

REVIEW ARTICLE

Melatonin and Major Neurocognitive Disorders: Beyond the Management of Sleep and Circadian Rhythm Dysfunction

Olakunle James Onaolapo¹, Adejoke Yetunde Onaolapo^{2*}

¹Behavioural Neuroscience/Neuropharmacology Unit, Department of Pharmacology, Ladoke Akintola University of Technology, Osogbo, Osun State, Nigeria

²Behavioural Neuroscience/Neurobiology Unit, Department of Anatomy, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria

ABSTRACT

Major neurocognitive disorders (dementias) are characterised by impairments in memory, cognition, and several aspects of behaviour. Sleep disorders arising from circadian rhythm and sleep-wake cycle dysfunctions are among the most-troubling challenges encountered in individuals with dementia; and for which administration of melatonergic agents is an important management option. However, in addition to this, melatonin and melatonin receptor agonists appear unique in their potential for modulating symptoms known to be associated with major neurocognitive disorders, or altering the course of the underlying pathology. Hence, they are being continuously investigated for their ability to prevent or reverse cognitive decline, as well as for their antioxidant/neuroprotective properties. In this review, we examine the roles of melatonin and melatonergic agents in the management of major neurocognitive disorders, by looking beyond their classic roles in the management of dementia-related sleep disorders, to other potential roles in the overall management of symptoms and improvement of the quality of life of individuals with dementia.

Keywords: Alzheimer disease, Cognition, Dementia, Sleep, Melatonin receptors, Parkinson's disease

INTRODUCTION

Major neurocognitive disorders (dementias) are characterised by substantial impairment of one or more domains of cognitive functioning (that represents a decline from a previous higher level of functioning); resulting in interference with independence in performance of normal daily activities (APA, 2013). This cognitive decline must not occur exclusively in the context of a delirium, or be better explained by the presence of a neuropsychiatric condition.

***Correspondence:** adegbayibiy@yahoo.com
Behavioural Neuroscience/Neurobiology Unit, Department of Anatomy,
Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.
Phone number: 2348062240434

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The cognitive domains that may be affected include those of executive functioning, language, visuospatial skills, praxis, judgment, personality, and abstract thinking; and these cognitive changes are also associated with behavioural and psychological symptoms, the most prominent of which are depression and apathy (Savaskan, 2015). Prevalence of dementia increases exponentially with increasing age (Jorm and Jolley, 1998), doubling every five years from the age of 65 years; and it continues to represent a growing public health concern as more cases are reported or projected (WHO, 2012). As life expectancy increases worldwide and the aging population in low- and middle-income countries also increase; the prevalence of dementia in these regions are expected to rise (Prince et al., 2014, 2015). In absolute numbers, over 35.6 million people worldwide were estimated to be living with dementia in the 1st decade of the 21st century, and by 2050, the numbers are projected to reach 115.4 million

people (Prince et al., 2013). "Dementia" is a multifactorial disorder for which an increasing age has been reported as the single most important risk factor, especially after the eighth decade of life (Hugo and Ganuli, 2014). Other risk factors include genetics (Srinivasan et al., 2006), environmental factors (Brown et al., 2005; Franco et al., 2010), pre-existing medical conditions like hypertension, heart failure and atrial fibrillation (Tilvis et al., 2004; Qui et al., 2006; Santangeli et al., 2012), inflammation (Schott et al., 2013), co-morbid neuropsychiatric conditions like depression (Panza et al., 2010) and head trauma (Fleminger et al., 2003). Generally, brain neurodegenerative and/or vascular changes, resulting in diffuse cortical neuronal atrophy (cortical dementia) or involving subcortical structures such as vasculature, thalamus and the basal ganglia (subcortical dementia) have been implicated in the pathogenesis of dementias (Spruyt and Gozal, 2010). While many forms of dementia exist, clinically, the commonest forms are Alzheimer disease, Lewy body dementia and vascular dementia (Cappuccio et al., 2010). Also, in the elderly, uraemic encephalopathy from end-stage renal disease and chronic partial sleep deprivation (due to obstructive and central sleep apnoea) are among the other causes of neuro-cognitive decline (Bugnicourt et al., 2013; Nigam et al., 2016).

In recent times, the important roles played by sleep in the maintenance of health and well-being has become increasingly apparent. It is generally accepted that sleep is critical to brain maturation, as well as the development and maintenance of cognitive functions (Lezak et al., 2004). Poor sleep or total sleep deprivation have also been associated with an increase in all-cause mortality (Buffington et al., 2013; Miller, 2015). There is also evidence that alterations in sleep architecture and sleep disorders may disrupt neuronal pathways that impact brain structure and function (as observed in subjects with obstructive sleep apnoea); presenting a significant risk for the development of neurodegenerative disorders and/or neurocognitive disorders (Ancoli-Israel et al., 1991; Ancoli-Israel et al., 2008; Kim et al., 2011; Kim et al., 2013). Alterations in sleep pattern, which may occur as a consequence of normal aging or neurodegenerative brain disease, has been reported to occur with increasing

prevalence in individuals with dementia (Pistacchi et al., 2014; Cipriani et al., 2015). Circadian system alteration, which may manifest as disruption in the daily rhythms of physiologic parameters such as sleep, activity and hormone secretion, have also been observed as a symptom of a number of neurocognitive disorders including Alzheimer disease (Musiek, 2015).

The circadian rhythm of endogenous melatonin has been considered important in the maintenance of normal sleep-wake rhythm and regulation of the biological clock. Studies have also demonstrated decreased levels of melatonin in patients with dementia (Tohgi et al., 1992; Mishima et al., 1999; Wu et al., 2003); with evidence that reduced levels of melatonin correlate with the severity of mental and sleep impairments in these patients (Mishima et al., 1999). Appropriate therapy for the management of sleep disorders in dementia is evolving; and with the understanding of melatonin's role in the modulation of the sleep rhythm, its association with the dementias, as well as evidence of significant benefits from the use of fast release melatonin as an adjunct to benzodiazepines (Cardinali et al., 2012); melatonin and melatonergic agents are considered important in the treatment of dementia-associated sleep disorders (Serfaty et al., 2002; Borja and Daniel, 2006). The overall possible roles of melatonin in the general management of dementia is still being evaluated; however, there are reports that melatonin supplements (given at bedtime) may in addition to sleep/wake cycle maintenance, improve cognitive and emotional performance in patients with dementia (Cardinali et al., 2012; Furio et al., 2007). In this review, we discuss the roles of melatonin and melatonergic agents in the management of dementias, by first examining the relationships of melatonin, sleep and cognition; especially as they may impact the development of neurocognitive disorders. Then, we look beyond the classic roles of melatonin and melatonergic agents in the treatment of dementia-associated sleep disorders, to other potential roles in the overall management of symptoms, modification of the course of disease, possible disease prevention, and improvement of the quality of life of individuals with neurocognitive disorders.

SLEEP

Normal sleep is a complex phenomenon, which is rooted in optimal neurologic function and characterised by an orderly progression from wakefulness {characterised by low voltage, fast electroencephalogram (EEG) activity, high muscle tone and phasic electromyogram (EMG) activity} to NREM sleep, and finally to REM sleep (Comai and Gobbi, 2014). The sleep cycle, which is measured from recordings of electrical activities of large groups of cortical neurons and muscle cells, consists of four different stages; the first three stages of which have been designated N1, N2, and N3. N1 is characterised by high-amplitude and low-frequency on the EEG, non-rapid eye movement (NREM) on the electro-oculogram (EOG), and reduced muscle tone on the EMG. Onset of stage 2 (N2) is defined by the presence of sleep spindles and K-complexes; while slow wave sleep (SWS) or deep sleep is representative of stage 3. The fourth stage is the rapid eye movement (REM) sleep, which is characterised by presence of low-voltage fast EEG activity, and the absence of muscle tone. Approximately 90–100 min cycles of the four stages occur in normal adults, although time spent in each stage varies with sleep progression.

