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REVIEW

Melatonin in drug addiction and addiction management: Exploring an evolving multidimensional relationship

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Abstract

Melatonin is a pleiotropic signalling molecule that regulates several physiological functions, and synchronises biological rhythms. Recent evidences are beginning to reveal that a dysregulation of endogenous melatonin rhythm or action may play a larger role in the aetiology and behavioural expression of drug addiction, than was previously considered. Also, the findings from a number of animal studies suggest that exogenous melatonin supplementation and therapeutic manipulation of melatonin/melatonin receptor interactions may be beneficial in the management of behavioural manifestations of drug addiction. However, repeated exogenous melatonin administration may cause a disruption of its endogenous rhythm and be associated with potential drawbacks that might limit its usefulness. In this review, we examine the roles of melatonin and its receptors in addictive behaviours; discussing how our understanding of melatonin's modulatory effects on the brain rewards system and crucial neurotransmitters such as dopamine has evolved over the years. Possible indications(s) for melatonergic agents in addiction management, and how manipulations of the endogenous melatonin system may be of benefit are also discussed. Finally, the potential impediments to application of melatonin in the management of addictive behaviours are considered.

Key words: Dopamine; Drug dependence; Biological rhythms; Neuroplasticity; Brain reward

Core tip: Melatonin is a pleiotropic signalling molecule that regulates several physiological functions, and synchronises biological rhythms. Recent evidences are beginning to reveal that a dysregulation of endogenous melatonin rhythm or action may play a larger role in the aetiology and behavioural expression of drug addiction, than was previously considered. This review, using inf-

ormation garnered from extant literature, examines the roles played by melatonin and its receptors in addictive behaviours, addiction related changes in brain chemistry and brain plasticity; and its possible benefits in the management of drug associated withdrawal syndrome, relapse and behavioural sensitisation.

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INTRODUCTION

Drug addiction or substance use disorder has been defined as a chronic disease of the brain which is characterised by uncontrollable and compulsive drug-seeking and use; and which is associated with the development of a negative emotional state in the absence of drug access[1,2]. There have been suggestions that drug addiction is both a social and a medical problem dating as far back as recorded human history[3] and which continues to be a cause for global health concern[4]. Reports suggest that an estimated total of 246 million people, or approximately 1 in 20 people aged between 15 and 64 years were exposed to illicit drug in 2013; with surveys showing that approximately 1 in 10 of these have a drug-addiction problem[5]. Substance use disorder is arguably a serious public health issue, with a significant economic and health burden on affected individuals and their families[5]. There is also a significant societal burden measured in lost productivity, lawlessness, crime and increased health-care costs. Substance-use disorders have also been associated with worsening of co-morbid psychiatric and/or medical illness, risky behaviours and increasing mortality. While the global and economic burden of addiction continues to increase worldwide, current psychopharmacological therapies are falling short of the desired goals of therapy[6,7].

Over the past few centuries, several theories (social, biological or psychological) have been proposed to aid in understanding the aetiology of drug addiction[8]. Also, while the distinct aetiological bases for drug addiction are yet unclear, advances in neuroscience have continued to aid our understanding of the possible mechanisms that underlie the alterations in emotional balance and decision-making ability that occur with drug addiction[9]. Genetic, environmental, neurodevelopmental and sociocultural factors have been listed as important contributors to the development of drug addiction[10]. These factors have also been shown to increase the susceptibility of an individual to initiation or sustenance of drug use; and potentiate the development of structural brain changes that perpetuate drug use and are characteristic of drug addiction[9,11,12].

Presently, there is a growing body of evidence associating disruptions in circadian rhythms and circadian genes with the development and progression of drug addiction[13,14]. Studies in human subjects have demonstrated circadian rhythm disruptions in individuals with addiction, with suggestions that environmental and/or genetic alteration of the normal sleep wake cycle increases vulnerability to drug use[13,15]. Studies in rodents have also demonstrated that diurnal variations in the behavioural responses to different addiction paradigms exist[16-18]. In rodents, an increase in cocaine self-administration, and the intake of drugs of abuse have been observed at night[16,17,19,20]. There have also been suggestions that the continued craving for drugs of abuse is potentiated through the entrainment of the circadian clock[16,21,22].

Melatonin is a neurohormone that is important in the entrainment of circadian rhythms, as well as in the modulation of behaviour and physiological functioning in all mammals[23]. Some studies have observed a reduction in melatonin levels, and a delay in attaining its nocturnal peak concentration in alcohol-dependent humans and rodents[23]. Studies have also demonstrated melatonin's ability to modulate the reinforcing effects of a number of drugs of abuse with suggestions that it may play a crucial role in drug addiction[24]. In this review, we examine the roles of melatonin and its receptors in drug addiction, by discussing how our understanding of melatonin's modulatory effects on the brain reward system and crucial neurotransmitters such as dopamine has evolved over the years. Possible indications(s) for melatonergic agents in addiction management, and how manipulations of the endogenous melatonin system may be of benefit are also discussed. Finally, the potential impediments to application of melatonergic agents in the management of addictive behaviours are considered.

