Can we induce lucid dreams? A pharmacological point of view

Firas Hasan Bazzari

Faculty of Pharmacy, Cairo University, Cairo, Egypt

Summary. The phenomenon of lucid dreaming, in which an individual has the ability to be conscious and in control of his dreams, has attracted the public attention, especially in the era of internet and social media platforms. With its huge popularity, lucid dreaming triggered passionate individuals, particularly lucid dreamers, to spread their thoughts and experiences in lucid dreaming, and provide a number of tips and techniques to induce lucidity in dreams. Scientific research in the field of sleep and dreams has verified the phenomenon of lucid dreaming for decades. Nevertheless, various aspects regarding lucid dreaming are not fully understood. Many hypotheses and claims about lucid dreaming induction are yet to be validated, and at present lucid dreaming still lacks efficient and reliable induction methods. Understanding the molecular basis, brain physiology, and underlying mechanisms involved in lucid dreaming can aid in developing novel and more target-specific induction methods. This review will focus on the currently available scientific findings regarding neurotransmitters' behavior in sleep, drugs observed to affect dreams, and proposed supplements for lucid dreaming, in order to discuss the possibility of inducing lucid dreams from a pharmacological point of view.

Keywords: Lucid dreaming, Dreams, REM sleep, Neurotransmitters, Supplements, Pharmacology of lucid dreaming.

1. Introduction

Lucid dreaming is a unique psychological phenomenon in which a dreaming individual is aware that he/she is dreaming (Voss, 2010). As many other distinctive unfamiliar incidences in science, lucid dreaming has been described as a preposterous beyond-belief phenomenon with a lot of skepticism. However, hypotheses about lucid dreaming have been trailblazing towards becoming close to a fact, with a wide number of individuals from all around the globe coming together to share their experience of lucidity while dreaming. It is also suggested that lucid dreaming has been practiced for centuries and since ancient times as some references may go back to ancient Greek (LaBerge, 1988). However, the term "lucid dream" was first used by the Dutch scientist Frederik van Eeden in his 1913 study "A study of dreams" (Van Eeden, 1913). In a 2016 systematic meta-analysis review assessing 34 published articles in the past 50 years in order to achieve approximate values of lucid dreaming prevalence and frequency. The study analysis obtained a prevalence mean of 55% in all 34 studies and a frequency mean of 23% in a set of 25 studies (Saunders et al., 2016). Multiple methods to induce lucid dreaming have been scientifically evaluated in some empirical studies to test their effectiveness. In a 2012 paper by Stumbrys et al., induction techniques were mainly categorized into; cognitive, external stimulation, and miscellaneous techniques, each containing a number of different methods and labeled according to the method's success rate in inducing lucid dreams. Techniques, such as mnemonic induced lucid dreams (MILD), reflection/reality testing, Tholey's combined technique, light stimulus, and wake back to bed (WBTB) (in combination with MILD), were labeled to be successful methods in inducing lucid dreams based on the findings of available scientific evidence (Stumbrys et al., 2012). Nowadays, lucid dreaming practitioners, who claim to practice and experience lucid dreaming frequently, are becoming more active on various social media platforms, in which they speak out to the public about the benefits of lucid dreaming, such as controlling nightmares and increasing creativity. Nonetheless, what is truly becoming a major concern is promoting products that insinuate their ability to induce lucid dreaming. Even though the products' efficacy is yet to be confirmed and validated, overexcited individuals who want to experience lucid dreaming would seek such products, which could be very dangerous and harmful in some cases. Therefore, the major question to be answered, is the current use of drugs considered a feasible and practical approach to induce lucid dreaming? In order to find a suitable answer for this question, a broad number of aspects related to the mechanism of dreaming should be examined and discussed. In pharmacology, the molecular basis and physiological mechanisms of the body form the targets for drug therapy; in other words, the drug's therapeutic activity is a result of an interaction between the drug and a target in the body, such as a specific enzyme or a receptor. Thus, in order to conclude the potential activity of a drug in inducing lucid dreams, there should be a clear view about its mechanism of action or at least a suggested hypothesis about its mechanism supported by a scientific evidence. This paper will overview several aspects including neurotransmission systems functionality, medical agents affecting dreams, supplements proposed for lucid dreaming, and a discussion of several factors that participate in hindering drug application in lucid dreaming.

Corresponding address:
Firas Hasan Bazzari, Pharmacology & Toxicology Department, El-Manial, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
Email: firas_hasan@rocketmail.com

Submitted for publication: November 2017
Accepted for publication: May 2018

2. Neurotransmitters in sleep & dreams

Neurotransmitters form the molecular basis of any signaling pathway in the brain. Changes in the behavior of neurotransmitters have been linked to many physiological and pathophysiological processes in the human body, some of which are well understood while the majority are surrounded by hypotheses that are yet to be verified. In pharmacology, neurotransmitters are considered vital targets for drug therapy, as various medical agents are available and known to control the levels of neurotransmitters whether to increase or inhibit their activity. This control can be achieved via several pathways on the level of neurotransmitter synthesis, release, receptor activation, reuptake, and enzymatic degradation. For example, antipsychotics used in the treatment of a number mental conditions; bipolar disorder, schizophrenia and others, are identified to exert their action via dopamine inhibition (Glick et al., 2001). Nevertheless, even with selective targeting of a single neurotransmitter; for example, selective serotonin reuptake inhibitors (SSRIs), there are several side effects reported with the use of these medical agents. The major point is that neurotransmission systems are widely distributed (i.e. not in a specific brain region) and function in harmony together in a very complex manner. Generally, a number of neurotransmitters; acetylcholine, histamine, norepinephrine, serotonin, hypocretin also known as "orexin", gamma-aminobutyric acid (GABA), and glutamate, are all suggested to take a part in both consciousness and sleeping (Siegel, 2004). GABA is considered the central player in suppressing neuronal activity and promoting sleep; in contrast, all of the previously mentioned neurotransmitters have, to some extent, an effect on GABAergic transmission; thus, participating in consciousness mechanism (Siegel, 2004). Acetylcholine has been strongly suggested to maintain consciousness and cognitive functions (Woolf & Butcher, 2011). In a 2016 study, the release of acetylcholine and norepinephrine from the ascending fibers is found to be highly active in the state of wakefulness (Becchetti & Amadeo, 2016). Moreover, neuromodulators other than the classic neurotransmitters system, such as nitric oxide (NO), were also suggested to play a role in the wake/sleep cycle (Cudeiro et al., 2000; Gautier-Sauvigné et al., 2005). The proposed mechanism of NO in the wake/sleep cycle is suggested to be via the transition between and maintenance of awaking and rapid eye movement (REM) sleep balance; moreover, it is suggested to have a role in the activation of the cortical cholinergic neurons (Mariño & Cudeiro, 2006). Other studies have also pointed out the potential of NO and adenosine in sleep homeostasis (Kalinchuk et al., 2011).

REM sleep cycle, also known as "paradoxical sleep", is suggested to be the core of dreams; in addition, lucid dreaming is frequently observed to be more prevalent during REM sleep compared to other sleep cycles (Stumbrys & Erlacher, 2012). Moreover, alterations in REM sleep have been linked to the development of some conditions, such as REM sleep behavior disorder (RBD), cataplexy, and narcolepsy (Dauvilliers et al., 2014; Peever et al., 2014). Thus, there has been an increased interest in determining the neuronal circuits involved in REM sleep. The pivotal REM-generating circuit in the brainstem is suggested to be localized in the mesopontine junction, and REM-active neurons can be found in the subcoeruleus nucleus (Fraigne et al., 2015). Furthermore, the dorsal paragigantocellular reticular nucleus in medulla, which contains mainly GABAergic neurons, is suggested to inhibit wake-promoting areas and promote REM-generation (Fraigne et al., 2015). In a suggested scenario of natural REM-generation, muscle paralysis (atonia) during REM is mainly achieved via the inhibition of skeletal motor neurons by GABAergic/glycine neurons in the spinal cord and ventromedial medulla (Brooks & Peever, 2012). While GABA agonists are observed to induce sedation and promote sleep, GABAergic activity in the pontine reticular formation is observed to increase wakefulness (Watson et al., 2012). In mice, blockade of $GABA_A$ receptors in the pontine reticular formation via bicuculline, a $GABA_A$ antagonist, was observed to reduce wakefulness and increase both non-rapid eye movement (NREM) and REM sleep (Flint et al., 2010). Glutamate exerts its excitatory action via binding to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainic acid (KARs), and *N*-methyl-D-aspartate (NMDA) receptors. Glutamatergic neurons constitute the majority of REM-active neurons in subcoeruleus nucleus, which suggests the involvement of glutamate in REM-generation; in addition, glutamate levels have been observed to be higher during REM compared to NREM sleep (Fraigne et al., 2015; Dash et al., 2009). Acetylcholine is suggested to participate in multiple pathways in REM sleep; for instance, cholinergic projections from the laterodorsal tegmental and pedunculopontine tegmental nuclei to the pontine reticular formation is found to promote REM-generation, and endogenous acetylcholine release in the pontine reticular formation is found to be higher during REM sleep compared to NREM or wakefulness (Watson et al., 2012). Moreover, acetylcholine is found to promote/trigger atonia either directly via activating neurons of sublaterodorsal nucleus or indirectly by increasing glutamate activity, which was assessed via using carbachol (a cholinergic agonist) and *in vitro* patch clamp recording (Weng et al., 2014). Despite the fact that acetylcholine was thought to be mandatory for REM sleep initiation, newer investigations suggest that REM-generation is acetylcholine independent (Grace et al., 2014). Nonetheless, blockade of cholinergic activity via scopolamine has reduced NREM to REM transition and lessened theta-oscillations in the hippocampus; thus, suggesting that acetylcholine is critical for maintaining REM sleep, yet it plays a minor role in REM initiation (Grace et al., 2014). Melanin-concentrating hormone neurons that are primarily found in dorsal raphe nucleus, are other REM active neurons. In a rat model, microinjections of melanin-concentrating hormone into the dorsal raphe nucleus has resulted in an elevated number of NRER to REM transitions, which suggests their importance in REM-generation (Lagos et al., 2009).