Sleep timing, depth, and duration in humans and diurnal animals is regulated by anatomical sites {such as the anterior hypothalamus, reticular activating system, suprachiasmatic nucleus (SCN), and the pineal gland} and governed by interactions between two processes; the homeostasis (process S) or the "sleep drive," and the circadian system or process C (Borbély, 1982; Fuller et al., 2006). Sleep and wakefulness are modulated by a master clock (endogenous biological clock) located in the suprachiasmatic nuclei (SCN) of the hypothalamus. This clock which controls sleep onset and offset also modulates waking up neurobehavioural performances, such as sleepiness, physiological alertness and cognition; and ensures circadian rhythmicity of these behaviours (Van Dongen and Dinges, 2003; Goel et al., 2013). This two-process mathematical model of sleep regulation has been used to describe the temporal profiles of sleep and wakefulness (Van Dongen and Dinges, 2003; Goel et al., 2013). The homeostatic process (process S) is a

neurobiological drive for sleep which varies (increasing with a saturating exponential during wakefulness, and decreasing alike during sleep); while the circadian system (process C) controls the daily oscillations of these threshold levels (wakefulness and sleep), and neurobiologically modulates the homeostatic drive for sleep (Goel et al., 2013). The interactions of these two processes also determine sleep timing (onset and offset), and the stability of waking up physiological and neurocognitive functions.

Sleep has been reported to change all through life (from childhood to adulthood) with documentations of specific age-related alterations in sleep (Bliwise, 2005). These changes involve sleep architecture, the circadian and homeostatic processes (Rowe and Kahn, 1987; Bliwise, 2005), and an increase in susceptibility to sleep disorders. In health, aging has been associated with a decline in the quality and duration of night-time sleep, and a decrease in the intensity, continuity and depth of sleep (Bliwise, 2005). There is also a concomitant decrease in the amplitude of circadian rhythm output signals for endogenous core body temperature (Dijk et al., 1999; Dijk and Duffy, 1999) and melatonin (Münch et al., 2005); with suggestions that the ensuing age-related sleep decline may be partly associated with a weaker circadian regulation of sleep and wakefulness. The consequence is that in older people, it takes longer to fall asleep, with increased sleep fragmentation and earlier wake-up times (Bliwise, 2005; Pace-Schott and Spencer, 2011; Miller et al., 2014). Aging has also been associated with a reduction in NREM and SWS (Van Cauter et al., 2000), and evidence of structural brain atrophy affecting the frontal lobe predominantly (Miller et al., 2014). In a recent study, a correlation between age-related atrophy of the medial prefrontal gray matter region and the degree of diminution of SWS activity (Sowell et al., 2003) was reported.

Role of Sleep in Cognition and Neurocognitive Decline

It is well-established that sleep plays an important role in the development and sustenance of cognitive functions like memory-consolidation and learning (Lezak et al., 2004). While research is ongoing to specifically

demonstrate the input and significance of the various stages of sleep, there is evidence suggesting that the consolidation of newly-learned material, or recently-acquired memory and skills occur during REM sleep (Karni et al., 1994); with the demonstration of a link between the timing/density of REM sleep, brain cholinergic activity and cognitive functioning (Spiegel et al., 1999). Thus, deficiencies of REM sleep might correlate with or predict cognitive deficits, especially in the elderly. The formation of long-term memories also requires consolidation which is facilitated by sleep; while the formation of hippocampal-dependent memories such as declarative memory have been reported to benefit from SWS (Born et al., 2006). Studies have also demonstrated that overnight verbal memory retention correlates significantly with an increase in the number of sleep spindles (Clemens et al., 2005). The transformation of hippocampal-dependent memory (episodic memories) to a hippocampus-independent memory has been linked to the process of consolidation that may occur during NREM and SWS (Nadel and Moscovitch, 1997; Walker, 2009; Diekelmann and Born, 2010); a process that is impaired by sleep deprivation after learning (Gais et al., 2007; Diekelmann and Born, 2010).

On the other hand, it is important to note that apart from impaired memory, lack of sleep has been linked to inattention and even suicidal tendency (Etindele Sosso, 2017a); while a complex combination of factors (including certain personal/family medical history) may be pointers to higher risks of development of neurocognitive disorders (Etindele Sosso, 2016). There have been suggestions that a possible bidirectional relationship exists between alterations in sleep rhythm and the development of dementias {particularly Alzheimer disease (AD)} (Ju et al., 2014; Guarnieri and Sorbi, 2015; Villa et al., 2015; Urrestarazu and Iriarte, 2016). This is based on the facts that; a) changes in sleep have been observed to predate the onset of cognitive symptoms in patients with dementia (AD), with a decline in sleep quality and/or circadian function occurring in parallel with both cognitive dysfunction and the progression of disease (see Ju et al., 2014 for review). b) sleep disturbances and disruption of the neural regulation of the sleep-wake

rhythm appear to be involved in the cellular and molecular mechanisms of cognitive decline (Guarnieri and Sorbi, 2015), and have been associated with severity of memory and cognitive impairment (Shin et al., 2014), c) alteration in sleep rhythm has a significant impact on physical, physiologic and cognitive functioning in individuals with dementias and are positively associated with the severity of behavioural dysfunction and cognitive impairment (Guarnieri and Sorbi, 2015). Studies have also reported that the concentrations of amyloid- β ($A\beta$) have a diurnal variation, with levels rising during wakefulness and the nadir during sleep (Huang et al., 2012; Lucey and Bateman, 2014); there are also reports that sleep facilitates $A\beta$ clearance, a function which may be impaired with sleep disturbance (Ju et al., 2014; Miller, 2015). In patients with Parkinson disease (PD), an association between sleep disorders, memory/executive function deficits has also been demonstrated (Pushpanathan et al., 2016). Overall, results from prospective studies evaluating sleep and cognitive outcomes, and from observational and experimental studies, point to the fact that poor sleep is a risk factor for cognitive decline and the development of dementia (particularly AD) (Spira et al., 2014) irrespective of geographical region (Foley et al., 2001; Jaussent et al., 2012).

Dementia-associated sleep disorders

The sleep changes observed in dementias (though similar to those reported in normal aging) are more severe than would be expected for the patient's age (Peter-Derex et al., 2015). In patients with dementia due to AD, sleep disturbances tend to occur more frequently than in the general population; it also appears early in the course of the disease Pistacchi et al., 2014; Urrestarazu and Iriarte, 2016), usually becoming more marked with progression of the disease. Studies have observed that these sleep disturbances are associated with increased memory and cognitive impairment (McCurry et al., 2000; Moran et al., 2005). Studies have also continued to characterise the variety of circadian and sleep-wake cycle disorders that may accompany either aging or dementia (Ju et al., 2014; Videnovic et al., 2014). Subjects diagnosed with dementia generally have been reported

to have co-morbid insomnia and other types of sleep disorders (Cipriani et al., 2015; with circadian rhythm dysfunction playing an important role in the aetiology of dementia-associated sleep disorders. The sleep disorders commonly reported in association with dementias include insomnia, hypersomnia, circadian rhythm alterations, aberrant nocturnal motor behaviour, reduction of sleep duration/rapid eye movement (REM) sleep (Savaskan, 2015), increased sleep latency, and decreased slow-wave sleep (Wu and Swaab, 2007). The common symptoms include fragmented sleep, early morning awakening and increased daytime somnolence (Vitiello and Borson, 2001). On the EEG, the change most specific to AD include a quantitative decrease in the REM sleep stage (Prinz et al., 1982; Petit et al., 2004), which has also has been proposed as a biological marker of AD (Petit et al., 2004).

