>1A</sub> and  $\alpha$ <sub>2C</sub>) receptors and a partial agonist at 5HT<sub>1A</sub> receptors and a weak antihistamine or histamine H<sub>1</sub> receptor inverse agonist [10].

Serotonin neurons are located in the brainstem raphe (midline) nuclei, and serotonin plays an important role in the orchestration of sleep [11], though the relationship is complex [12]. Serotonergic neurons comprise the most widely expansive neurochemical network in the vertebrate CNS [13], and the activity of these neurons decreases during SWS and ceases during REM sleep [14]. An interesting side note is that LSD, a 5-HT-2A serotonin receptor partial agonist (the opposite of the effect of trazodone on this receptor), inhibits the firing of serotonin neurons [15],

potentially explaining why LSD hallucinations are similar to REM sleep mentation. So, there is a question of what the exact role of serotonin is with respect to trazodone's clinical benefits for insomnia, PTSD, and AD, but a significant possibility is that the benefit of trazodone relates to its effect to deepen the restorative deep SWS stages and delay REM sleep.

Norepinephrine neurons are mostly located in the locus coeruleus and play a critical role in a variety of brain functions, including cognition and the sleep-wake cycle [16]. Norepinephrine may play a significant role in sleep, through wake-dependent accumulation of sleep need, leading to increase of slow-wave activity during sleep [17]. Norepinephrine neurons project to the cortex, particularly to the prefrontal cortex, and these frontally-projecting neurons are more susceptible to fatigue [18], and extended wakefulness metabolically compromises the locus coeruleus neurons [19]. A significant association of locus coeruleus activity is that sleep modulates the homeostatic balance of synaptic plasticity [20]. Thus, there is also a conceptual connection between norepinephrine function, sleep, and cognitive function.

Histamine neurons are also important in brain function and sleep, but this monoamine has not been studied as extensively as serotonin or norepinephrine, and its relationship with AD is not known [21].

### **ENERGY MANAGEMENT, SLEEP, LEARNING, AND SEROTONIN AND NOREPINEPHRINE**

Serotonin is a biochemical which was well developed in invertebrates, likely having a fundamental role in systemic energy homeostasis [22]. The brain serotonin system appears to have a critical role in the coordination of food intake and body weight [23], and is involved in the control of feeding and satiety [24]. Sleep developed in mammals, and multiple energy management systems, including thermoregulation, are related to sleep [25]. Sleep has evolved to serve specific ecological and constitutional functions related to environmental energy requirements [26]. Serotonin is also related to the fatigue effect in energy management [27]. Of relevance, the most common drugs for treating depression and schizophrenia affect serotonergic mechanisms, suggesting that these common psychiatric disorders involve imbalance of systems responsible for energy management. Thus, complex internal processes and external behaviors related to serotonin have important roles in homeostasis.

The critical factor which may explain the underlying function of serotonin as a neurotransmitter is its role in classical conditioning in invertebrates [28], leading to a fundamental role in learning and memory in vertebrates. In fact, serotonergic neurons are mostly located in the midline raphe nuclei of the brainstem, where they regulate numerous aspects of energy. Many basic functions which require energy or conserve energy, including appetite, feeding, temperature regulation, aggression, fear, mood, and sexual behavior, as well as sleep, are modulated by serotonin. Thus, serotonin implements energy homeostatic actions through fundamental learning mechanisms and plays a basic role in neuroplasticity, thus also guiding overt behavior.

Norepinephrine also plays a major role in cognition [29]. Processes related to norepinephrine, development of neuronal fatigue, and neuronal recovery may be essential for neuroplasticity [17, 30]. The natural fatigue that occurs with normal cognitive function is also related to critical energy management systems in the brain, and excess stress on this system can adversely affect locus coeruleus neurons [19].

### **ALZHEIMER'S DISEASE, TREATMENT, AND SEROTONIN AND NOREPINEPHRINE**

Serotonin and norepinephrine dysfunction in AD have long been known [31, 32]. Serotonin neurons are also among the earliest affected in the AD brain, before the first obvious signs of dementia [33, 34], preceded only by pathology in the norepinephrine neurons of the locus coeruleus [35–37]. AD pathology is basically related to an attack on critical neuroplastic mechanisms in the brain, which likely involve serotonin and norepinephrine [38]. Specifically, serotonin and norepinephrine promote the non-amyloidogenic pathway of metabolism of the amyloid- $\beta$  protein precursor (A $\beta$ PP), interacting with ADAM10 [39], providing support for the central role of neuroplasticity and serotonin and norepinephrine in the development of AD pathology [40]. Thus, understanding the significant role which serotonin and norepinephrine play in cognition and the development of AD is critical for developing AD treatments [41].

Disappointingly, extensive efforts to treat AD with serotonergic agents have not shown beneficial effects on cognitive deterioration [42–45]. There are three possible explanations for this failure: 1) the

medications tested have are not associated with a beneficial effect on sleep as is seen with trazodone; 2) serotonergic medications, including SSRIs and the tested receptor agonists, will have little effect if the critical serotonin neuron pathways have already deteriorated; and 3) some other serotonergic mechanism is the critical target.