Generally, other neurotransmitters; serotonin, noradrenaline, dopamine, hypocretin and histamine, are believed to promote wakefulness (Watson et al., 2010). However, their exact effects on sleep architecture are still not unclear. Serotonin has a wide range of various receptors subfamilies ($5\text{-}HT_1$ – $5\text{-}HT_7$), which adds up to the complexity of its underlying mechanisms involved in sleep (Fink & Göthert, 2007). Earlier studies have suggested that serotonin plays a permissive role in sleep; nevertheless, newer evidence observed high levels of serotonin during waking state in most of the cortical and subcortical regions (Portas et al., 2000). In some studies, a number of serotonin receptors that influence REM sleep have been identified; for instance, serotonin activation of; $5HT_{1A}$, $5HT_{1B}$, and $5HT_{2A/2C}$, is suggested to lower REM sleep (Watson et al., 2010). Moreover, serotonin is also found to suppress cataplexy, as serotonin

neurons in the dorsal raphe nucleus are considered the downstream target of hypocretin (Hasegawa et al., 2017). On the other hand, serotonin microinjection into amygdala during NREM reduced the transition latency to REM sleep in rats (Sanford et al., 1995). Dopamine is strongly associated with wakefulness and reduction of both NREM and REM sleep (Isaac & Berridge, 2003; Andersen et al., 2009). Dopamine also participates in RBD pathophysiology via inhibiting dorsal subcoeruleus nucleus neurons, which is suggested to be through its activity on α_2-adrenergic receptors instead of its endogenous receptors (Yang et al., 2014). In a study on patients with Parkinson disease to investigate the role of the dopaminergic system in dream recall, has found that dreams visual vividness positively correlates to the volume of amygdala and the thickness of subcortical medial prefrontal cortex. The study concluded that these findings may suggest the involvement of the dopaminergic system in dream generation and recall (De Gennaro et al., 2016). The noradrenergic system of locus coeruleus is found to promote wakefulness and decrease REM sleep (Watson et al., 2010). Noradrenaline pathway in inhibiting REM sleep is suggested to be by acting on the cholinergic REM-active neurons; however, noradrenaline release is inhibited by GABA for normal REM regulation (Pal & Mallick, 2006). While noradrenaline major action is to inhibit REM sleep, bilateral microinjections of prazosin (α_1-antagonist), clonidine (α_2-agonist), and propranolol (ß-antagonist) into the pedunculopontine tegmentum, a group of cholinergic neurons posterior to substantia nigra and next to the superior cerebellar peduncle, have increased the total time spent in REM sleep (Pal & Mallick, 2006). At last, increased histamine activity has a prominent role in wakefulness regulation (Ramesh et al., 2004). Histamine deficiency in histidine-decarboxylase knockout mice has shown high-amplitude theta wave bursts during REM (Bastianini et al., 2016). Successful dream recall is found to be associated to a higher theta activity in the frontal brain region with values of 5 – 7 Hz, especially after REM morning awakening (Marzano et al., 2011). However, it has been observed that monoamine containing neurons, such as adrenergic, serotonergic, and histaminergic neurons, are highly active during wakefulness and their activity lessen during NREM and further reduced in REM sleep. Therefore, it is thought that they are not essential for REM-generation, but more likely modulate REM expression (Siegel, 2005).

3. Drugs affecting sleep & dreams

In this section, a number of medical agents observed to have an effect on sleep and dreams will be discussed. Medical agents will be categorized according to their major pharmacological classes. The rationale is attempting to determine potential drug candidates for lucid dreaming induction and/or exclude less relevant ones, based on their effects observed in clinical investigations. In addition, clinical findings regarding drugs that target neurotransmitters may enhance the current understanding of the neurotransmission systems' behavior in relation to sleep and dreams.

3.1. Central nervous system drugs

Medical agents in this group have a superior ability to penetrate into the central nervous system (CNS); thus, having more tendency to alter sleep and dreams. Acetylcholinesterase inhibitors (AChEIs) top the list, as they are not only observed to affect dreams but also recommended as substances to enhance dream recall and lucidity with low adverse events (LaBerge, 2004). Their mode of action is to boost cholinergic activity via inhibiting acetylcholinesterase, an enzyme responsible for acetylcholine degradation in the synapses (Colovic et al., 2013). Examples include medical agents used mainly for the treatment of Alzheimer's disease, such as donepezil, rivastigmine, and galantamine (Stumbrys & Erlacher, 2014). Further studies have established more evidence regarding the use of AChEIs; for instance, galantamine administration increased the dreams' length and vividness in lucid dreamers compared to non-galantamine users (Sparrow et al., 2015). The use of serotonergic antidepressants; selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, sertraline, citalopram) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine), has resulted in a reduction of REM sleep duration and an increase REM latency (Winkelman & James, 2004). On the other hand, the withdrawal of; SSRIs, SNRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), led to more vivid dreams incidences (Keks et al., 2016). Antipsychotics effects on sleep are still not clear, while some studies have shown promising findings in reducing nightmares associated with post-traumatic stress disorder, others observed an increase in dreams frequency and nightmares (Adetunji et al., 2005; Stanniland & Taylor, 2000). Loxapine, chlorpromazine, trifluoperazine, and haloperidol, are all observed to increase sleep quantity, decrease sleep latency, prolong REM latency, and lower REM duration (Foral et al., 2011). Dopamine agonists used in the treatment of Parkinson disease are observed to have a general increase in bad dreams and excessive daytime sleepiness (Happe et al., 2001). Chronic treatment with levodopa, a dopamine precursor used in Parkinson disease, has participated in the development of vivid dreams, night terrors, and nightmares (Sharf et al., 1978). Vivid dreams as adverse events were also reported with use of other dopamine agonists, such as ropinirole, bromocriptine, and pramipexole (Im et al., 2003; Pinter et al., 1999). In a study on controlled-release anticonvulsants, carbamazepine, lamotrigine, and gabapentin were used to assess their effects on nocturnal sleep in epileptic patients. The study findings showed that acute administration of carbamazepine has reduced REM sleep and increased REM fragmentation. In contrast, lamotrigine increased REM sleep and decreased percentage of slow-wave sleep (SWS), and gabapentin increased REM sleep duration with a lower number of awakenings (Placidi et al., 2000). Older anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine) tend to lower sleep latency, reduce REM, and increase daytime drowsiness. On the other hand, newer ones (e.g. levetiracetam, lamotrigine, gabapentin) are observed to increase REM sleep (Bazil, 2003). In a case report of a 42-year old woman with bipolar disorder, lamotrigine dose of 100mg/day was observed to lower sleep continuity and increase vivid dream-like experiences; however, lowering lamotrigine dose has ameliorated these events (Uher & Jones, 2006). Such findings may highlight the importance of considering dose-dependent events in order to evaluate the actual effects of drugs. Therefore, it is well recommended to include a range of different drug dose in any futuristic studies intended to test drug-induced lucid dreams. Lastly, benzodiazepines are mainly found to shorten sleep latency, reduce REM sleep, reduce SWS, increase sleep continuity, and daytime somnolence (Bazil, 2003).

3.2. Drugs for cardiovascular conditions

Vivid dreams and nightmares have been reported with the use of beta-blockers (Chrysant et al., 2008). The relative lipophilicity of some beta-blockers; for instance, propranolol, atenolol, metoprolol, and carvedilol, may explain their CNS related adverse events (Bazzari et al., 2018). Their exact effect on sleep cycles and dreams are yet to be determined; nonetheless, they are suggested to have a REM sleep suppressive activity (Thompson et al., 1999). Angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics are also found to induce sleep disturbances (Morgan et al., 2001). Different doses of clonidine, a centrally acting antihypertensive agent (α_2-agonist), were observed to vary in their effects on sleep. Single administration of a small 25µg clonidine dose was observed to significantly increase REM and decrease NREM; in contrast, medium dose of 150µg had the opposite effects. A possible explanation is that the low dose acts pre-synaptically on α_2-adrenergic receptor of noradrenergic neurons in locus coeruleus, which in turn reduces the release of noradrenaline. On the other hand, medium dose acts primarily on post-synaptic neurons (Miyazaki et al., 2004). Other centrally acting agents, such as methyldopa and ketanserin, were observed to induce sleep disturbances and reduce REM sleep (Novak & Shapiro, 1997; Bazzari, 2017).

3.3. Lipid-lowering Drugs

Statins have been investigated for their neuroprotective properties in neurodegenerative diseases (Van der Most et al., 2009). The use of; lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin, has been associated with the development of peripheral neuropathy, insomnia, unusual dreams, and sleep or concentration problems (Clark, 2003). Nevertheless, limited data available to explain their exact mode in precipitating these events.

3.4. Anesthetics

The use of anesthetics has been linked to influence the dreams of patients undergoing medical procedures. Earlier studies have reported that between 1 – 57% of patients were able to recall dreaming during anesthesia (Samuelsson et al., 2008). In a postoperative report of patients underwent cholecystectomy and gastroplasty, anesthesia was induced using thiopental, nitrous oxide (N2O), isoflurane, and fentanyl. Sleep disruption and fragmentation was noted during the first two nights after operations with absence of SWS and REM; however, in the successive 2 – 4 nights REM cycle reappeared in a greater amount than preoperative values with patients reports of having distressing dreams or vivid nightmares (Knill et al., 1990). The incidence of dreams reported was also found to differ significantly regarding anesthetics used, as patients who received total intravenous anesthesia reported to have more dreams (Brandner et al., 1997). In a 2015 randomized-controlled trial, evoked images and suggestions directly prior anesthesia were used in order to assess any influence on dreams content and recall. The study findings showed a significant increase in dream frequency and dream recall in patients who had preoperative suggestions applied before and during anesthesia induction; in addition, formation of dreams and dream recalls were observed to be dependent on the anesthetic technique used. Moreover, the use of these psychological techniques was observed to guide the content of dream recalls with a 90% probability, and increase recallable dream ratio independently from anesthetic method used (Gyulaházi et al., 2015). Many studies have reported on the elevated vivid and recallable dreams incidence during or after anesthesia with propofol and ketamine use (Eer et al., 2009; Blagrove et al., 2009). Generally, ketamine was linked to a prolonged REM sleep; however, propofol possess a REM suppressive activity (Lazic et al., 2017; Kondili et al., 2012). Ultimately, even there is a number of distinct physiological differences between sleep and anesthesia; however, developing evidence suggests that they are more similar than previously thought, and anesthesia may exert its action via the activation of neural circuits commonly related to sleep (Tung & Mendelson, 2004).

3.5. Substances of abuse

Common substances of abuse; alcohol, cocaine, heroin, amphetamines, and opiates, are found to influence individuals' dreams in a phenomenon usually referred to as "Drug Dreams" (Johnson, 2001). This phenomenon is more common in addictive users undergoing detoxification, in which they frequently report dreaming about the drug use and/or drug craving, frequently accompanied with lack of sleep. The upregulation of neurotransmitters receptors due to chronic drug exposure may explain the acute urge of such events; however, these side effects usually ease with time after drugs discontinuation (Christo & Franey, 1999). Alcohol use was observed to suppress REM sleep and increase REM latency; however, acute withdrawal was observed to increase REM sleep and lower overall sleep duration (Brower, 2001). In a rat model, cocaine effects on REM were observed to differ according to the dose; REM decreased with cocaine injections of 5 – 10mg/kg, and increased at lower doses of 2.5 – 5mg/kg (Knapp et al., 2007). Opiates (e.g. morphine) use is generally found to suppress both NREM and REM sleep (de Andrés & Corpas, 1991). In acute heroin withdrawal, EEG data showed a decrease in SWS and REM sleep (Howe et al., 1980). Methylenedioxymethamphetamine also known as "MDMA" or "Ecstasy", was observed to induce a permanent alteration in natural sleep, which is characterized by a shortening in NREM and overall sleep duration (Allen et al., 1993). Lysergic acid diethylamide (LSD) was found to increase REM sleep first and second periods by 30 – 240% and shortening in the following periods with an overall prolongation of REM sleep, when low doses were administered 1 hour before sleep (Passie et al., 2008). N,N-Dimethyltryptamine (DMT) was found to inhibit REM and SWS in healthy individuals (Barbanoj et al., 2008). However, is has been suggested that LSD and DMT-induced psychedelic experiences may share some neuropharmacological similarities with lucid dreaming, as it is argued to be an induced state of consciousness which enhance self-knowledge and psychological insight (Kraehenmann, 2017; Kraehenmann et al., 2017). Phencyclidine also known as "angel dust" was firstly proposed for anesthesia; however, it was abandoned due to its unpleasant side effects (Siegel, 1978). Similar to ketamine in its mode of action on NMDA receptors; vivid dreams, nightmares, frightening hallucinations, and delusions, were reported with the use of phencyclidine (Miller, 1991).