Dementia-associated sleep disorders have been linked to multiple causes; a) the physiologic changes that accompany the disorder; b) primary sleep disorders like sleep apnoea and restless legs syndrome; c) medical and psychiatric morbidity; d) side-effects of medications; and e) poor "sleep hygiene" (McCurry et al., 2000).

In patients with AD, sleep disturbances are believed to be a result of a progressive neurodegeneration resulting in a decrease in the number of neurones in the SCN, causing fluctuations in neurohormones like melatonin that are critical in the maintenance of the circadian rhythm (Wu and Swaab, 2007). A significant number of patients also have disturbed sleep-wake rhythms which have been linked with reduced amounts of secreted melatonin; and melatonin rhythm abnormalities, such as variations in phasing of the peak (Mishima et al., 1999). There have also been suggestions that in a number of these patients, the quality of sleep correlated directly with their quality of life; as such, the sleep disorders also increase the health burden for both patients and caregivers, raising the possibility that the management of sleep disorder may alter the course of the disease and quality of life (Urrestarazu and Iriarte, 2016). This possibility has been highlighted by studies that show that in patients with untreated obstructive sleep apnoea (OSA), initiation of continuous positive airway pressure

(CPAP) titration was associated with a REM rebound and increased REM sleep duration (Nigam et al., 2017). Other studies had also reported SWS rebound (Osuna et al., 2008; Brillante et al., 2012). As said earlier, since both hippocampal-dependent memories and hippocampus-independent memory require NREM sleep and SWS (Nadel and Moscovitch, 1997; Walker, 2009; Diekelmann and Born, 2010), a restoration of normal sleep pattern is essential for normal cognitive functioning, and it may be a putative mechanism through which progression of neuro-cognitive decline can be arrested.

MELATONIN

Melatonin is an indoleamine neurohormone which is synthesised from serotonin, and secreted by the pineal gland in a distinct circadian rhythm (Arendt, 1988; Comai and Gobbi, 2014). The production of melatonin is controlled by the photoperiod via the suprachiasmatic nucleus (SCN) with peak levels at night and nadirs during the day. Melatonin is crucial to the regulation of the mammalian biologic rhythms, such as seasonal adaptation, sleep-wake cycle, mediation of photoperiodic information and pubertal development (Chan and Wong, 2013). It is also important in the synchronisation of cell physiology, regulation of a number of physiologic processes like cardiac function, mood, anxiety and appetite (Reiter, 2003; Hardeland et al., 2011); and the control of body posture and balance (Fraschini et al., 1999). Melatonin exerts its effects on biologic systems or the brain through its ability to bind to melatonin receptors (MT₁ and MT₂) (Jockers et al., 2008), orphan nuclear receptors (Ekmekcioglu, 2006) and intracellular proteins, like calmodulin (Pandi-Perumal et al., 2008). Documented effects of endogenous or exogenous melatonin include the control of anxiety-related behaviours (El Mrabet et al., 2012; Onalapo AY et al., 2017a, 2017b), modulation of memory and memory formation (He et al., 2013; Onalapo OJ et al., 2014; Onalapo AY, et al., 2017b), neurogenesis (Liu Jetal., 2013), neuroprotection (Kondoh et al., 2002), anti-inflammation (Genovese et al., 2005), antitumour (Blask et al., 2002) and antioxidant properties (Sofic et al., 2005). Stimulation of the visual cortex might

have effects on melatonin secretion, circadian rhythmicity, sleep, and by extension, memory; and in an experiment using mice, it was found that stimulation of the visual cortex (using gratings and dot) affects neuronal inhibition-excitation balance, eventually disturbing memory-processing and short-term plasticity (Etindele Sosso, 2017b).

Results of several studies had shown that exogenous melatonin is generally safe, and some of the most frequently-reported side-effects are nausea, headache, dizziness and drowsiness (Buscemi et al., 2005). Other less-frequently reported side-effects are mild tremor, anxiety, abdominal cramps, irritability, reduced alertness, confusion/disorientation and hypotension (Bauer, 2017). Also, exogenous melatonin can interact with other drugs such as anticoagulants (leading to increased risk of bleeding), anti-platelet drugs, anticonvulsants, oral hypoglycaemic drugs and contraceptive agents (Bauer, 2017). Use of melatonin in the elderly had been reported to cause hypothermia (Zhdanova et al., 2001). However, administered melatonin has a short half-life; and unlike drugs such as benzodiazepines, it has not been associated with long-term adverse effects. Also, reports from a number of studies suggest that exogenous melatonin does not show any addictive potential and is therefore safe for long-term use (Cardinali et al., 2012).

In photoperiod species in which reproduction is dependent on the seasonal changes in night length encoded as changes in melatonin secretion or levels; this hormonal signal modulates the onset of the reproductive cycle (Tamarkin et al., 1985; Van Cauter et al., 2001). However, in humans and other non-photoperiod species, the circadian rhythm of melatonin secretion is believed to be involved more in the synchronisation of other circadian clock functions like the consolidation of sleep (Dijk and Cajochen, 1997) and the reciprocal effect of maintaining the circadian clock in the SCN (McArthur et al., 1991). Its known effects on the circadian clock stems from observations in primates, in which exogenous melatonin entrains free-running rhythms (Redman et al., 1983), contrary to its effect in photoperiod birds (Turek et al., 1976). Studies have also demonstrated the expression of high levels of melatonin receptors on SCN neurons; with

evidence of acute alteration in neuronal activity (Liu et al., 1997) and phase-shift in neuronal firing-rate, following the use of exogenous melatonin at times corresponding to dusk or dawn (McArthur et al., 1991).

Melatonin and Its Role in Sleep

The circadian rhythm of endogenous melatonin has been considered an important marker of internal time, during periods of low ambient light. It is closely linked to the endogenous circadian rhythm of sleep (process C). During the 16 hour wake period, the circadian pacemaker opposes the decreases in physiologic and behavioural function that is usually associated with an increased homeostatic drive for sleep (process S) that occurs with sustained wakefulness. At night however, extension of the wake episode past the evening rise of melatonin levels has been associated with marked reduction of these functions, largely due to the loss of the inhibitory impulse of the circadian pacemaker, resulting in the promotion of sleep (Dijk and Czeisler, 1994). Coinciding with the loss of stimulatory effect of process C is a concomitant thermoregulatory cascade modulated by night-time rise in melatonin levels that presents as a decrease in core body temperature (Krauchi et al., 2000), rise in blood flow in the distal skin regions and hence heat loss; a physiological predictor for the rapid onset of sleep (Krauchi et al., 1991).