A focus on norepinephrine as a treatment approach for AD has also been considered [36], but there are few clinical trials focusing on this approach. In particular, a beta-agonist, formoterol, has been found to be beneficial in a mouse model of AD [46]. However, such studies have not been conducted, though there have been considerations of how to protect norepinephrine neurons from degeneration [16].

The La et al. article [1] provides strong evidence that the benefit of trazodone occurs over a relatively long period of time, and this benefit is associated with subjective sleep improvement. Given the established effect of trazodone on SWS, there is a possibility that the beneficial effect was due to an increase of SWS. However, the pathway from this finding to a benefit on AD pathology is not clear. The question is if the modification of serotonergic and/or noradrenergic functions by trazodone might have a benefit for AD through a positive effect on serotonin and/or noradrenergic functions or an indirect benefit through its effect on SWS.

### **ALZHEIMER'S DISEASE PATHOLOGY, SLEEP, AND SEROTONIN AND NOREPINEPHRINE**

Changes in sleep/wake patterns are associated with AD [47], increasing in severity with the progressive development of cognitive dysfunction [48–50]. Further, there is a connection between the amyloid- $\beta$  pathology of AD, SWS, and disruption of memory consolidation coordinated by the hippocampus [51]. The problem is establishing the causal chain of events [52]. While sleep is related to serotonergic and noradrenergic mechanisms, serotonin and norepinephrine are not only important in memory formation, but they play a role in controlling the A $\beta$ PP switch, which decides synapse creation or destruction, the central factor in neuroplasticity and whose disruption appears to be a key to AD pathology [40].

So, the question is at what point serotonin and norepinephrine dysfunction contribute to AD pathology, by their effect on A $\beta$ PP, by their effect on SWS, or through another energy management mechanism.

The immediate consideration is whether mechanisms associated with the A $\beta$ PP are being targeted by trazodone. A $\beta$ PP turnover decreases during sleep, and the molecular changes associated with A $\beta$ PP appear to be closely related to AD pathology and the cognitive impairment associated with AD [52–57]. With the demise of the “amyloid hypothesis of AD”, there is a new focus on the control of A $\beta$ PP. Balancing the alpha and beta pathways of A $\beta$ PP metabolism is a promising area of study for finding an approach to AD treatment and prevention. Trazodone could play a role in setting the balance away from the AD predilection to cognitive decline and neurodegeneration.

### **ENERGY MANAGEMENT: LEPTIN, THE UNFOLDED PROTEIN RESPONSE (UPR), AND OTHER PATHWAYS**

Neuroplasticity is the underlying neural mechanism serving the cognitive processes of learning and memory. The evolutionary impetus for developing neuroplasticity and cognition is for the individual to perceive the environment more clearly to improve the management of resources, particularly energy, for an increased chance of survival. Some component of this function is the factor attacked by AD pathology. While the importance of serotonin and norepinephrine in many basic functions and pathological processes is known, other neurotransmitter systems, including acetylcholine, glutamate, and GABA (somatostatinergic) are also important in neuroplasticity. And these systems are also affected by AD pathology.

Several hormonal factors are important in energy management, including leptin, which interacts with and complements serotonin in the regulation of appetite and energy expenditure [56–58]. Leptin directly affects receptors in the ventral hypothalamus, which plays a major role in sleep regulation [59], and leptin and related hormones affect diet and energy balance and have important roles in regulating locomotor behavior and sleep [60]. Leptin similarly targets cellular mechanisms associated with neuroplasticity and can affect amyloid- $\beta$  levels [61, 62]. Low plasma leptin levels are associated with the cognitive impairment of AD [63]. Restoring a balance of serotonin and leptin mechanisms could also be a benefit for AD.

While the potential relationship between trazodone therapy and AD may be linked to its effect on monoamines, which is supported by substantial

scientific evidence, there could also be alternative explanations for such a benefit. For example, the unfolded protein response (UPR) may have a role in neurodegenerative diseases, and trazodone has been found to be a partial inhibitor of the UPR and could have a substantial benefit through this mechanism [64].

### **ALZHEIMER'S DISEASE CAUSATION, GENETICS, AND APOE**

While the AD field has focused on the treatment of the symptoms and the pathological changes observed in the brain, the real fundamental questions are what causes AD and how causative factors can be controlled. The biggest factor associated with AD causation is the apolipoprotein E (APOE) genotype [65]. Neuroplasticity, the basic function of the brain, requires a tremendous amount of energy, including the management of the energy for maneuvering the lipids associated with synapse creation and removal, which may be related to the actions of APOE. APOE appears to have an important role in neuroplasticity and the life-long susceptibility to AD, which may be related to the generation of toxic substances [66], and such toxic substances may be cleared during SWS. The question for the consideration of trazodone is whether this medication may be remedying the demise of serotonin and/or norepinephrine neurons or whether it is modulating the role of serotonin and/or norepinephrine in energy management and sleep modulation beneficially against the specific adverse effect of APOE genotype which predisposes to AD.