3.6. Medicinal plants

Hypericum perforatum (St. John's wort) was found to increase REM sleep latency with no effects on the other sleep stages (Sharpley et al., 1998). *Valeriana officinalis* (Valerian) use was observed to reduce sleep latency (Leathwood & Chauffard, 1985). Valerian did not show any significant effect on sleep stages; however, elevated delta activity was observed during NREM (Shinomiya et al., 2005). *Ginkgo biloba* (Ginkgo) has been widely used for its cognitive and memory enhancing abilities (Bazzari et al., 2018). Ginkgo was found to promote sleep continuity, reduce number of awakenings, enhancing SWS, and reduce REM sleep (Hemmeter et al., 2001). *Panax ginseng* is suggested to enhance sleep quality with minor effects on SWS and REM sleep (Rhee et al., 1990). *Myristica fragrans* (Nutmeg), commonly used to treat gastrointestinal conditions, such as diarrhea and stomach spasm, is speculated to increase dream recall and dream vividness; however, these claims still lack proper supportive evidence (Nagano, 2008). Olfactory exposure of lavender oil was observed to promote sleep and increase SWS; however, effects on REM sleep varied between genders; decreased in women and increased in men, for unexplained reasons (Goel et al., 2005). *Jasminum officinale* flowers were observed to have a CNS suppressive and sleep promoting activity (Elisha et al., 1988).

3.7. Hormonal supplementation

Hormonal supplementation was found to influence individuals sleep. Decreased overall sleep quality and REM sleep are usually observed in old men with low levels of circulating testosterone (Andersen & Tufik, 2008). However, testosterone supplementation was also observed to impair sleep, increase number of awakenings, and nightmares, in male and female subjects, which suggests that both low and high levels of testosterone may influence sleep (Andersen et al., 2011). Low doses of estradiol administered in women with hot flashes were observed to enhance sleep quality and ameliorate insomnia (Ensrud et al., 2015). Estrogens administration in hypogonadal women was associated with increased REM sleep and lower sleep latency (Schiff et al., 1979). Progesterone was also found to increase sleep quality and duration, which is suggested to be via interacting with GABA; nonetheless, no significant difference was observed in REM sleep (Caufriez & Copinschi, 2016).

3.8. Miscellaneous drugs

First generation antihistamines use is commonly associated with increased nightmares (Pagel, 2010). However, classical antihistamines (e.g. chlorpheniramine, a histamine H1-blocker) were observed to increase REM sleep latency and reduce REM duration (Ozdemir et al., 2014). Nightmares as a side effect were reported with the use of some antimicrobial agents, such as amantadine, ciprofloxacin, erythromycin, fleroxacin, ganciclovir, and gusperimus (Pagel & Helfter, 2003). Dexmedetomidine, a potent α_2-adrenergic agonist used to induce mild/moderate sedation in critically-ill patients, was observed to promote NREM sleep, enhance overall sleep quality, and lessen sleep fragmentation with no significant difference in SWS or REM sleep (Alexopoulou et al., 2014). A study has investigated dexmedetomidine and dreaming during sedation, the study findings have shown a significant reduction in dreams among individuals who received dexmedetomidine (Nirmala et al., 2016). Dextromethorphan, an over-the-counter (OTC) cough suppressants, is sometimes abused by individuals for its over-dose adverse events referred to as "high-state", which is described as a separation from the surrounding environment accompanied with euphoria (Hilmas, 2001). Vivid dreams and hallucinations are common side effects of dextromethorphan (Hilmas, 2001). Dextromethorphan mode of action as a noncompetitive agonist of NMDA receptors may explain the occurrence of such events (Martinak et al., 2017).

4. Supplements for lucid dreaming

A number of synthetic and natural products have been speculated for their potential in inducing or enhancing lucid dreaming. Some of which have been previously mentioned and suggested by Thomas Yuschak (2006) in his book "Advanced Lucid Dreaming: The Power of Supplements". The author provided a number of pharmacokinetic/dynamic properties of these agents in order to find a reasonable link between them and the suggested hypotheses of lucid dreaming. Other supplements may only have poor or anecdotal evidence. However, using the term "supplements" and their OTC availability are perhaps the major reasons behind the huge popularity of these products among the community, as they frequently provide the sense of using safe options with no potential harm. Agents may contribute to lucid dreaming induction in various ways; for instance, reducing sleep latency (i.e. sedative activity), altering neurotransmitters, or via other pathways. This section will provide an overview of the available clinical findings on supplements suggested to induce/enhance lucid dreaming, in order to evaluate their actual potential.

4.1. Huperzine A

Huperzine A is a potent AChEIs, which is naturally derived from *Huperzia serrata*, and used in the management of Alzheimer's disease. In animal studies, huperzine A is found to reduce neuronal inflammation, oxidative stress, and enhance behavioral recovery after repetitive traumatic brain injury in mice (Mei et al., 2017). Furthermore, huperzine A is also observed to have an anticonvulsant activity, antidepressant-like properties, enhanced recent verbal memory, and showed to be effective in ameliorating cognitive impairments associated with neurodegenerative diseases (Ferreira et al., 2016; Du et al., 2017; Solomon et al., 2016). In clinical trials, intense dreams were reported with the use of huperzine A dose of 400 µg/b.i.d (Little et al., 2008). Similar to galantamine in its main mode of action as AChEIs explains the rationale behind its potential in lucid dreaming induction (LaBerge, 2004). However, both agents are observed to differ in their activity on NMDA receptors. Galantamine was observed to potentiate NMDA receptors activity, which is suggested to partially contribute to cognitive and learning enhancement in Alzheimer's disease patients (Moriguchi et al., 2004). On the other hand, huperzine A was found to antagonize NMDA receptors and provide protection against NMDA-induced seizures (Coleman et al., 2008). Unfortunately, even huperzine A is a powerful candidate for lucid dreaming induction/enhancement, yet it still lacks a strong conclusive scientific evidence to support its use in lucid dreaming induction. However, a comparative study of huperzine A and galantamine would be interesting, not only to test huperzine A actual potential, but also to shed some

light on NMDA receptors role in lucid dreaming.

4.2. Alpha-GPC

Alpha-glycerylphosphorylcholine (α-GPC) is a prodrug of choline, an acetylcholine precursor, and considered an essential nutrient to boost acetylcholine levels. In epilepsy, α-GPC use was observed to reduce disruptions of the blood-brain barrier (BBB), lower neuronal death, promote neurogenesis, and enhance cognitive functions (Lee et al., 2017). In theory, elevated acetylcholine activity is linked to lucid dreaming enhancement, such as the case of AChEIs; thus, α-GPC has been suggested in a number of anecdotal findings as a proposed supplement for lucid dreaming. However, α-GPC was tested in a double-blind placebo-controlled trial of 33 individuals with a little to advanced experience in lucid dreaming. The study results showed neither a significant difference in lucid dreaming incidence nor alterations in dream content (Kern et al., 2016). These findings may limit the actual potential of α-GPC as a supplement for lucid dreaming induction.

4.3. Nicotine

Following the same principle of increasing the cholinergic activity for lucid dreaming induction/enhancement, nicotine serves as an exogenous agonist for acetylcholine nicotinic receptors (Gotti et al., 2006). In 2006, a study was conducted on 15 smokers to test the effects of wearing 24-hour transdermal nicotine patches on sleep and dreams. The study results showed an increase in sleep fragmentation, no effects on NREM sleep, reduced REM duration, and an increase in REM-dreams quality with a higher frequency of recallable visual imagery reports (Page et al., 2006). In addition, previous reports have shown that sleep disturbances, such as increased sleep latency, daytime sleepiness, sleep fragmentation, are linked to nicotine stimulation in both male and female smokers (Wetter & Young, 1994). The use of nicotine is controversial due to potential risks associated with its use, such as nicotine dependence observed in smokers. Therefore, risks of using tobacco smoking alternatives in non-smokers are still unclear yet. However, reduced confusion, increased reaction time (assessed via vigilance task performance), and improved total mood, were observed with the use of nicotine transdermal patches 7mg/24hr, with a total time of 6 hours in healthy non-smokers participants (McComas et al., 2015). Nonetheless, further investigations should be undertaken in order to obtain more conclusive findings regarding nicotine use for lucid dreaming.

Varenicline, a drug used for smoking cessation, can possibly be an alternative to nicotine. The nicotinic acetylcholine receptor $\alpha_4ß_2$ subtype is abundant in the human brain, and it is suggested to be responsible for mediating nicotine dependence (Benowitz, 2009). While nicotine exhibits full agonism on $\alpha_4ß_2$, varenicline exerts partial agonistic and competitive inhibition activity with nicotine on $\alpha_4ß_2$ receptors. Varenicline activity on $\alpha_4ß_2$ receptors is found to reduce mesolimbic dopamine release, which results in lowering craving symptoms (Elrashidi & Ebbert, 2014). Despite varenicline partial agonistic activity on heteromeric neuronal nicotinic receptors, it is found to have a potent full-agonistic activity on α_7-nicotinic receptor (Mihalak et al., 2006). Decreased activity of α_7-nicotinic receptors in the human brain was found in a number of neurological and psychiatric disorders. In addition to its acetylcholinesterase inhibition activity, galantamine was also observed to enhance 7-receptors activity (Texidó et al., 2005). In clinical trials, varenicline sleep-related side effects, include; insomnia, sleep fragmentation, NREM parasomnias, REM sleep aggression (similar to RBD), and vivid/lucid dreams (Savage et al., 2015; Patterson et al., 2017). Theoretically, such findings may correlate to varenicline potential in lucid dreaming; nonetheless, it is still a hypothetical assumption that requires further clinical assessment.