Evidence of the relationship between endogenous melatonin rhythm and sleep have been demonstrated in subjects with non 24-sleep-wake cycle syndrome (McArthur et al., 1996; Uchiyama et al., 2000), and in blind subjects in whom the circadian pacemaker is not entrained (Nakagawa et al., 1992; Lockley et al., 1997). Dijk and Cajochen (1997) also reported that the daily circadian increase in melatonin secretion coincided with a decrease in wakefulness during periods of scheduled sleep. Evidence from these studies led researchers like Cajochen and colleagues (2003), to consider the availability of a feedback mechanism linking the pineal gland to both the circadian pacemaker and thermoregulatory centres; melatonin weakens the circadian signal from the SCN, promoting heat loss which induces sleepiness via the preoptic area of the anterior

hypothalamus. These results also piqued the research interests into examining the role of melatonin as an internal facilitator of sleep in humans (Cajochen et al., 2003) and its possible use in the management of sleep disorders. Initial studies examining the role of melatonin as a modulator of sleep and thermoregulatory mechanisms in humans concluded that it was not critical to sleep onset, since only moderate incidence of sleep irregularity was reported in pinealectomised patients (Macchi et al., 2002); and melatonin production did not correlate with sleep quality in the elderly subjects (Youngstedt et al., 1998). However, further studies using exogenous melatonin reported that administration of exogenous melatonin (especially during day-time) was associated with acute effects on sleep and thermoregulation in humans; eliciting all the physiological effects associated with night-time rise in levels of endogenous melatonin. Melatonin's modulation of the sleep rhythm has also been linked to receptor activity; MT_1 receptor decreases neuronal firing rates, whereas MT_2 receptor regulates phase shifts (Dubocovich et al., 2003; Comai and Gobbi, 2014).

Exogenous melatonin administration has been associated with the induction of sleep, especially during periods of: insufficient sleep drive (process S), inhibition of the drive for wakefulness arising from the circadian pacemaker, and induction of phase shifts in the circadian clock; so that the circadian phase of increased sleep propensity occurs at a new set time (Cajochen et al., 1997, 2003; Deacon and Arendt, 1995; Krauchi et al., 1997).

Melatonin and sleep disorders

Sleep disorders are a broad group of clinical conditions that include all kinds of sleep-related dysfunctions such as insomnia, circadian rhythm disorders, parasomnias, and sleep-related movement or breathing disorders (Amihaesei and Mungiu, 2012; Xie Zetal., 2017). The consequences of poor sleep or sleep disorders include fatigue, anxiety, restlessness; and impaired learning, memory, logical or abstract reasoning. The role of melatonin as an internal facilitator of sleep in humans (Cajochen et al., 2003), its effect in modulating the circadian rhythm of sleep, as well as the effects of

exogenous melatonin on the induction of sleep (Cajochen et al., 1997, 2003; Krauchi et al., 1997) all support a role for melatonin, either in the pathophysiology of sleep disorders or its management. The sleep-wake rhythm in humans is regulated by the circadian timing system, and disorders of this system have been characterised as circadian rhythm sleep disorders (CRSD). CRSD, which occur commonly in patients with dementias (Savaskan, 2015) can be divided into a) disorders emanating from alteration of the endogenous circadian clock such as delayed sleep phase disorder, advanced sleep phase disorder, free-running disorder and irregular sleep wake rhythm; b) disorders involving alteration of the external environment relative to the endogenous circadian clock as observed in shift-work disorder or jet-lag. The overall effect of CRSD irrespective of aetiology is the maladjustment of normal phase-shift timing. Although the distinct aetiopathogenetic mechanisms of CRSDs are still being studied; the associations of CRSDs with alterations in the rhythm of melatonin secretion (Lockley et al., 1997; Kayumov et al., 2001), as well as mitigation of symptoms following normalisation of the melatonin secretion cycle are evidences of melatonin's possible role in this condition (for a detailed review see Xie et al. (2017).

Insomnia has been defined as persistent difficulty with sleep initiation and sleep consolidation, resulting in poor quality of sleep quality (AASM, 2014). Insomnia is reported to occur commonly in PD patients; with its emergence related to uncontrolled motor symptoms, nocturia, depression, and circadian cycle disruption (Iranzo, 2016). There have been reports of age-related decline in the levels of melatonin levels with older adults being more prone inadequate levels (Leger et al., 2004). Concomitantly, there is also an age-related decline in sleep, with increased incidences of sleep disorders with increasing age. This association has led to suggestions that reduced melatonin secretion may be involved in the mechanism of insomnia (Takaesu et al., 2015). This has also been buttressed by results from studies that have demonstrated the beneficial effects of melatonin in the management of insomnias (Shechter et al., 2012; Scheer et al., 2012; Bartlett et al., 2013; Holvoet and Gabriels, 2013; Goldman et al., 2014), with its approval in Europe

for the management of primary insomnia in adults aged 55 years or more.

Melatonin and melatonin agonists have also been reported to play significant roles in the treatment of insomnia, via the ability to activate melatonin receptors (MT₁ and MT₂). Selective MT₂ receptor agonists have been associated with increased NREMS duration compared to either melatonin or non-selective MT₁/MT₂ agonists (Ochoa-Sanchez et al., 2014). By activating MT₁ and MT₂ receptors, melatonin and non-selective MT₁/MT₂ receptor agonists have been used to improve sleep quality; sleep efficiency and increase total sleep time; while decreasing sleep onset latency in insomnia patients (Xie et al., 2017).

Melatonin and Its Role in Cognition

The demonstration of melatonin receptors (Reppert et al., 1994; Wan et al., 1999; Musshoff et al., 2002) in the hippocampus (a brain region associated with memory-processing) raised suspicions regarding the possible role of melatonin in modulation of learning and memory processes. Results from electrophysiological studies have demonstrated the role of melatonin in modulating synaptic transmission in the hippocampus (Wan et al., 1999; Hogan et al., 2001; Musshoff et al., 2002) and regulation the electrical activity of hippocampal neurons (Zeise and Semm, 1985; Musshoff et al., 2002); as well as its ability to alter synaptic transmission between neurons in this region. The effect of melatonin on hippocampal long-term potentiation (LTP) has also been demonstrated (Wang et al., 2005). LTP is measured by stimulating Schaffer collaterals and recording field excitatory postsynaptic potential (fEPSP) from the CA1 dendritic layer, variations in the strength of this synaptic connection (SC-CA1) are important in the understanding of how synaptic plasticity and learning and are regulated by signalling pathways which may be modulated by melatonin (Collins and Davies, 1997; El-Sherif et al., 2003). Melatonin has also been reported to cause a concentration-dependent inhibition of the induction of long-term potentiation (El-Sherif et al., 2003). While evaluating the possible mechanism involved in melatonin's effect on LTP, Collins and Davies (1997) demonstrated