Neurobiological and neurochemical basis of drug addiction

Substance dependence can be described as a disorder which involves the motivational systems of the brain[25]. Repeated exposure to drugs of abuse has been linked to the development of long-lasting alterations in brain structure and neuronal circuitry. In the last decade or more, studies have demonstrated that repeated use of addictive drugs can alter the neural circuitries that are involved in reward/ motivation, learning/memory, affect, stress response and decision-making[26]. These regions which include the ventral tegmental area (VTA), nucleus accumbens (NAc) and amygdala form a part of the mesolimbic dopaminergic system and are important in reward-related processes[27]. Adaptations in cortical regions, including the prefrontal cortex, orbitofrontal cortex and the anterior cingulate gyrus, which form the mesocortical pathway, have also been implicated in addiction[28]. Increase in dopamine release in the mesolimbic or mesocortical brain regions have been sug-

gested to occur in parallel, appearing to mediate different phases or aspects of drug addiction. The mesolimbic regions (amygdala and hippocampus) have been linked to mediating conditioned learning in addiction; while the prefrontal cortex, orbitofrontal cortex and the anterior cingulate gyrus mediate executive control and emotional response to drugs[26].

Chronic drug use has also been associated with alterations in the "anti-reward" pathway which include the hypothalamic-pituitary-adrenal axis[29,30]. Adaptations in stress response, involving levels of corticosterone cortisol releasing factor and the adrenocorticotrophic hormone have also been reported to occur with drug addiction[31,32].

Brain neurotransmitter/neuromodulator changes also occupy a central role in the establishment, management and extinction (or otherwise) of addictive behaviours. In the brain, the neurochemical targets for a number of drugs of addiction have been identified[33]. Also, while the pharmacological profiles of the drugs of addiction are diverse, drug-receptor interactions can largely explain the wide range of physiological and behavioural changes that occur with drug use[26]. Also, there have been reports that suggest that despite the diversity of behavioural responses, drugs of addiction may share a common reward neural circuitry. Studies have shown that most of the addictive drugs appear to activate the reward system, directly or indirectly stimulating dopamine release[34,35].

Research has shown that dopaminergic (DA) neurons that project from the VTA to the NAc play a crucial role in the processing of stimuli associated with substance-related reward[36]. As a part of their pharmacological effects, substances with abuse potentials stimulate the brain reward system by increasing DA release from the NAc[37]. Also, there are reports that drugs of abuse induce their initial reinforcing effect by stimulating supraphysiologic levels of DA in the NAc. These DA surges (acting *via* D1 receptors) activate the striatal pathway (direct), while inhibiting the striato-cortical pathway (indirect) through D2 receptors[10]. Repeated drug use has also been associated with triggering neuroplastic changes that involve the glutamatergic inputs to the striatum and midbrain DA neurons, these alterations enhance the ways the brain reacts to drug cues, weakening self-regulation, reducing sensitivity to non-drug rewards and increasing sensitivity to stress[10].

There is also ample scientific evidence to suggest that there are DA-independent reinforcement pathways in the acute rewarding or pleasurable effects of addictive drugs. A number of studies in animals have shown that alcohol, opioids, nicotine and amphetamines may produce reinforcing effects *via* DA-independent mechanisms[38-40].

The involvement of some other neurochemicals and neuromodulators such as opioids, gamma-aminobutyric acid, glutamate, noradrenaline, cannabinoids and serotonin in drug addiction have also been suggested[41]. Reports from brain imaging studies have demonstrated an increase in opioid receptors density in persons experiencing withdrawal from alcohol[42], opioids[43] and cocaine[44]. Studies have also shown that the corticostriatal glutamate pathway may be important in the initiation and/or expression of a number of addictive behaviours; examples include conditioned place preference, drug seeking behaviour and locomotor sensitisation[45]. The overall conclusion is that although a number of neurotransmitters and neuromodulators are involved in the short-term reinforcing effects of addictive drugs; the dopaminergic reward pathway is central to the reinforcing properties of drugs and the initiation of the cycle of addiction. However, other mediators are believed to exert their influence *via* dopamine modulation[26,41].

The roles played by neuropeptides in addiction-related behaviours have also been examined; and for the most part, neuropeptides including signalling molecules like substance P, endogenous opioids, and neuropeptide Y have been studied extensively as possible therapeutic targets for addiction management[26].

Drug addiction and circadian rhythm/gene abnormalities

There is ample scientific evidence to suggest the importance of chronological events like the biological rhythms in determining response to drugs of abuse. Earlier studies have argued that chronobiological variables including time of day, sleep-wake patterns and light-dark cycles may modulate the development and maintenance of drug addiction[46]. More recent evidences derived from animal models suggest and support the existence of strong links between appetitive processes and various circadian genes[47]. Also, while details of the exact mechanisms are still being studied; it is becoming more obvious that a strong relationship exists between disturbance of circadian rhythms (as a result of factors like alteration of normal light-dark cycle) and the development of addiction[48].