4.4. 5-hydroxytryptophan

5-hydroxytryptophan (5-HTP) is an intermediate metabolite in the biosynthesis of the neurotransmitter serotonin from its amino acid precursor L-tryptophan (Kato et al., 1974). 5-HTP is found to be clinically-effective in increasing levels of serotonin in the CNS and suggested to have a number of therapeutic applications, such as depression, chronic headache, and insomnia (Birdsall, 1998). Furthermore, the use of GABA/5-HTP mixture, in a caffeine-treated fruit flies model, was found to be effective in promoting sleep, which is observed through its ability in modulating; sleep episodes, night-time activity, and sleep duration (Hong et al., 2016). In 2012, a dietary supplement product, containing; 5-HTP, *Calea ternifolia*, Vinpocetine, melatonin (as a secondary ingredient), and a number of vitamins, received a patent as a method to promote sleep and lucid dreaming (Luciano, 2012). While the product description presents a summary of the role of its ingredients, limited clinical data provided to support claims about 5-HTP role in lucid dreaming induction. Therefore, 5-HTP is still in need of a robust clinical trial to support its use in lucid dreaming.

"REM sleep rebound" is a common term among lucid dreamers, which is defined as an occurrence of prolonged REM sleep as a result of previous periods of REM suppression (Yuschak, 2006). Elevated levels of serotonin are linked to REM suppression, which can also be observed with the use of serotonergic antidepressants; SSRIs and SNRIs (Ursin, 2002; Winkelman & James, 2004). Moreover, acute withdrawal of serotonergic antidepressants was observed to increase vivid dreams incidence (Keks et al., 2016). Hypothetically, these findings seem consistent with the REM sleep rebound effect; therefore, the use of 5-HTP was proposed as an indirect method to increase REM sleep duration, and in turn, increase the chance of having a lucid dream (Yuschak, 2006). Nonetheless, REM sleep deprivation to achieve REM sleep rebound is a questionable approach. In a number of human and animal studies, REM sleep deprivation has resulted in a number of neurobiological and behavioral alterations, such as increased hyperactivity, aggressiveness, cellular stress, glial dysfunction, impaired spatial memory, and a reduction in BrdU+ hippocampal cells (Soto-Rodriguez et al., 2016). REM sleep suppression was also found to enhance emotional reactivity (Rosales-Lagarde et al., 2012). Regardless of REM deprivation consequences, there is an apparent inconsistency in 5-HTP effects on sleep architecture observed in clinical data. In early investigations, 5-HTP was observed to slightly reduce NREM, increase REM sleep duration, reduce REM latency, increase dreaming frequency and dream recall in human subjects (Mandell et al. 1965; Oswald et al. 1966; Wyatt et al., 1971). However, when 5-HTP was tested in cats, there was a complete absence of REM for 6 hours after 5-HTP administration (Ursin, 1976). While results in animal experiments may not always correlate to humans, 5-HTP was further assessed by Na-

kazawa et al. (1980), in which no effects were observed on sleep stages, except for stage 1, with the use of 200mg/p.o. 5-HTP. However, when individuals were deprived from sleep for one night, followed by administration of 5-HTP on the first recovery night, 5-HTP inhibited SWS rebound for the next two consecutive nights. Moreover, an increase in REM sleep was observed on the second night after both; 5-HTP and sleep deprivation, recovery phase (Nakazawa et al., 1980). Para-chlorophenylalanine (pCPA), a selective irreversible inhibitor of tryptophan hydroxylase that results in a significant depletion of serotonin in the CNS, is commonly used to induce insomnia in animals characterized by a marked inhibition of SWS and REM (Borbély et al., 1981). In numerous studies, 5-HTP administration following pCPA treatment was successful in restoring normal sleep patterns, which gave a rise to the "serotonin sleep theory" (Smith & Kennedy, 2003). An introduced possible explanation is that the depletion of serotonin levels due to sleep deprivation increases the metabolism of 5-HTP and bypass into nerve terminals; in contrast, during normal sleep serotonin levels in the CNS are self-sufficient, which lessen the uptake of exogenous 5-HTP (Nakazawa et al., 1980). Nonetheless, due to the fact that there is no hypnogenic target identified in order to explain 5-HTP activity in restoring sleep following pCAP, the "serotonin sleep theory" was dismissed (Jouvet, 1999). Recent investigations have provided some insight about serotonin role in sleep, as serotonin was found to differentially modulate neurons; GABAergic and glutamatergic, of the ventrolateral preoptic nucleus, which is the main structure responsible for triggering NREM (Sangare et al., 2016). Up to date, the role of serotonin in sleep/wake regulation is still not fully understood and considered a point of debate. Combined all together, there is neither a clear view about the exact 5-HTP molecular mode of action nor a conclusive evidence to support the anecdotal claims about its potential in lucid dreaming.

4.5. Magnesium L-threonate

Magnesium L-threonate (MgT) is a novel compound with a high ability to cross the BBB. Numerous studies have investigated its beneficial role in memory enhancement, neurological conditions with related memory-loss, and synaptoprotective properties (Li et al., 2014; Lou et al., 2017). Generally, magnesium (Mg) has shown efficacy and tolerability in the management of sleep disturbances and anxiety in patients receiving chemotherapy, and it is suggested to be via its relative muscle relaxing activity (Carson, 2017). Furthermore, Mg is also found to be vital in modulating the brain biochemistry, and low dietary intake of Mg has been attached to a number of medical conditions; for instance, depression, apathy, agitation, delirium, anxiety, and confusion (Serefko et al., 2016). Moreover, extracellular Mg+2 ions in the brain were observed to modulate the activity of the NMDA receptor, as reduced Mg+2 levels greatly potentiate NMDA receptor activity and vice versa (Nowak et al., 1984). Reduced NMDA receptor excitatory activity was observed to provide neuroprotection, sedation, induce reversible consciousness loss and loss of righting reflux (Franks, 2008). Mg deficiency was also observed to affect sleep architecture, which is characterized by an increase in light SWS and a decrease in REM sleep duration, in patients with restless leg syndrome caused by Mg deficiency (Popoviciu et al., 1993). At last, Mg major role in enhancing lucid dreaming may only be related to its ability to promote sleep, lower sleep latency, reduce sleep fragmentation, and increase overall sleep quality (Peuhkuri et al., 2012).

4.6. Melatonin

N-acetyl-5-methoxy tryptamine, also known as "melatonin", is a hormone produced by the penial gland, which regulates sleep/wake cycle, circadian rhythm, and has an immune-stimulatory and cytoprotective activity (Hardeland et al., 2006). In sleep and circadian rhythm regulation, melatonin exerts its action via binding to melatonin; MT_1 and MT_2 receptors, found in the suprachiasmatic nucleus (SCN) of the hippocampus (Srinivasan et al., 2009). MT_1 action was observed to inhibit neuronal firing in SCN, while MT_2 was found to inhibit phase shift circadian firing rhythms in the SCN (Dubocovich, 2007). In both human and animal models, melatonin use was found to promote sleep and improve overall sleep quality (Zhdanova et al., 1997; Garfinkel et al., 1995). Melatonin use is also found to affect sleep architecture. In early investigations, the use of 5mg melatonin prior bedtime has increased REM latency, with no alterations in overall REM duration and percentage (James et al., 1987). In addition, using 250mg/q.i.d melatonin for 6 consecutive days has shown a significant increase in stage 2 sleep, and a lesser duration of stage 4 sleep (Anton-Tay, 1974). In a 2004 randomized placebo-controlled trial on individuals with reduced REM sleep duration, the use of 3mg melatonin for 4 weeks significantly improved REM sleep percentage and continuity (Kunz et al., 2004). These findings have led to the suggestion that elevated melatonin levels enhance sleep stages (i.e. stage 2 and REM), in which dreams commonly occur (Kahan et al., 2000). In patients with RBD, melatonin was observed to suppress REM motor activity, yet it did not completely eliminate it; in addition, high doses of melatonin were associated with an increase in nightmares (Howell et al., 2011). In a placebo-controlled study on 22 college students to assess melatonin effects on dreams, the study results have shown an increase in dream recall, vividness, and bizarreness. In addition, there was no effect observed in REM sleep duration; nonetheless, EEG data showed a marked increase in REM density (i.e. high amplitude waves during REM) (Kahan et al., 2000). While the available data may support the anecdotal claims that melatonin promotes REM sleep, and in turn, increase dream frequency and vividness, further investigations should be undertaken in order to confirm such claims.

Melatonin interaction mechanisms with neurotransmitters is still not fully understood. However, the increased interest in melatonin activity in regulating sleep and circadian rhythm has led to the development of a number of medical agents that are more selective and have a higher affinity to melatonin receptors. For instance, tasimelteon, a selective melatonin MT_1 and MT_2 receptors agonist, is the first drug to be approved by the food and drug administration (FDA) in the United States for treating non-24-hour sleep-wake disorder (Lavedan et al., 2015). Tasimelteon possess a unique pharmacological profile, as it is not only a full agonist of melatonin receptors (with more affinity for MT_2) but also did not show any affinity to other pharmacologically related receptors, such as GABAergic, adrenergic, dopaminergic, nicotinic, histamine, serotonin, and many other receptors (Lavedan et al., 2015). Tasimelteon was observed to reduce sleep latency, increase sleep efficiency, and reduce REM sleep latency (i.e. REM occurred more rapidly) in individuals receiving 20, 50, and 100mg tasimelteon compared to

placebo or with a lower dose of 10mg (Bonacci et al., 2015). Furthermore, nightmares and abnormal dreams were also reported with the use of tasimelteon (Leger et al., 2015). These findings may highlight the potential of melatonin receptors selective agonists as target-specific candidates for lucid dreaming. However, further investigations are needed in order to confirm this assumption and to explore their exact underlying mechanisms.

4.7. Herbal supplements

Herbal products are widely used in traditional Chinese and Ayurvedic medicine for the management of various medical conditions. A number of which are identified to have nootropic properties and CNS stimulating/suppressing activity that are commonly observed among users. While some have been observed to affect sleep and sleep architecture in scientific research (see section 3.6.), there was no conclusive evidence to validate their use for dream recall or lucid dreaming. However, isolation and standardization of chemically active components with a clear image of their mode of action, such as huperzine A derived from *Huperzia serrata*, may aid in introducing novel products for lucid dreaming. Up to date, the use of a number of herbal products with relative sedative and sleep-promoting activity (e.g. St. John's wort, valerian, lavender) may explain the anecdotal claims regarding their use for enhancing lucid dreaming.

4.8. B vitamins

A number of B vitamins; B_3, B_6, B_{12}, are observed to influence sleep and dreams via multiple suggested roles. B_3 administration was observed to increase REM sleep and improve sleep quality in patients with moderate/severe insomnia (Robinson et al., 1977). B_3 is biosynthesized from tryptophan via kynurenine pathway; thus, it is speculated that B_3 supplementation would increase the amount of tryptophan available for melatonin and serotonin synthesis (i.e. negative feedback on kynurenine pathway) (Peuhkuri et al., 2012). In a double-blind placebo-controlled study on 12 college students, B_6 is found to increase dream vividness and bizarreness, which is speculated to be via increased cortical arousal during REM (Ebben et al., 2002). Generally, B6 mainly contribute to the synthesis of 5-HTP, and further serotonin, from tryptophan, which may explain their influence on dreams. At last, B_{12} is also found to participate in melatonin synthesis/secretion and regulation of sleep-wake cycle (Peuhkuri et al., 2012). Hypothetically, the use of B vitamins for lucid dreaming seems promising, yet still require further investigations to test their efficacy.