that melatonin's ability to inhibit LTP was not mediated by the blockade of the N-methyl-D aspartate (NMDA) receptor. Mechanisms that have been verified include melatonin's ability to modulate neuron excitability and/or synaptic transmission within the hippocampus (Wan et al., 1999; Hogan et al., 2001; Musshoff et al., 2002). Wang et al. (2005) demonstrated that melatonin altered synaptic plasticity via melatonin receptor (MT₂)-mediated regulation of the adenylyl cyclase-protein kinase A (AC-PKA) pathway. Rhythmicity in melatonin production has also been suggested to be involved in the modulation of hippocampal function, thereby influencing the complex learning and memory processes. Memory formation and consolidation have for long been classified by a relationship with time; and temporal windows exist for the various forms of memory, including short-term memory and long term memory (McGaugh, 2000). There have been reports to suggest that the circadian rhythm is extensively involved in the modulation of cognitive processes and this occurs in a phase-specific manner (Wright et al., 2006); also, the circadian modulation of long-term memory has been demonstrated in mammals (Rudy and Pugh, 1998; Chaudhury and Colwell, 2002; Valentinuzzi et al., 2004). There have also been suggestions that melatonin may regulate the circadian rhythm effects on learning and memory acquisition and consolidation. Results from studies in zebra fish (using a modified active-avoidance conditioning (AAC) paradigm) revealed that, although pinealectomy had no effect on acquisition or consolidation of daytime AAC performance, night-time memory performance for AAC was similar for normal daytime trained animal. This led to the conclusions that endogenous night-time melatonin inhibited night-time AAC performance; suppressing memory consolidation following night-time acquisition (Rawashdeh et al., 2007; Rawashdeh and Maronde, 2012). The possibilities of endogenous melatonin's modulation of the circadian rhythm effect on memory in healthy humans are still been evaluated; studies in subjects with cognitive decline either from age or disease have reported evidence of melatonin production or receptor deficits which correlate with severity of cognitive decline (Mishima et al., 1999; Zhou et al., 2003; Savaskan, 2015). In

rats, melatonin has been reported to phase-specifically enhance memory during the day while impairing it at night (Takahashi et al., 2013); enhanced cognitive performance was demonstrated in mice with genetic deletions of both high-affinity G-protein coupled melatonin receptors ($MT_1^{-/-}$; $MT_2^{-/-}$) (O'Neal-Moffitt et al., 2014). There have also been suggestions of melatonin-receptor specificity of melatonin action on cognitive performance, with evidence of MT_2 receptor deletion impairing hippocampal long-term memory (Larson et al., 2006). The overall conclusions in recent times have been that while melatonin may link the circadian system with learning or memory performance, the actions of melatonin may vary with circadian phase, receptor signalling or task specificity (Krishnan and Lyons, 2015).

Melatonin and neurocognitive disorders

There is growing evidence that interactions between the circadian and homeostatic processes are linked to the temporal modulation of sleepiness and alertness throughout the day; these interactions have also been reported to impact neurocognitive performance (Cajochen et al., 2004; Gerstner and Yin, 2010). Alterations or irregularities in the interactions between the circadian and homeostatic systems had been linked to sleep and/or behavioural disorders that accompany advancing age and/or neurocognitive disorders. Melatonin is important in the regulation of the normal sleep-wake cycle; and has also been linked not only to the development of sleep abnormalities, but also the pathogenesis of Alzheimer (AD) type dementia.

In neurocognitive disorders like AD and Parkinson disease (PD), alterations in the pattern of the circadian rhythm of melatonin have been associated with the development of disease (Uchida et al., 1996; Mishima et al., 1999; Wu et al., 2003; Videnovic et al., 2014); while a reduction in the cerebrospinal fluid (CSF) levels of melatonin has been reported in the preclinical stages of AD (Mishima et al., 1999; Wu et al., 2003), with further reductions observed as the disease progresses (Zhou et al., 2003). The reduction in melatonin levels has been suggested to be linked to alterations in the neural impulses from the master clock (which lies in the SCN),

resulting in a reduction in the expression of clock genes and a loss of the noradrenergic control in the pineal gland (Wu et al., 2006; Coogan et al., 2013). Low CSF levels of melatonin also correlated with the presence of the ApoE4 allele, (a known genetic risk factor for AD) (Liu et al., 1999), and also to the presence of sleep disorders like REM sleep reduction and obstructive sleep apnoea (Liu et al., 1999; Gottlieb et al., 2004; Hita-et al., 2013). The demonstration of low CSF levels of melatonin has been suggested as an early trigger or possible marker for AD (Wu et al., 2003; Zhou et al., 2003). Although what is yet to be demonstrated is if the relative melatonin deficiency is a factor of neurodegeneration that precedes the development of AD or the consequence of neurodegeneration; however, what seems clear is that a decrease in melatonin worsens the disease, and that early circadian disruption may be an important deficit to be considered (Cardinali et al., 2012). There have also been suggestions that melatonin has other beneficial effects such as antioxidation, anti-amyloidogenesis {it regulates the metabolism of amyloid precursor protein (Lahiri, 1999) and prevention of aggregation of amyloid- β (Lahiri et al., 2004)}; therefore, its deficit could influence disease progression (Lin et al., 2013). Melatonin (either in neuroblastoma cells or in rats) was reported to inhibit tau hyperphosphorylation induced by wortmannin (Liu et al., 2002; Deng et al., 2005), calyculin A (Li et al., 2005; Yang et al., 2011), isoproterenol (Wang et al., 2005) and constant light illumination (Ling et al., 2009). The mechanisms underlying the inhibitory effect of melatonin on tau hyperphosphorylation has been linked to its ability to alter the activities of protein kinases and phosphatases, as well as inhibit oxidative stress induced by these agents (Zhu et al., 2004; Gong et al., 2005). However, there have also been reports that melatonin has no effect once deposition of amyloid- β protein has commenced (Quinn et al., 2005; Lin et al., 2013).

In Huntington disease (HD), a delay in circadian rhythm of nocturnal melatonin production has been reported (Aziz et al., 2009). However, in subjects with PD, there have been conflicting results on the circadian melatonin rhythm during the course of the disease, with reports of no alteration (Fertl et al., 1991), small phase

alterations (Bordet et al., 2003), or decreased production of melatonin (Videnovic et al., 2014). Videnovic et al (2014) reported that decreased levels of melatonin correlated with excessive daytime sleepiness. In a number of neurocognitive disorders, apart from the impaired production of melatonin or rhythm abnormalities, melatonin receptor alterations have also been reported. In AD and PD, impairment of brain expression of both melatonin and nicotinic alpha-7 ($\alpha 7nAc$) (Uchida et al., 1996; Brunner et al., 2006; Savaskan, 2015) receptors was demonstrated; with reduced expression of both MT_1 and MT_2 receptors in the amygdala and substantia nigra (Brunner et al., 2006) in PD patients, decreased expression of MT_1 and MT_2 in the cortex and in the pineal gland in PD (Adi et al., 2010), and reduced expression of MT_1 in the SCN in AD (Wu et al., 2007).

MELATONIN, MELATONERGIC AGENTS AND THE MANAGEMENT OF NEUROCOGNITIVE DISORDERS

The potential applications of melatonin in the management of dementias are directly related to its numerous effects on the brain (Figure 1). For instance, melatonin's effects on the maintenance of the circadian rhythm, mediation of photoperiodic information and regulation of the sleep-wake cycle had been, and are still being employed in the management of dementia-associated sleep disorders; while its neuroprotective, antioxidant and immune-modulation effects are being

explored in the management of neurodegeneration and cognitive decline in dementias (Figure 1). Also, the roles of abnormalities of melatonin secretion and ligand-receptor interactions in the pathogenesis of dementias are being investigated. Melatonin secretion normally decreases with age, but the decline is more marked in dementias like AD; and this marked decrease has been postulated to be responsible for the circadian disorganisation, decrease in sleep efficiency and impaired cognitive function seen in the patients (Cardinali et al., 2010). In Alzheimer dementia, there is decreased serum and cerebrospinal fluid (CSF) melatonin and loss of melatonin diurnal rhythm (Wu and Swaab, 2007); also levels of melatonin in CSF decrease with the progression of AD (Zhou et al., 2003). In early AD, reduction of melatonin levels in the CSF and in the post-mortem pineal gland predates cognitive decline (Zhou et al., 2003). Also, a number of human studies have demonstrated melatonin's effectiveness in the management of AD and impaired cognition (Table 1). Data from clinical trials indicate that melatonin supplementation improves sleep, ameliorates 'sundowning' (bouts of evening-time anxiety, confusion, agitation and aggression seen in about one-fifth of AD patients), and slows down the progression of cognitive impairment in Alzheimer-type dementia (Lin et al., 2013) (other studies are as listed in Table 1). Therefore, beyond the management of sleep disorders, melatonergic agents are likely to play other crucial roles in dementia management.