There are many additional genetic factors which contribute small amounts to AD causation. Well-established but rare young-onset factors mostly affect A $\beta$ PP. Other genetic factors accounting for small percentages of change in risk have been identified as affecting such systems as immune mechanisms, inflammation, and nerve growth factors, which are also affected by sleep. A common thread to link these genetic mechanisms would help with understanding AD and developing prevention approaches.

### **BRAINSTEM PATHOLOGY AND ALZHEIMER'S DISEASE**

While much attention has been given to the plaque and tangle pathology of neocortex as well as the hippocampus and amygdala, recent attention has focused

on brainstem mechanisms because it is now understood that the earliest pathological changes involving hyperphosphorylation of the microtubule-associated protein-tau are actually in locus coeruleus and dorsal raphe nuclei [31, 33–35, 37]. The change of focus has considerable implications for understanding AD pathology as well as developing new approaches to its prevention and treatment.

PTSD, anxiety, depression, and traumatic brain injury (TBI) are all associated with increased AD risk [67]. Serotonergic medications are approved for the treatment of PTSD. PTSD likely causes some underlying derangement in the brainstem which involves serotonin and sleep mechanisms. A relationship between anxiety and norepinephrine and the locus coeruleus is also well known and related to nocturnal behavior [68]. And depression is commonly treated with serotonin and norepinephrine medications, implicating brainstem mechanisms in this broad condition, and depression has also been studied as a frequent prodromal condition of AD. TBI is frequently associated with loss of consciousness and memory problems which implicates brainstem mechanisms; so, addressing the serotonin and norepinephrine systems in individuals who have suffered a significant TBI is also relevant. Thus, a major consideration which may apply to PTSD, anxiety, depression, and TBI is whether trazodone could benefit affected individuals to delay their long-term risk of developing AD and dementia.

### **CLINICAL EXPERIENCE IN TRAZODONE PRESCRIPTION**

Trazodone has been in use in the US since 1981, so there is a great deal known about its benefits and side-effects [69]. Trazodone antagonizes alpha 1-adrenergic receptors, a property which may be associated with postural hypotension. Trazodone also causes sedation and can cause uncomfortable feelings. Trazodone is predominantly metabolized in liver microsomes, so patients with liver damage are more sensitive to this medication and should have lower doses prescribed. The half-life of trazodone is 3 to 5 hours. Because of the individual variability of potency and side-effects, dosing must be done carefully for each patient (start low: 12.5 mg at bedtime; go slow: 12.5 mg increments).

Trazodone has minimal effects on muscarinic cholinergic receptors, in contrast to older antidepressant medications. Trazodone produces a higher

quality of sleep for those patients who work with the dosing than the GABA agonists (e.g., benzodiazepines), anti-cholinergics, or anti-histamines (e.g., diphenhydramine), which are widely used but impair cognitive function short-term and are now being considered as contributors to the development of dementia and AD pathology long-term.

Trazodone has a generally positive effect on sexual desire [70] and male erectile function, but it is also known to cause priapism, an emergency condition, similar to what can be associated with medications used to treat erectile dysfunction. It is estimated that abnormal erectile function occurs in about one in 6,000 male, mostly younger, patients treated with trazodone.

Trazodone is also useful for agitation [9]. (There are anecdotes that 12.5 mg under the tongue decreases road-rage.)

Trazodone is relatively safer than most other antidepressants in overdose situations. Fatalities are rare, and uneventful recoveries have been reported after ingestion of doses as high as 6,000–9,200 mg.

Trazodone may also be effective as a treatment for obstructive sleep apnea with worsening hypoxemia [71, 72], which could also be beneficial for cognition and AD prevention. This effect could be related to serotonin, norepinephrine, or histamine mechanisms.

### **TRAZODONE, SLEEP, AND FUTURE DEVELOPMENT FOR ALZHEIMER'S DISEASE TREATMENT**

Given the positive report of La et al. [1] and the large amount of information about serotonin, norepinephrine, sleep, and AD, as well as the great importance of controlling AD, further study of the effects of trazodone is clearly indicated. The question remains as to whether the benefit for AD is more directly related to serotonin, norepinephrine, or SWS. However, sleep is a known problem associated with AD, and other approaches to improve SWS should also be considered, including melatonin, 5-hydroxytryptophan, and magnesium (orally or Epsom Salts baths), as well as “sleep hygiene” and cognitive behavioral therapy for insomnia. Further understanding of basic mechanisms causing AD pathology and their primary control are also strongly needed.

Large, careful studies of the long-term benefit of trazodone should be considered. Population studies, including the data in the Veterans Administration, could be analyzed to determine a relationship

between drug treatments and diagnosis [73, 74]. There are numerous registries of subjects which have been developed and have information about medications and progression over time [75]. Ultimately, a double-blind study should be conducted comparing trazodone to another sleep-inducing substance, such as melatonin, also comparing the long-term outcomes with placebo control, using sensitive measures of cognitive function [76] and sleep to determine the mechanism of action and suggest further directions.

## ACKNOWLEDGMENTS

Dr. Ashford is supported by the War Related Illness and Injury Study Center (WRIISC) of the Department of Veterans' Affairs.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-1106r1>).

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