4.9. Homeopathy

Homeopathy is generally referred to as pseudoscience (i.e. misrepresented as true science), which has many practice flaws and lacks any scientific plausibility and evidence (Smith, 2012). In 2015, the Australian National Health and Medical Research Council (NHMRC) published an information paper regarding the effectiveness of homeopathy in health conditions. The paper concluded that homeopathy is not effective in the management of any medical condition and lacks any high-quality placebo-controlled studies to support its use (NHMRC, 2015). Therefore, homeopathy is not a reliable approach for lucid dreaming and, if any, positive outcomes observed with the use of homeopathic products, it may not exceed the "placebo effect".

5. Factors hindering drug application in lucid dreaming

While there are many potential candidates for lucid dreaming, yet, for now, limited evidence available to support their use. This might be due to a number of factors that hinder drugs' use for lucid dreaming, which can either be; individuals, drugs, or research related factors. These factors are summarized in the sections below:

5.1. Individuals related factors

Individuals' variations are critical when it comes to the process of drug discovery and development. Even with a large sample size, there is always a need for pharmacovigilance and post-marketing surveillance for further assessment. Similarly, a number of studies have identified a number of individuals related factors that may influence lucid dreaming. For instance, in a study on students from different nationalities in a Japanese university, there was a significant difference in lucid dreaming incidence between individuals from different countries; in addition to, a difference between individuals unaware about the concept of lucid dreaming compared to individuals who claim they had experienced a lucid dream (Erlacher et al., 2008). Moreover, individuals' personality may also correlate to the frequency of lucid dreaming. Several studies have indicated that a number of the Big Five personality factors, such as neuroticism, openness, and agreeableness, had a small, yet, a significant correlation to lucid dreaming frequency (Schredl & Erlacher, 2004; Hess et al., 2017). Furthermore, age and gender are also found to influence lucid dreaming, as lucid dreaming is found to be negatively correlated to age, and women had a higher lucid dreams recall (Schredl & Erlacher, 2011). In addition to the previously mentioned involuntary factors, a number of individuals' daily-life habits are also found to alter sleep and dreams in general. For example, tobacco smoking and alcohol consumption are both observed to affect sleep and dream (see sections 3.5. & 4.3.). Diet is also found to influence sleep; for example, a diet with high-carbohydrate low-fat content was observed to reduce SWS and increase REM sleep; in contrast, a fat-rich diet with low-carbohydrate percentage had the opposite effects (Peuhkuri et al., 2012). At last, individuals' health status (i.e. healthy vs. non-healthy) is a very important factor to be considered, which may also influence other major factors (i.e. Drugs & Research related factors). As the risk of drugs' toxicity rises in patients with liver and/or renal impairments. In addition, patients with chronic health conditions, who are maintained on certain drugs, may elevate the risk of drug-drug interactions, and, most importantly, patients with CNS disorders who already have a disturbed neurotransmitters' behavior.

5.2. Drugs related factors

Multiple concerns surround the use of medical agents that may influence their efficacy, especially that, there is no clear image about their actual potential for lucid dreaming with a lot of speculations. In a general context, most of the medical agents have a well-established evidence regarding their major mechanism of action, and in some cases, EEG recordings have helped in identifying their effects on sleep

architecture. Nonetheless, the complex nature of the CNS limits the full understanding of all molecular interactions of the drugs and how they correlate to the physiology of sleep and dreams. Moreover, the drug dose is a vital factor that influences its behavior, such as the case of clonidine (see section 3.2.) or medical agents with narrow therapeutic index; therefore, in practice, using different drug doses is well-recommended. Furthermore, drug-delivery into the CNS may not be a major issue, since drug candidates are relatively lipophilic and have the ability to cross BBB. However, it can be an issue if the aim is to target a specific sleep stage (e.g. REM). Pharmaceutical formulations, such as modified or sustained-release formulation, may be a good and simple option compared to other techniques; for instance, waking-up individuals to administer the drug or using intravenous infusions/injections, which may interfere with individuals' sleep and reduce their compliance. Moreover, selective targeting of a particular brain region, such as REM sleep-active neurons in the subcoeruleus nucleus (Fraigne et al., 2015), is not a practical approach in humans. Nonetheless, further investigations using animal models can, to some extent, enhance the understanding of the drugs' local effects on various brain regions and neuronal circuits. Considering a combination of multiple agents, with minimal drug-drug interactions, in order to target multiple neurotransmitters pathways or a combination with sleep enhancers, may aid in promoting lucid dreaming. For example, the lucid dreaming patented supplement product, which contains multiple natural and synthetic agents that are intended to play multiple roles in lucid dreaming induction (see section 4.4.) (Luciano, 2012). However, further studies are required in order to introduce medical agents for lucid dreaming with more target-specificity, clear mode of action, and a standardized dose.

5.3. Research related factors

These factors address the gaps in research between different fields; neurophysiology, neuropharmacology, and sleep research, in regards to lucid dreaming. Despite the huge efforts invested in CNS research for decades, yet no conclusive findings on drug-induced lucid dreaming. Multiple factors have participated in this, one of which is that drugs' effects on sleep and dreams were not within the scope (i.e. endpoints) or a major concern of the majority of previously undertaken clinical research. While in some cases, when medical agents are observed to affect sleep and/or dreams nature, they are usually being reported as side effects of the drug use, such as increased nightmares or vivid dreams, with no further assessment (see sections 3.1. – 3.8.). Even in studies that have used EEG, to assess medical agents reported to alter sleep architecture and dreams, did not address lucid dreaming in their investigations. Moreover, there is a debate in the field of dream research of whether dreams are REM sleep phenomenon or not, and was recently reviewed by Montangero (2018), in which the author presented both sides of the argument supported by evidence. In addition, Montangero has highlighted the consequences of the scientific denial in hindering the progress of dream research (Montangero, 2018). Some studies have reported on lucid dreaming occurrence during NREM sleep; nonetheless, lucid dreaming is observed to be more common during REM and its incidence in NREM is found to be rare and hard to achieve (Stumbrys & Erlacher, 2012). Earlier investigations have provided a decent knowledge about neurotransmitters' behavior, especially during REM sleep, as their activity is more profound compared to NREM. However, further studies should be undertaken to focus more on neural mechanisms during NREM and sleep as a whole, which may aid in explaining the increase in dreams frequency with the use of medical agents that are identified to have a REM suppressive activity, such as propofol (Kim et al., 2011; Kondili et al., 2012).

In the field of lucid dreaming, it is observed that there has been a greater focus on cognitive induction techniques compared to other methods, which is, perhaps, due to over exaggeration by lucid dreamers about the efficacy of such techniques. However, many of which failed to show any significance or conclusive evidence in inducing lucid dreams (Stumbrys et al., 2012; Dyck et al., 2017). While the use of supplements and a number of medical agents for lucid dreaming has recently started to gain some momentum, yet it seems that it is following the same pattern as the previously suggested cognitive techniques. With limited evidence to support their use, the scientific research favorably tends to test these agents based on poor or anecdotal claims surrounding their use. For instance, even with boosting acetylcholine activity hypothesis to support α-GPC use for lucid dreaming, it did not show any promising outcomes (Kern et al., 2016). Testing every single agent claimed to increase lucid dreaming, especially with no theory to back its use, is a time and effort consuming approach. It can be argued that it is better than testing random agents; nonetheless, it may distract researchers from investigating other major players in sleep that may participate in lucid dreaming, such as GABA or glutamate (see section 2.). Since the public has a restricted access to a vast number of drugs and only limited to medical purposes, no claims can be observed about their potential for lucid dreaming. Nevertheless, previous clinical findings serve as a valuable source of data about the drugs' effects on sleep and dreams nature, which may correlate to lucid dreaming. For example, drugs observed to increase dreams' vividness may possibly be candidates to enhance lucid dreaming, and since there is a relatively clear view about their mode of action; hence, they may aid in understanding neural mechanisms mediating lucid dreaming.

6. Conclusion

With the continuous increase in understanding neuronal circuits and neurotransmitters' behavior involved in sleep; in addition to, a wide range of medical agents full of possibilities, there is no doubt that drug application will become a major and more reliable method for lucid dreaming induction in the future. Identifying potential drug candidates for lucid dreaming puts us a one step closer towards achieving successful outcomes. However, extensive investigations should be undertaken, not only in testing various medical agents but also to obtain more knowledge about the underlying mechanisms and the validity of the current hypotheses surrounding lucid dreaming.

Disclaimer

Unless for medical/scientific purposes and under the supervision of medical experts, the author does not promote or support the use of any of the medical agents or supplements mentioned earlier in this paper for lucid dreaming, dream recall, or any other indication. The main and only aim of this paper is to investigate their potential in lucid dream-

ing by exploring the related scientific evidence. The author declares no conflict of interest or received any funding for this work.

References

Adetunji, B., Mathews, M., Williams, A., Budur, K., Mathews, M., Mahmud, J., & Osinowo, T. (2005). Use of antipsychotics in the treatment of post-traumatic stress disorder. Psychiatry (Edgmont), 2(4), 43-47.

Alexopoulou, C., Kondili, E., Diamantaki, E., Psarologakis, C., Kokkini, S., Bolaki, M., & Georgopoulos, D. (2014). Effects of Dexmedetomidine on Sleep Quality in Critically Ill PatientsA Pilot Study. Anesthesiology: The Journal of the American Society of Anesthesiologists, 121(4), 801-807.

Allen, R. P., McCann, U. D., & Ricaurte, G. A. (1993). Persistent effects of (±) 3, 4-methylenedioxymethamphetamine (MDMA,"ecstasy") on human sleep. Sleep, 16(6), 560-564.

Andersen, M. L., Alvarenga, T. F., Mazaro-Costa, R., Hachul, H. C., & Tufik, S. (2011). The association of testosterone, sleep, and sexual function in men and women. Brain research, 1416, 80-104.

Andersen, M. L., Margis, R., Frey, B. N., Giglio, L. M., Kapczinski, F., & Tufik, S. (2009). Electrophysiological correlates of sleep disturbance induced by acute and chronic administration of D-amphetamine. Brain research, 1249, 162-172.

Andersen, M. L., & Tufik, S. (2008). The effects of testosterone on sleep and sleep-disordered breathing in men: its bidirectional interaction with erectile function. Sleep Medicine Reviews, 12(5), 365-379.

Anton-Tay, F. (1974). Melatonin: effects on brain function. Advances in biochemical psychopharmacology, 11, 315-324.

Barbanoj, M. J., Riba, J., Clos, S., Giménez, S., Grasa, E., & Romero, S. (2008). Daytime Ayahuasca administration modulates REM and slow-wave sleep in healthy volunteers. Psychopharmacology, 196(2), 315-326.

Bazil, C. W. (2003). Effects of antiepileptic drugs on sleep structure. CNS drugs, 17(10), 719-728.