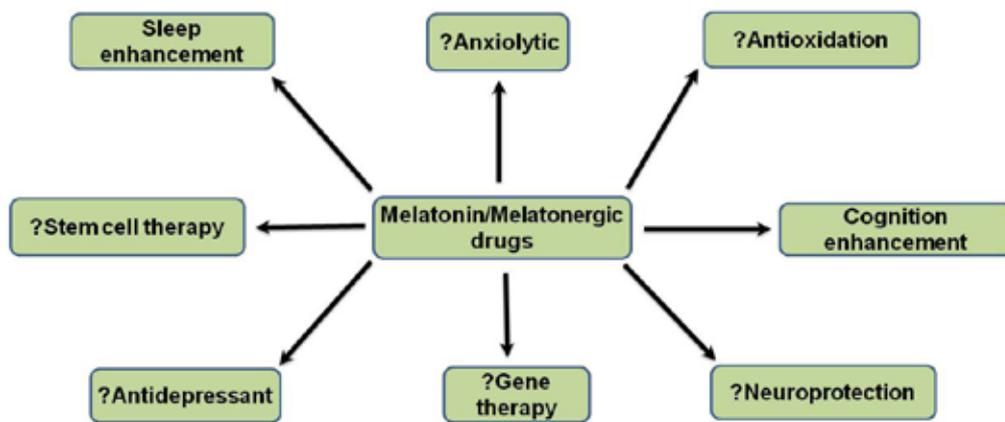


Figure 1. Showing melatonin in the management of AD

Table 1: Showing studies in which melatonin was used in the management of different Alzheimer's disease symptoms

Design	Subjects	Treatment	Period	Measured	Results	REF
Open-label study	Human	bed time melatonin (3 mg p.o./ daily)	3 weeks	Caregiver measured daily sleep and wake quality logs	7 out of 10 showed a significant (P<0.05) decrease in sun-downing and reduced variability in time of sleep onset	Fainstein et al., 1997
Open-label study	Human	bed time melatonin (9 mg p.o./ daily)	22 - 35 months	Caregiver measured daily sleep and wake quality logs with Neuro-psychological assessment	Sundowning undetectable or improvement of sleep quality. Militated against disease progression and cognitive deficits	Brusco et al., 1998
Retrospective Twin study	Human	bed- time melatonin at 9 mg p.o./ daily.	36 months	Neuro-psychological and neuroimaging assessment	Severe impairment of sleep/ cognitive function in the twin not receiving melatonin, compared to treated	Brusco et al., 1998
Double-blind, placebo-controlled study	Human	Placebo or bed- time melatonin at 3 mg p.o./ daily.	4 weeks	Actigraphy and Neuro-psychological assessment	Significantly prolonged sleep time and decreased night activity with melatonin. Improved cognitive function.	Asayama et al., 2003
Retrospective study	Human	Bed- time melatonin at 5-10 mg p.o./ daily.	20 months	Polysomno-graphy	Suppression of REM sleep behaviour disorder.	Anderson et al., 2008
Double-blind, placebo-controlled, crossover study	Human	Bed- time melatonin at 6 mg p.o./ daily.	10 days	Actigraphy and neuro-psychological assessment	Improved sleep quality. Improved cognitive ability and reduction of depression	Jean-Louis et al., 1998
Double-blind, placebo-controlled pilot study	Human	Placebo or Bed- time melatonin at 1 mg p.o./ daily.	4 weeks	Sleep questionnaire and cognitive tests	Improved sleep-latency after nocturnal awakening. Improved scores on the California Verbal Learning Test-interference substest.	Peck et al., 2004
Double-blind randomised placebo-controlled trial	Human	Placebo or 8.5 mg immediate release and 1.5 mg timed release	10 days	Total Sleep Time measured at night	No significant effects of melatonin	Gehrman et al., 2009.
Double-blind randomised, placebo-controlled, multicenter trial.	Human	Placebo or 2 mg prolonged-release melatonin	24 weeks	Total Sleep Time at night plus MMSE (ADAScog)	Improvement in cognitive functioning and sleep maintenance	Wade et al., 2014

ADAScog: Alzheimer's disease Assessment Scale-cognitive subscale., MMSE Mini mental state examination

Melatonin, Melatonergic Agents and Dementia-Associated Sleep Disorders

Pharmacologic treatment is generally an option for short-term management of dementia-associated sleep disorders. Antidepressants, benzodiazepines, non-benzodiazepine agents and antihistamines have been commonly used, although limited empiric evidence exists for their long-term safety and use. Undesirable effects of these various classes of drugs like sedation, somnolence, dizziness, cognitive impairment and weight gain in the older adult population preclude their long-term use; hence the search for medications with lesser side effects. Administration of different courses of melatonin has been reported to be associated with variable improvements in indices related to sleep disorders in dementia. Evidence showing that combination of bright light and melatonin treatment may improve sleep in AD (Riemersma-van der Lek et al., 2008) has been reported. A 21 days oral course of melatonin was first tried in a small non-homogenous group of elderly patients with primary insomnia associated with dementia; the results showed 70 % reduction in sundowning and reduced variability of sleep onset time (Fainstein et al., 1997). In another study, 6 mg of melatonin for 4 weeks in patients who exhibited irregular sleep-wake cycles was associated with a significantly reduced percentage of night-time activity as compared to a placebo group (Mishima et al., 1999, 2000). Long-term administration (2-3 years) of melatonin at 6-9 mg/day to AD patients with sleep disorders and sundowning agitation led to improved sleep quality (Brusco et al., 1998). A meta-analysis of randomised controlled trials using melatonin for sleep disorders in dementia concluded that melatonin administration prolonged total sleep time, and marginally improved sleep efficacy; especially when administered for more than four weeks (Xu et al., 2015). Prolonged release melatonin (Circadin) was licensed in the European Union in 2007 for the short-term treatment of primary insomnia in patients aged 55 years and older. The drug is designed to combat age-related decline in melatonin production by mimicking the release pattern of endogenous melatonin (Wade et al., 2010, 2011). It has been shown to

significantly improve sleep latency and quality of sleep in patients with primary insomnia (Lemoine et al., 2007; Lemoine and Zisapel, 2012); also, its long term efficacy and safety data showed that unlike the classical sedative hypnotics, uninterrupted treatment with Circadin can be sustained for up to 3 months without significant undesired effects (Wade et al., 2010, 2011). Melatonin agonists like ramelteon which has a high selectivity for MT₁ and MT₂ receptors, both of which are important in mediating the hypnotic effects of melatonin (Kato et al., 2005) have also been studied. Ramelteon is believed to target sleep onset; and is not associated with rebound insomnia, withdrawal symptoms, or dependence which are common with other hypnotic drugs (Cajochen, 2005; Srinivasan et al., 2011). It has been approved (by the FDA) since 2005 for the treatment of insomnia characterised by difficulty with sleep onset. Following a treatment period of 5-weeks (using 4 mg and 8 mg of ramelteon), significant reductions in sleep onset latency (SOL) and increases in total sleep time (TST) had been reported in elderly outpatients with chronic insomnia (Roth et al., 2006); these effects were confirmed by further studies establishing its efficacy in the management of chronic insomnia (Roth et al., 2007; Mayer et al., 2009) Zammit et al., 2009). Tasimelteon is another melatonin agonist developed for the treatment of circadian rhythm sleep disorders (Rajaratnam et al., 2009; Cardinali et al., 2011) and approved (by the FDA) in 2014 for the treatment of non-24 hour sleep-wake disorder in the blind (Dhillon and Clarke, 2014). Generally, in the management of sleep disorders, melatonin agonists have been associated with better-tolerability and lesser side-effects; however, their suitability for use in patients with dementia will continue to be investigated.

Melatonin, Melatonergic Agents and Dementia-Associated Behavioural Changes

Melatonin, melatonergic agents and dementia-associated cognitive decline

Medications, such as the acetylcholinesterase inhibitor, donepezil slow cognitive decline in some patients with AD; but may cause sleep and behavioural disturbances

(Dauvilliers, 2007). Over the years, in the search for drugs with higher efficacy and improved tolerability, research has looked in the direction of melatonergic agents for combating cognitive decline. An earlier study showed that melatonin therapy is associated with an improved ability to remember previously-learned items in patients with mild cognitive impairment (Jean-Louis et al., 1998). A retrospective study also demonstrated that treatment with melatonin (3-9 mg daily) for 9-18 months improved the Mini Mental Status Exam (MMSE) scores, and the Alzheimer Disease Assessment Scale cognitive subscale scores in patients with mild cognitive impairment (Furio et al., 2007); while another study concluded that a combination of bright light and melatonin treatment might probably attenuate cognitive deterioration in AD (Riemersma Van der Lek et al., 2008). However, a meta-analysis of randomised controlled trials concluded that while melatonin therapy may be effective in improving SE and prolonging TST in patients with dementia, there is no evidence that these add up to significant improvement in cognitive function (Brusco et al., 1998). Presently, there appears to be no data on the efficacy of melatonin agonists in the management of cognitive deficits in dementia. However, based on results obtained with the use of melatonin for mild cognitive impairment (MCI) in AD patients, and the ability of melatonin receptor agonists to improve sleep parameters without impairing memory consolidation; it is likely that these drugs will be useful in improving cognitive function in dementia (Laudon and Frydman-Marom, 2014).

Melatonin, melatonergic agents and depression

Depression in the context of dementia is common, and contributes to poorer outcomes in both patients and caregivers. Estimates of the prevalence of major depression in dementia range from 11-25% (IPA, 2012). Non-pharmacological treatments are the preferred initial approach to management despite the fact that data in support of their efficacy is scarce; therefore, there is always room for pharmacological treatment options (Ford and Almeida, 2017). Generally, antidepressant drugs have been used for the management of depression in patients with dementia. However, depression in patients with

dementias is usually associated with a heterogeneous aetiology, and controversies regarding the efficacy of drugs persist (Chi et al., 2014), notably in patients with PD; therefore, newer agents are always been investigated (Chaudhuri and Schapira, 2009). Melatonin is one of such compounds that show beneficial effects for depression (Mack et al., 2016); and the potential therapeutic effect of melatonin in the management of mood disorders has been demonstrated in several animal models of depression (Mantovani et al., 2003; Detanico et al., 2009; Binfaré et al., 2010). Melatonin was also reported to mitigate depression in a rodent model of PD (Bassani et al., 2014).

Synthetic analogues of melatonin like agomelatine (a known activator of MT1 and MT2 receptors, and an inhibitor of 5HT-2B/5HT-2C receptors) have exhibited good antidepressant efficacy and favourable tolerability profile in acute, short-term, and long-term treatment (Plesničar, 2014). In patients with major depression, agomelatine was of comparable effectiveness to paroxetine, sertraline, venlafaxine and fluoxetine; and was associated with a lower relapse rate when compared to placebo (Dolder et al., 2008; Carney et al., 2011). It is now recommended as an alternative second line agent in the pharmacological management of severe major depression (Ambresin and Gunn, 2014). Agomelatine enhances noradrenaline and dopamine release in the frontal cortex, and also normalises the circadian rhythm. However, while the usefulness of melatonergic agents in mitigating depression in animal models of dementia, and in the general human population is being revealed; their exact role in the management of depression in patients suffering from dementia is yet to be fully understood.

Melatonin, melatonergic agents and anxiety-related behaviours

Generalised anxiety disorder is a common late-life psychiatric disorder with a community prevalence of 2-7%, and of about 10 % in patients presenting to primary care (Beekman et 1998). However, in people with dementia, prevalence of anxiety disorders could go as high 72 % (Ballard et al., 2000). Anxiety is seen in a majority

of patients with AD (Levenson et al., 2014); and 10% to 45% of patients with mild cognitive impairment (MCI) (Lyketsos et al., 2002; Feldman et al., 2004). In patients with PD, it presents as the second most-common mood disorder (Yamanishi et al., 2013). Anxiety may also be one of the first signs of cognitive disorders, and its presence correlates with a faster progression of illness (Taragano and Allegrim 2003; Dillon et al., 2013). In its management, counselling and psychological treatments are generally considered before application of drugs. Pharmacological management of anxiety in dementia patients utilises drugs such as citalopram, sertraline and fluoxetine, which are proven to have a safe profile, and are evidently effective in reducing anxiety; in addition, citalopram appears to improve behavioural symptoms (Badrakalimuthu and Tarbuck, 2012). Benefits that may be derivable from the use of drugs such as clomipramine or imipramine might be offset by their association with cognitive decline. Benzodiazepines also have limited use, because of cognitive side-effects, increased risks of falls, paradoxical agitation, and tolerance; hence, they could be only be considered for a short duration (Pinquart and Duberstein, 2007; Badrakalimuthu and Tarbuck, 2012). Drugs such as clonidine, venlafaxine, mirtazapine, pregabalin and buspirone are also considered under special circumstances. Therefore, till present, pharmacological management of anxiety in dementia is still a major challenge. The role of melatonin in the management of anxiety in dementia patients is not yet defined. However, melatonin's ability to increase gamma-aminobutyric acid (GABA) levels in several brain regions, via its activity at MT₂ receptors (Comai and Gobbi, 2014) is likely to prove useful in this case. An enhanced GABA level generally causes a reduction in anxiety-related behaviours; and this corroborates the results of studies that had reported the anxiolytic effects of melatonin in experimental animals (Onaolapo AY et al., 2017b). Melatonin and melatonergic agents also hold advantage over several other drugs, in that they are more tolerable in both short-term and long-term use and their use will not cause deterioration in cognition. As it stands now, studies into the appropriate use (if any) of melatonergic agents for the management of anxiety in dementia patients are still needed.