Bazzari, A. H., & Bazzari, F. H. (2018). Medicinal plants for Alzheimer's disease: An updated review. Journal of Medicinal Plants Studies, 6(2), 81-85.

Bazzari, F. H., & Bazzari, A. H. (2018). Drug-Induced Delirium: A Mini Review. BMH Medical Journal, 5(2), 51-56.

Bazzari, F. H. (2017). Centrally acting antihypertensive agent Ketanserin potential role in delirium management: A review. Open Science Journal, 2(3).

Benowitz, N. L. (2009). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annual review of pharmacology and toxicology, 49, 57-71.

Birdsall, T. (1998). 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Alternative medicine review: a journal of clinical therapeutic, 3(4), 271-280.

Blagrove, M., Morgan, C. J., Curran, H. V., Bromley, L., & Brandner, B. (2009). The incidence of unpleasant dreams after sub-anaesthetic ketamine. Psychopharmacology, 203(1), 109-120.

Bonacci, J. M., Venci, J. V., & Gandhi, M. A. (2015). Tasimelteon (Hetlioz™) A New Melatonin Receptor Agonist for the Treatment of Non-24-Hour Sleep-Wake Disorder. Journal of pharmacy practice, 28(5), 473-478.

Borbély, A. A., Neuhaus, H. U., & Tobler, I. (1981). Effect of p-chlorophenylalanine and tryptophan on sleep, EEG and motor activity in the rat. Behavioural brain research, 2(1), 1-22.

Brandner, B., Blagrove, M., McCallum, G., & Bromley, L. M. (1997). Dreams, images and emotions associated with propofol anaesthesia. Anaesthesia, 52(8), 750-755.

Brooks, P. L., & Peever, J. H. (2012). Identification of the transmitter and receptor mechanisms responsible for REM sleep paralysis. Journal of Neuroscience, 32(29), 9785-9795.

Brower, K. J. (2001). Alcohol's effects on sleep in alcoholics. Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism, 25(2), 110-125.

Carson, C. (2017). Magnesium oxide supplements for the treatment of post-chemotherapy sleep disturbance. Journal of Clinical Oncology, 35(Suppl 5), 175.

Caufriez, A., & Copinschi, G. (2016). U.S. Patent No. 9,504,697. Washington, DC: U.S. Patent and Trademark Office.

Christo, G., & Franey, C. (1996). Addicts drug-related dreams: their frequency and relationship to six-month outcomes. Substance Use & Misuse, 31(1), 1-15.

Chrysant, S. G., Chrysant, G. S., & Dimas, B. (2008). Current and Future Status of Beta blockers in the Treatment of Hypertension. Clinical cardiology, 31(6), 249-252.

Clark, L. T. (2003). Treating dyslipidemia with statins: the risk-benefit profile. American heart journal, 145(3), 387-396.

Coleman, B. R., Ratcliffe, R. H., Oguntayo, S. A., Shi, X., Doctor, B. P., Gordon, R. K., & Nambiar, M. P. (2008). [+]-Huperzine A treatment protects against N-methyl-D-aspartate-induced seizure/status epilepticus in rats. Chemico-biological interactions, 175(1-3), 387-395.

Cudeiro, J., Rivadulla, C., & Grieve, K. (2000). A possible role for nitric oxide at the sleep/wake interface. Sleep, 32(6), 829-835.

Dash, M. B., Douglas, C. L., Vyazovskiy, V. V., Cirelli, C., & Tononi, G. (2009). Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. Journal of Neuroscience, 29(3), 620-629.

Dauvilliers, Y., Siegel, J.M., Lopez, R., Torontali, Z.A., & Peever, J.H. (2014) Cataplexy – clinical aspects, pathophysiology and management strategy. Nature Reviews Neurology, 10(7), 386–395.

de Andrés, I., & Corpas, I. (1991). Morphine effects in brainstem-transected cats: II. Behavior and sleep of the decerebrate cat. Behavioural brain research, 44(1), 21-26.

De Gennaro, L., Lanteri, O., Piras, F., Scarpelli, S., Assogna, F., Ferrara, M., Caltagirone, C. & Spalletta, G. (2016). Dopaminergic system and dream recall: an MRI study in Parkinson's disease patients. Human brain mapping, 37(3), 1136-1147.

Du, Y., Liang, H., Zhang, L., & Fu, F. (2017). Administration of Huperzine A exerts antidepressant-like activity in a rat model of post-stroke depression. Pharmacology Biochemistry and Behavior, 158, 32-38.

Dubocovich, M. L. (2007). Melatonin receptors: role on sleep and circadian rhythm regulation. Sleep medicine, 8, 34-42.

Dyck, S., Schredl, M., & Kühnel, A. (2017). Lucid dream induction using three different cognitive methods. International Journal of Dream Research, 10(2), 151-156.

Ebben, M., Lequerica, A., & Spielman, A. (2002). Effects of pyridoxine on dreaming: a preliminary study. Perceptual and motor skills, 94(1), 135-140.

Eer, A. S., Padmanabhan, U., & Leslie, K. (2009). Propofol dose and incidence of dreaming during sedation. European Journal of Anaesthesiology, 26(10), 833-836.

Elisha, E. E., Al-Maliki, S. J., & Ibrahem, D. K. (1988). Effects ofJasminum officinale Flowers on the Central Nervous System of the Mouse. International Journal of Crude Drug Research, 26(4), 221-227.

Elrashidi, M. Y., & Ebbert, J. O. (2014). Emerging drugs for the treatment of tobacco dependence: 2014 update. Expert opinion on emerging drugs, 19(2), 243-260.

Ensrud, K. E., Guthrie, K. A., Hohensee, C., Caan, B., Carpenter, J. S., Freeman, E. W., LaCroix, A.Z., Landis, C.A., Manson, J., Newton, K.M. & Otte, J. (2015). Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. Sleep, 38(1), 97-108.

Erlacher, D., Schredl, M., Watanabe, T., Yamana, J., & Gantzert, F. (2008). The incidence of lucid dreaming within a Japanese university student sample. International Journal of Dream Research, 1(2), 39-43.

Ferreira, A., Rodrigues, M., Fortuna, A., Falcão, A., & Alves, G. (2016). Huperzine A from Huperzia serrata: a review of its sources, chemistry, pharmacology and toxicology. Phytochemistry reviews, 15(1), 51-85.

Fink, K. B., & Göthert, M. (2007). 5-HT receptor regulation of neurotransmitter release. Pharmacological reviews, 59(4), 360-417.

Flint, R. R., Chang, T., Lydic, R., & Baghdoyan, H. A. (2010). GABAA receptors in the pontine reticular formation of C57BL/6J mouse modulate neurochemical, electrographic, and behavioral phenotypes of wakefulness. Journal of Neuroscience, 30(37), 12301-12309.

Foral, P., Knezevich, J., Dewan, N., & Malesker, M. (2011). Medication-induced sleep disturbances. The Consultant Pharmacist®, 26(6), 414-425.

Fraigne, J. J., Torontali, Z. A., Snow, M. B., & Peever, J. H. (2015). REM sleep at its core–circuits, neurotransmitters, and pathophysiology. Frontiers in neurology, 6, 123.

Franks, N. P. (2008). General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nature Reviews Neuroscience, 9(5), 370-386.

Garfinkel, D., Laudon, M., Nof, D., & Zisapel, N. (1995). Improvement of sleep quality in elderly people by controlled-release melatonin. The Lancet, 346(8974), 541-544.

Gautier-Sauvigné, S., Colas, D., Parmantier, P., Clement, P., Gharib, A., Sarda, N., & Cespuglio, R. (2005). Nitric oxide and sleep. Sleep medicine reviews, 9(2), 101-113.

Glick, I., Murray, S., Vasudevan, P., Marder, S., & Hu, R. (2001). Treatment with atypical antipsychotics: new indications and new populations. Journal of psychiatric research, 35(3), 187-191.

Goel, N., Kim, H., & Lao, R. P. (2005). An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiology International, 22(5), 889-904.

Gotti, C., Zoli, M., & Clementi, F. (2006). Brain nicotinic acetylcholine receptors: native subtypes and their relevance. Trends in pharmacological sciences, 27(9), 482-491.

Grace, K. P., Vanstone, L. E., & Horner, R. L. (2014). Endogenous cholinergic input to the pontine REM sleep generator is not required for REM sleep to occur. Journal of Neuroscience, 34(43), 14198-14209.

Gyulaházi, J., Varga, K., Iglói, E., Redl, P., Kormos, J., & Fülesdi, B. (2015). The effect of preoperative suggestions on perioperative dreams and dream recalls after administration of different general anesthetic combinations: a randomized trial in maxillofacial surgery. BMC anesthesiology, 15(1), 11.

Happe, S., Berger, K., & FAQT Study Investigators. (2001). The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease. Journal of neurology, 248(12), 1062-1067.

Hardeland, R., Pandi-Perumal, S. R., & Cardinali, D. P. (2006). Melatonin. The international journal of biochemistry & cell biology, 38(3), 313-316.

Hasegawa, E., Maejima, T., Yoshida, T., Masseck, O. A., Herlitze, S., Yoshioka, M., Sakurai, T. & Mieda, M. (2017). Serotonin neurons in the dorsal raphe mediate the anticataplectic action of orexin neurons by reducing amygdala activity. Proceedings of the National Academy of Sciences, 114(17), E3526-E3535.

Hemmeter, U., Annen, B., Bischof, R., Brüderlin, U., Hatzinger, M., Rose, U., & Holsboer-Trachsler, E. (2001). Polysomnographic effects of adjuvant ginkgo biloba therapy in patients with major depression medicated with trimipramine. Pharmacopsychiatry, 34(02), 50-59.

Hess, G., Schredl, M., & Goritz, A. (2017). Lucid Dreaming Frequency and the Big Five Personality Factors. Imagination, Cognition and Personality, 36(3), 240-253.

Hilmas, E. (2001). Adolescent dextromethorphan abuse. Toxalert. Maryland Poison Center: University of Maryland School of Pharmacy, 18, 1-3.

Hong, K., Park, Y., & Suh, H. (2016). Sleep-promoting effects of a GABA/5-HTP mixture: Behavioral changes and neuromodulation in an invertebrate model. Life sciences, 150, 42-49.

Howe, R. C., Hegge, F. W., & Phillips, J. L. (1980). Acute heroin abstinence in man: I. Changes in behavior and sleep. Drug & Alcohol Dependence, 5(5), 341-356.

Howell, M. J., Arneson, P. A., & Schenck, C. H. (2011). A novel therapy for REM sleep behavior disorder (RBD). Journal of clinical sleep medicine, 7(6), 639-644A.

Im, J. H., Ha, J. H., Cho, I. S., & Lee, M. C. (2003). Ropinirole as an adjunct to levodopa in the treatment of Parkinson's disease. Journal of neurology, 250(1), 90-96.

Isaac, S. O., & Berridge, C. W. (2003). Wake-promoting actions of dopamine D1 and D2 receptor stimulation. Journal of Pharmacology and Experimental Therapeutics, 307(1), 386-394.

James, S. P., Mendelson, W. B., Sack, D. A., Rosenthal, N. E., & Wehr, T. A. (1987). The effect of melatonin on normal sleep. Neuropsychopharmacology, 1(1), 41-44.

Johnson, B. (2001). Drug dreams: a neuropsychoanalytic hypothesis. Journal of the American Psychoanalytic Association, 49(1), 75-96.

Jouvet, M. (1999). Sleep and serotonin: an unfinished story. Neuropsychopharmacology, 21(S1), 24S.

Kahan, T., Hays, J., Hirashima, B., & Johnston, K. (2000). Effects of melatonin on dream bizarreness among male and female college students. Sleep and Hypnosis, 2(2), 74-83.

Kalinchuk, A., McCarley, R., Porkka Heiskanen, T., & Basheer, R. (2011). The time course of adenosine, nitric oxide (NO) and inducible NO synthase changes in the brain with sleep loss and their role in the non rapid eye movement sleep homeostatic cascade. Journal of neurochemistry, 116(2), 260-272.

Kato, Y., Nakai, Y., Imura, H., Chihara, K., & Ohgo, S. (1974). Effect of 5-hydroxytryptophan (5-HTP) on plasma prolactin levels in man. The Journal of Clinical Endocrinology & Metabolism, 38(4), 695-697.

Keks, N., Hope, J., & Keogh, S. (2016). Switching and stopping antidepressants. Australian prescriber, 39(3), 76-83.

Kern, S., Appel, K., Schredl, M., & Pipa, G. (2017). No effect of α GPC on lucid dream induction or dream contentKeine Wirkung von α GPC auf die Induktion von Klarträumen oder Trauminhalte. Somnologie, 21(3), 180-186.

Kim, D. K., Joo, Y., Sung, T. Y., Kim, S. Y., & Shin, H. Y. (2011). Dreaming in sedation during spinal anesthesia: a comparison of propofol and midazolam infusion. Anesthesia & Analgesia, 112(5), 1076-1081.

Knapp, C. M., Datta, S., Ciraulo, D. A., & Kornetsky, C. (2007). Effects of low dose cocaine on REM sleep in the freely moving rat. Sleep and biological rhythms, 5(1), 55-62.

Knill, R. L., Moote, C. A., Skinner, M. I., & Rose, E. A. (1990). Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. Anesthesiology, 73(1), 52-61.

Kondili, E., Alexopoulou, C., Xirouchaki, N., & Georgopoulos, D. (2012). Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. Intensive care medicine, 38(10), 1640-1646.

Kraehenmann, R. (2017). Dreams and psychedelics: neurophenomenological comparison and therapeutic implications. Current neuropharmacology, 15(7), 1032-1042.

Kraehenmann, R., Pokorny, D., Aicher, H., Preller, K. H., Pokorny, T., Bosch, O. G., Seifritz, E. & Vollenweider, F. X. (2017). LSD Increases Primary Process Thinking via Serotonin 2A Receptor Activation. Frontiers in pharmacology, 8, 814.

Kunz, D., Mahlberg, R., Müller, C., Tilmann, A., & Bes, F. (2004). Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. The Journal of Clinical Endocrinology & Metabolism, 89(1), 128-134.

LaBerge S. Lucid dreaming in western literature. InConscious mind, sleeping brain 1988 (pp. 11-26). Springer, Boston, MA.

LaBerge, S., 2004. Substances that enhance recall and lucidity during dreaming. U.S. Patent Application 10/604,138.

Lagos, P., Torterolo, P., Jantos, H., Chase, M. H., & Monti, J. M. (2009). Effects on sleep of melanin-concentrating hormone (MCH) microinjections into the dorsal raphe nucleus. Brain research, 1265, 103-110.

Lavedan, C., Forsberg, M., & Gentile, A. J. (2015). Tasimelteon: a selective and unique receptor binding profile. Neuropharmacology, 91, 142-147.

Lazic, K., Petrovic, J., Ciric, J., Kalauzi, A., & Saponjic, J. (2017). REM sleep disorder following general anesthesia in rats. Physiology & behavior, 168, 41-54.

Leathwood, P. D., & Chauffard, F. (1985). Aqueous extract of valerian reduces latency to fall asleep in man. Planta medica, 51(02), 144-148.

Lee, S. H., Choi, B.Y., Kim, J.H., Kho, A.R., Sohn, M., Song, H.K., Choi, H.C., & Suh, S.W. (2017). Late treatment with choline alfoscerate (l-alpha glycerylphosphorylcholine, -GPC) increases hippocampal neurogenesis and provides protection against seizure-induced neuronal death and cognitive impairment. Brain research, 1654, 66-76.

Leger, D., Quera-Salva, M. A., Vecchierini, M. F., Ogrizek, P., Perry, C. A., & Dressman, M. A. (2015). Safety profile of tasimelteon, a melatonin MT1 and MT2 receptor agonist: pooled safety analyses from six clinical studies. Expert opinion on drug safety, 14(11), 1673-1685.

Li, W., Yu, J., Liu, Y., Huang, X., Abumaria, N., Zhu, Y., Huang, X., Xiong, W., Ren, C., Liu, X. G., & Chui, D. (2014). Elevation of brain magnesium prevents synaptic loss and reverses cognitive deficits in Alzheimer's disease mouse model. Molecular brain, 7(1), 65.

Little, J. T., Walsh, S., & Aisen, P. S. (2008). An update on huperzine A as a treatment for Alzheimer's disease. Expert opinion on investigational drugs, 17(2), 209-215.

Lou, Z., Chen, W., Xue, W., Ding, J., Yang, Q., & Wang, H. (2017). Dietary intake of magnesium-L-threonate alleviates memory deficits induced by developmental lead exposure in rats. RSC Advances, 7(14), 8241-8249.

Luciano, J. (2012). U.S. Patent No. 8,092,840. Washington, DC: U.S. Patent and Trademark Office.

Mandell, M. P., Mandell, A. J., & Jacobson, A. (1965). Biochemical and neurophysiological studies of paradoxical sleep. Recent advances in biological psychiatry, 7, 115-122.

Mariño, J., & Cudeiro, J. (2006). How does the brain wake up? The nitric oxide blow. Revista de neurologia, 42(9), 535-541.

Martinak, B., Bolis, R. A., Black, J. R., Fargason, R. E., & Birur, B. (2017). Dextromethorphan in Cough Syrup: The Poor Man's Psychosis. Psychopharmacology bulletin, 47(4), 59-63.

Marzano, C., Ferrara, M., Mauro, F., Moroni, F., Gorgoni, M., Tempesta, D., Cipolli, C. & De Gennaro, L. (2011). Recalling and forgetting dreams: theta and alpha oscillations during sleep predict subsequent dream recall. Journal of Neuroscience, 31(18), 6674-6683.

McComas, M., Harvey, A., & Hahn, B. (2015, December). Relationship Between the Effects of Nicotine on Subjective State and Vigilance Task Performance in Healthy Nonsmokers. In NEUROPSYCHOPHARMACOLOGY (Vol. 40, pp. S354-S355). Macmillan Building, 4 Crinan St, London N1 9xw, England: Nature Publishing Group.

Mei, Z., Zheng, P., Tan, X., Wang, Y., & Situ, B. (2017). Huperzine A alleviates neuroinflammation, oxidative stress and improves cognitive function after repetitive traumatic brain injury. Metabolic Brain Disease, 1-9.

Mihalak, K. B., Carroll, F. I., & Luetje, C. W. (2006). Varenicline is a partial agonist at 4 2 and a full agonist at 7 neuronal nicotinic receptors. Molecular pharmacology, 70(3), 801-805.

Miller, N. S. (1991). The Pharmacology of Phencyclidine. In The Pharmacology of Alcohol and Drugs of Abuse and Addiction (pp. 259-264). Springer, New York, NY.

Miyazaki, S., Uchida, S., Mukai, J., & Nishihara, K. (2004). Clonidine effects on all night human sleep: Opposite action of low and medium dose clonidine on human NREM–REM sleep proportion. Psychiatry and clinical neurosciences, 58(2), 138-144.

Montangero, J. (2018). Dreaming and REM-sleep: History of a scientific denial whose disappearance entailed a reconciliation of the neuroscience and the cognitive psychological approaches to dreaming. International Journal of Dream Research, 11(1), 30-45.

Morgan, T. O., Anderson, A. I., & MacInnis, R. J. (2001). ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. American journal of hypertension, 14(3), 241-247.

Moriguchi, S., Marszalec, W., Zhao, X., Yeh, J. Z., & Narahashi, T. (2004). Mechanism of action of galantamine on N-methyl-D-aspartate receptors in rat cortical neurons. Journal of Pharmacology and Experimental Therapeutics, 310(3), 933-942.

Nagano, I. (2008). Myristica fragrans: an exploration of the narcotic spice. The Entheogen Review. Vernal Equinox, 16(1):15-24.

NHMRC (2015, March). NHMRC Statement on Homeopathy and NHMRC Information Paper - Evidence on the effectiveness of homeopathy for treating health conditions. Retrieved from https://www.nhmrc.gov.au/guidelines-publications/cam02

Nirmala, B. C., Sowmya, G., Supriya, D. P., & Vinita, V. T. (2016). A comparative study of sedation with dexmedetomidine or midazolam during spinal anesthesia. AAnaesth Pain & Intensive Care, 20(3), 328-333.

Nakazawa, Y., Hasuzawa, H., Kotorii, T., Ohkawa, T., Sakurada, H., Nonaka, K., & Dainoson, K. (1980). Study on the Effects of L 5HTP on the Stages of Sleep in Man as Evaluated by Using Sleep Deprivation. Psychiatry and Clinical Neurosciences, 34(2), 83-87.

Novak, M., & Shapiro, C. M. (1997). Drug-induced sleep disturbances. Drug safety, 16(2), 133-149.

Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., & Prochiantz, A. (1984). Magnesium gates glutamate-activated channels in mouse central neurones. Nature, 307(5950), 462-465.

Oswald, I., Ashcroft, G. W., Berger, R. J., Eccleston, D., Evans, J. I., & Thacore, V. R. (1966). Some experiments in the chemistry of normal sleep. The British Journal of Psychiatry, 112(485), 391-399.

Ozdemir, P. G., Karadag, A. S., Selvi, Y., Boysan, M., Bilgili, S. G., Aydin, A., & Onder, S. (2014). Assessment of the effects of antihistamine drugs on mood, sleep quality, sleepiness, and dream anxiety. International journal of psychiatry in clinical practice, 18(3), 161-168.

Page, F., Coleman, G., & Conduit, R. (2006). The effect of transdermal nicotine patches on sleep and dreams. Physiology & behavior, 88(4-5), 425-432.

Pagel, J. F. (2010). Drugs, dreams, and nightmares. Sleep Medicine Clinics, 5(2), 277-287.

Pagel, J. F., & Helfter, P. (2003). Drug induced nightmares—an etiology based review. Human Psychopharmacology: Clinical and Experimental, 18(1), 59-67.