Melatonin, Melatonergic Agents as Antioxidative and/or Neuroprotective Agents in Dementia

Melatonin is a well-established antioxidant that exerts its effects through several mechanisms such as: 1) inhibition of nitric oxide synthase leading to reduced production of free radical nitric oxide. 2) stimulation of the production of several antioxidative enzymes, including glutathione 3) reduction of free radical production at the level of the mitochondria in a process called radical avoidance (Reiter et al., 2010). Melatonin also enhances DNA repair capacity in some cells, and through this, it may also counteract free radical activities (Liu et al., 2013). Its anti-amyloidogenic properties are supported by evidences which indicate that melatonin actively decreases levels of soluble plaque-forming amyloid beta (A β) by interfering with its full maturation, thereby making it more prone to proteolytic degradation (He et al., 2010); melatonin also inhibits A β generation, aggregation and formation of amyloid fibril (Hoppe et al., 2010). It also attenuates tau hyper phosphorylation (Hoppe et al., 2010). Considerable evidences are in support of melatonin's neuroprotective effects in animal models of Parkinsonism. Systemic administration of melatonin prevented apomorphine-induced circling behaviour in 6-hydroxydopamine (6-OHDA)-lesioned rats (Dabbeni-Sala et al., 2001); it also potentiated the effects of low dose 1-3,4-dihydroxyphenylalanine (L-DOPA) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced experimental Parkinsonism in mice (Naskar et al., 2013). In a chronic experimental model of Parkinson disease, melatonin administration prevented neuronal death in the nigrostriatal region (Antolin et al., 2002).

In addition to its potential for improvement of sleep quality in AD and other neurodegenerative diseases; the melatonin agonist ramelteon is also believed to have neuroprotective effects (Lauterbach et al., 2010). While it appears to have no intrinsic antioxidant activity, its MT₁/MT₂ receptor-mediated effects on the upregulation of several antioxidant enzymes may be responsible for its neuroprotective effects (Tan et al., 1994; Mathes et al., 2008). Also, in cultured mouse cerebellar granule cells, ramelteon increased the neural content of BDNF; a finding

that supports its potential in the management of neurodegenerative diseases (Imbesi et al., 2008).

MELATONIN AND THE FUTURE OF NEUROCOGNITIVE DISORDERS MANAGEMENT

Melatonin's Possible Role in Stem-Cell Therapy for Dementia

A growing consensus in dementia management is that currently-approved pharmacologic interventions do little to reverse disease progression, probably because they are generally introduced late in the course of disease. Therefore, there are suggestions of novel treatment options that target earlier stages of the disease (possibly before the onset of neurodegeneration and/or overt dementia) (Tong et al., 2015). Stem cell therapy, which has the capacity to generate and replenish the various neuron types implicated in the neurodegeneration process of dementias, has continued to be examined as a potential therapeutic option for reversing neuronal loss in AD. Four types of stem cells that can be generated from the human body and potentially used include: neural, mesenchymal, embryonic and induced pluripotent stem cells (Martínez-Morales et al., 2013). In a number of animal studies, use of the different stem cell types have yielded promising results (Tang et al., 2008; Xuan et al., 2008; Yun et al., 2013; Hallett et al., 2015); although a few, inconsistencies in results, coupled with the risks of the development of tumours, ethical limitations and immune rejection have limited the transition of these animal studies to human trials. More recently however, a number of clinical trials using mesenchymal stem cells (MSCs) were approved. In a recently-completed open-label phase I clinical trial, using intracranially-injected allogeneic human umbilical cord blood-derived MSCs; MSC transplantation did not appear to alter AD pathology or slow cognitive decline over the follow-up period, there was also no obvious evidence of neuroprotection (Kim et al., 2015). Failure to achieve therapeutic goal in this study may not be unrelated to the survival rates of the MSCs that were transplanted in a background of disease. A few studies have demonstrated the efficacy of MSC transplantation in treating cerebral

ischaemia, which was limited by the low survival rate of transplanted MSCs due to the ischaemic microenvironment; however pre-treatment with melatonin was reported to improve survival rates and function (Tang et al., 2014). The role of exogenous melatonin as a possible primer (administered prior to stem cell transplantation) to reduce oxidative stress and facilitate survival of cells also needs to be considered; as studies have shown that melatonin modulated proliferative activity in the dentate gyrus in postnatal rats, increased differentiation of rat midbrain neural stem cells (Kong et al., 2008), and modulated the survival of new neurons in the hippocampus of adult mice (Ramírez-Rodríguez et al., 2009).

Melatonin's Possible Role in Gene-Therapy for Dementia

The presence of the apolipoprotein E-ε4/4 genetic allele has been associated with decreases in melatonin, and this variant allele is strongly correlated with the development of AD (Liu et al., 1999; Grandy, 2013). This and several other genetic and epigenetic defects (Cacabelos et al., 2015) so far identified in dementias allude to the important roles played by genes in the aetiopathogenesis of the disease, as well their possible role in the development of new therapeutic strategies. Gene therapy-based approaches are providing new tools for the study and understanding of neurodegenerative disorders; and they may also prove beneficial in their management. Lentiviruses and more recently, adeno-associated viruses (rAAVs) represent viable viral delivery systems for gene sequences under study (Combs et al., 2016). These viral delivery systems provide control over both temporal and spatial expression of the transduced genes, allowing control over timing (stage in lifespan of animal) of expression of pathology, and the brain sites that exhibit them; also, transduced cells continue to maintain expression of the protein product without additional influences (Combs et al., 2016).

Early studies in mice and rats had used rAAV-2/2 to express full-length human tau with the P301L mutation which led to increased levels of tau protein in the brain that persisted for at least 8 months (Lewis et al., 2000; Klein et al., 2004). Lentiviruses insert themselves into the

host genome and also have a larger capacity for genetic material, and a number of studies had used them to express wild-type or mutant forms of tau protein in various brain regions of rodents (Osinde et al., 2008; Combs et al., 2016). The use of these viral vectors is not only advancing our understanding of neurodegenerative illnesses, but it is also presenting opportunities for potential insertion of desired genetic materials into neurons or other cells; which may lead to improved expression of desired forms of proteins. The NGF is a potent neuroprotective agent for cholinergic neurons, and it is known to improve the function of basal forebrain neurons (Fischer et al., 1987). A phase I clinical trial conducted in AD patients, using an AAV2/2 vector containing full length nerve growth factor (NGF) transgene under control of the CMV/ β -actin promoter and the human polyadenylation signal (Mandel et al., 1999) showed that vector therapy was well-tolerated, generally safe and with no systemic toxicity (Rafii et al., 2014). However, the efficacy of this approach remains to be known, and the application of gene therapy to dementia management is still in its infancy. The role of melatonin as a regulator of gene expression suggests exogenous melatonin might also prove to be of value in this regard, via its potential regulation of transduced genes, and synthesis/release of their protein products.

Also it had been shown that injection of melatonin at physiological concentrations, directly regulates NGF synthesis in the submandibular gland of mouse; leading to significantly increased content of NGF, as detected by immunohistochemistry (Pongsa-Asawapaiboon et al., 1998). Whether this effect is directly attributable to gene up-regulation or not, is not known, and the possibility of this occurring in central neurons is worth further research;

hence, the potential uses of exogenous melatonin in the gene-therapy of dementia is an area that remains to be explored.

CONCLUSION

Research has continued to show that melatonin and melatonergic drugs are likely to eventually occupy a central position in the management of neurocognitive disorders; due to their potentials for influencing symptomatology, progression, or even pathogenesis of the disorders, and play a role in the emergence of novel therapies. While at present, their best-known application is for the management of sleep/circadian rhythm dysfunctions; future research may yield a single melatonin-based 'superdrug' that caters for every aspect of dementia management, avoiding the usage of multiple medications that multiply the risks of side-effects. Also, melatonin-assisted gene or stem-cell therapy targeting brain neurons may encourage melatonin production in other non-pineal brain sites, to manage melatonin deficiency. Therefore, it is expected that research will continue to reveal other possible applications of melatonin-based drugs in neurocognitive disorders management.

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