Pal, D., & Mallick, B. N. (2006). Role of noradrenergic and GABA-ergic inputs in pedunculopontine tegmentum for regulation of rapid eye movement sleep in rats. Neuropharmacology, 51(1), 1-11.

Passie, T., Halpern, J. H., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: a review. CNS Neuroscience & Therapeutics, 14(4), 295-314.

Patterson, F., Grandner, M. A., Malone, S. K., Rizzo, A., Davey, A. & Edwards, D. G. (2017). Sleep as a Target for Optimized Response to Smoking Cessation Treatment. Nicotine & Tobacco Research, ntx236.

Peever, J., Luppi, P. H., & Montplaisir, J. (2014). Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. Trends in neurosciences, 37(5), 279-288.

Peuhkuri, K., Sihvola, N., & Korpela, R. (2012). Diet promotes sleep duration and quality. Nutrition research, 32(5), 309-319.

Pinter, M. M., Pogarell, O., & Oertel, W. H. (1999). Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. Journal of Neurology, Neurosurgery & Psychiatry, 66(4), 436-441.

Placidi, F., Diomedi, M., Scalise, A., Marciani, M. G., Romigi, A., & Gigli, G. L. (2000). Effect of anticonvulsants on nocturnal sleep in epilepsy. Neurology, 54(5 Suppl 1), S25-32.

Popoviciu, L., A gian, B., Delast-Popoviciu, D., Alexandrescu, A., Petru iu, S., & Bagathal, I. (1993). Clinical, EEG, electromyographic and polysomnographic studies in restless legs syndrome caused by magnesium deficiency. Revue Roumaine de Neurologie et Psychiatrie.

Portas, C. M., Bjorvatn, B., & Ursin, R. (2000). Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. Progress in neurobiology, 60(1), 13-35.

Ramesh, V., Thakkar, M. M., Strecker, R. E., Basheer, R., & McCarley, R. W. (2004). Wakefulness-inducing effects of histamine in the basal forebrain of freely moving rats. Behavioural brain research, 152(2), 271-278.

Rhee, Y. H., Lee, S. P., Honda, K., & Inoué, S. (1990). Panax ginseng extract modulates sleep in unrestrained rats. Psychopharmacology, 101(4), 486-488.

Robinson, C. R., Pegram, G. V., Hyde, P. R., Beaton, J. M., & Smythies, J. R. (1977). The effects of nicotinamide upon sleep in humans. Biological psychiatry, 12(1), 139-143.

Rosales-Lagarde, A., Armony, J. L., del Río-Portilla, Y., Trejo-Martínez, D., Conde, R., & Corsi-Cabrera, M. (2012). Enhanced emotional reactivity after selective REM sleep deprivation in humans: an fMRI study. Frontiers in behavioral neuroscience, 6, 25.

Samuelsson, P., Brudin, L., & Sandin, R. H. (2008). BIS does not predict dreams reported after anaesthesia. Acta Anaesthesiologica Scandinavica, 52(6), 810-814.

Sanford, L. D., Tejani-Butt, S. M., Ross, R. J., & Morrison, A. R. (1995). Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. Archives italiennes de biologie, 134(1), 81-99.

Sangare, A., Dubourget, R., Geoffroy, H., Gallopin, T., & Rancillac, A. (2016). Serotonin differentially modulates excitatory and inhibitory synaptic inputs to putative sleep-promoting neurons of the ventrolateral preoptic nucleus. Neuropharmacology, 109, 29-40.

Saunders, D. T., Roe, C. A., Smith, G., & Clegg, H. (2016). Lucid dreaming incidence: A quality effects meta-analysis of 50 years of research. Consciousness and cognition, 43, 197-215.

Savage, R. L., Zekarias, A., & Caduff-Janosa, P. (2015). Varenicline and abnormal sleep related events. Sleep, 38(5), 833-837.

Schiff, I., Regestein, Q., Tulchinsky, D., & Ryan, K. J. (1979). Effects of estrogens on sleep and psychological state of hypogonadal women. Jama, 242(22), 2405-2407.

Schredl, M., & Erlacher, D. (2004). Lucid dreaming frequency and personality. Personality and Individual Differences, 37(7), 1463-1473.

Schredl, M., & Erlacher, D. (2011). Frequency of lucid dreaming in a representative German sample. Perceptual and motor skills, 112(1), 104-108.

Serefko, A., Szopa, A., & Poleszak, E. (2016). Magnesium and depression. Magnesium research, 29(3), 112-119.

Sharpley, A. L., McGavin, C. L., Whale, R., & Cowen, P. J. (1998). Antidepressant-like effect of Hypericum perforatum (St John's wort) on the sleep polysomnogram. Psychopharmacology, 139(3), 286-287.

Shinomiya, K., Fujimura, K., Kim, Y., & Kamei, C. (2005). Effects of valerian extract on the sleep-wake cycle in sleep-disturbed rats. Acta Med Okayama, 59(3), 89-92.

Siegel, J. (2004). The neurotransmitters of sleep. Journal of Clinical Psychiatry, 65(Suppl 16), 4-7.

Siegel, J. M. (2005). REM sleep. Principles and practice of sleep medicine, 4, 120-135.

Siegel, R. K. (1978). Phencyclidine and ketamine intoxication: a study of four populations of recreational users. NIDA Res Monogr, 21(21), 119-147.

Smith, K. (2012). Homeopathy is unscientific and unethical. Bioethics, 26(9), 508-512.

Smith, R. L., & Kennedy, C. H. (2003). Increases in avoidance responding produced by REM sleep deprivation or serotonin depletion are reversed by administration of 5-hydroxytryptophan. Behavioural brain research, 140(1-2), 81-86.

Solomon, T., Leech, J., deBros, G., Murphy, C., Budson, A., Vassey, E., & Solomon, P. (2016). A randomized, double blind, placebo controlled, parallel group, efficacy study of alpha BRAIN® administered orally. Human Psychopharmacology: Clinical and Experimental, 31(2), 135-143.

Soto-Rodriguez, S., Lopez-Armas, G., Luquin, S., Ramos-Zuñiga, R., Jauregui-Huerta, F., Gonzalez-Perez, O., & Gonzalez-Castañeda, R. E. (2016). Rapid eye movement sleep deprivation produces long-term detrimental effects in spatial memory and modifies the cellular composition of the subgranular zone. Frontiers in cellular neuroscience, 10, 132.

Sparrow, G. S., Hurd, R., & Carlson, R. (2016). Assessing the perceived differences in post-Galantamine lucid dreams vs. non-Galantamine lucid dreams. International Journal of Dream Research, 9(1), 71-74.

Srinivasan, V., Pandi-Perumal, S. R., Trahkt, I., Spence, D. W., Poeggeler, B., Hardeland, R., & Cardinali, D. P. (2009). Melatonin and melatonergic drugs on sleep: possible mechanisms of action. International Journal of Neuroscience, 119(6), 821-846.

Stanniland, C., & Taylor, D. (2000). Tolerability of atypical antipsychotics. Drug safety, 22(3), 195-214.

Stumbrys, T., & Erlacher, D. (2012). Lucid dreaming during NREM sleep: Two case reports. International Journal of dream research, 5(2), 151-155.

Stumbrys, T., & Erlacher, D. (2014). The science of lucid dream induction. Lucid Dreaming: New Perspectives on Consciousness in Sleep, 1, 77-102.

Stumbrys T, Erlacher D, Schädlich M, Schredl M (2012). Induction of lucid dreams: A systematic review of evidence. Consciousness and Cognition, 21(3),1456-1475.

Texidó, L., Ros, E., Martín Satué, M., López, S., Aleu, J., Marsal, J., & Solsona, C. (2005). Effect of galantamine on the human 7 neuronal nicotinic acetylcholine receptor, the Torpedo nicotinic acetylcholine receptor and spontaneous cholinergic synaptic activity. British journal of pharmacology, 145(5), 672-678.

Thompson, D. F., & Pierce, D. R. (1999). Drug-induced nightmares. Annals of Pharmacotherapy, 33(1), 93-98.

Tung, A., & Mendelson, W. B. (2004). Anesthesia and sleep. Sleep medicine reviews, 8(3), 213-225.

Uher, R., & Jones, H. M. (2006). Hallucinations during lamotrigine treatment of bipolar disorder. American Journal of Psychiatry, 163(4), 749-750.

Ursin, R. (1976). The effects of 5-hydroxytryptophan andl-tryptophan on wakefulness and sleep patterns in the cat. Brain research, 106(1), 105-115.

Ursin, R. (2002). Serotonin and sleep. Sleep medicine reviews, 6(1), 55-67.

Van der Most, P. J., Dolga, A. M., Nijholt, I. M., Luiten, P. G., & Eisel, U. L. (2009). Statins: mechanisms of neuroprotection. Progress in neurobiology, 88(1), 64-75.

Van Eeden, F. (1913). A study of dreams. Proceedings of the Society for Psychical Research, 26(47), 431-461.

Voss, U. (2010). Lucid dreaming: Reflections on the role of introspection. International Journal of Dream Research, 3(1), 52-53.

Watson, C. J., Baghdoyan, H. A., & Lydic, R. (2010). Neuropharmacology of sleep and wakefulness. Sleep medicine clinics, 5(4), 513-528.

Watson, C. J., Baghdoyan, H. A., & Lydic, R. (2012). Neuropharmacology of sleep and wakefulness: 2012 update. Sleep medicine clinics, 7(3), 469-486.

Weng, F. J., Williams, R. H., Hawryluk, J. M., Lu, J., Scammell, T. E., Saper, C. B., & Arrigoni, E. (2014). Carbachol excites sublaterodorsal nucleus neurons projecting to the spinal cord. The Journal of physiology, 592(7), 1601-1617.

Wetter, D. W., & Young, T. B. (1994). The relation between cigarette smoking and sleep disturbance. Preventive medicine, 23(3), 328-334.

Winkelman, J. W., & James, L. (2004). Serotonergic antidepressants are associated with REM sleep without atonia. Sleep, 27(2), 317-321.

Woolf, N., & Butcher, L. (2011). Cholinergic systems mediate action from movement tohigher consciousness. Behavioural brain research, 221(2), 488-498.

Wyatt, R. J., Zarcone, V., Engelman, K., Dement, W. C., Snyder, F., & Sjoerdsma, A. (1971). Effects of 5-hydroxytryptophan on the sleep of normal human subjects. Clinical Neurophysiology, 30(6), 505-509.

Yang, N., Zhang, K. Y., Wang, F. F., Hu, Z. A., & Zhang, J. (2014). Dopamine inhibits neurons from the rat dorsal subcoeruleus nucleus through the activation of 2-adrenergic receptors. Neuroscience letters, 559, 61-66.

Yuschak, T. (2006). Advanced Lucid Dreaming, The Power of Supplements. Lulu Enterprises, Raleigh.

Zhdanova, I. V., & Wurtman, R. J. (1997). Efficacy of melatonin as a sleep-promoting agent. Journal of Biological Rhythms, 12(6), 644-650.