It also appears that circadian phase-shifting activities such as repeated travels across time zones may influence the pattern of consumption of certain substances with addictive potentials; and this has also been demonstrated in experimental animals[49]. Using male Sprague-Dawley rats, Doyle *et al*[49] studied the effects of experimentally-induced chronic jet lag on methamphetamine consumption; and concluded that pre-exposure to methamphetamine (*via* 2 wk of forced consumption through drinking water) was associated with a significantly higher consumption of methamphetamine in phase-shifted rats (four consecutive 6-h advancing phase shifts of the light-dark cycle) during the second week following abstinence, when compared to those with undisturbed rhythms[49].

Earlier studies in humans had observed that drug-seeking behaviours are probably linked to mutations in certain key genes that are related to circadian rhythm maintenance; suggesting a link between abnormalities of circadian rhythm maintenance and addiction[47]. However, the associations between these genetic alterations and addiction have also been demonstrated in animals by using specific experimental paradigms. In male

Wistar rats, a month of constant light exposure exerts a significant effect on voluntary consumption of morphine, exhibition of withdrawal symptoms, plasma concentration of melatonin [evaluated by enzyme-linked immunosorbent assay (ELISA)] and the mRNA expression of period homolog genes (Per1, Per2) and dopamine (D1) receptors in the striatum and prefrontal cortex[48]. One month exposure to constant light caused a significant decrease in melatonin concentration, an upregulation of mRNA levels of Per2 and D1 receptor in the striatum and prefrontal cortex, up-regulation of Per1 gene in the striatum of rats under constant light (in comparison to those under standard light cycle), increased morphine consumption and preference ratio, and also a significant increase in severity of naloxone-induced withdrawal syndrome[48]. In humans, more studies are beginning to demonstrate that core genes that are involved in circadian rhythm maintenance are also important regulators of reward-related behaviours which occur in response to common substances of abuse[50]. On the other hand, substance use has been known to cause disruptions in circadian rhythms and affect functions such as the sleep/wake cycle; hence, the relationship that exists between substance abuse/addiction and circadian rhythm abnormalities is bidirectional, such that one could lead to the other, and vice versa. Also, abnormalities of sleep and circadian rhythms appear intimately linked to substance abuse, and they could appear as either predictors or consequences of substance abuse[47]. Documented effects of substance use on sleep is not only dependent on the class of agents, but also on the phase of usage, with acute sleep effects, chronic sleep effects, and sleep effects due to withdrawal or abstinence being described. Acute ingestion of drugs such as cocaine and amphetamine which have stimulant effects have been associated with a light, restless and disrupted sleep[51]; while ingestion of drugs with depressant effects such as benzodiazepines, alcohol and opiates can have an initial sleep-promoting effect (increased daytime sleepiness and reduced sleep latency) but sleep disruptions (increased night awakenings) later in the night, as a result of acute withdrawal effects[51,52].

There are reports that chronic use of substances may alter sleep quality and quantity in ways that are similar across different substances[53]. Extended sleep onset latency (SOL), a reduction in total sleep time (TST), increased frequency of night-time awakenings, reduced slow-wave sleep (SWS) and rapid eye movement (REM) sleep have all been described[47]. However, withdrawal from alcohol or stimulants may be associated with distinct time-related changes in pattern of TST and REM sleep[51,54]. Acute withdrawal from substance use may also be associated with sleep disturbances such as extended SOL, reduced TST, and reduced SWS[51]. Also, sleep disturbances such as REM sleep disturbances may continue weeks into abstinence; and polysomnographic evidences in cocaine-dependent participants still show increased SOL, and decreased TST, SWS, and REM sleep[55]. In heavy marijuana users, polysomnography had shown that over two weeks of abstinence, increases in wake time after sleep onset (WASO) and decreases in TST, sleep efficiency and REM sleep had been observed[56]. A persistence of sleep disturbances is believed to be a risk factor for relapse[55,56]. Overall, the relationship between circadian rhythm abnormalities/sleep disorders and addiction/substance abuse appears to be a complex one; with one pair increasing the predisposition to the other pair, and vice-versa.

MELATONIN

Melatonin is an endogenously-produced indolamine that is predominantly secreted by the pineal gland, and widely recognised as a regulator of several physiological functions. Melatonin production is controlled by the photoperiod through the suprachiasmatic nucleus (SCN), with production peaking at night and being at its lowest in daytime. In mammals, melatonin is a master synchroniser of biological rhythms, a regulator of physiological processes such as cardiac function; and an important modulator of behaviours, body posture and balance[57-59]. Fluctuations in melatonin levels (in a 24 h period) tune the body's cellular activities to the actual time-of-day; and while high levels of melatonin potentiate behaviours and physiological functions associated with darkness, low levels attenuate such behaviours and functions[23].

In biological systems, melatonin's effects are exerted *via* interactions with melatonin receptors (MT_1 and MT_2), orphan nuclear receptors, and intracellular proteins like calmodulin[60-62]. As an ampiphillic molecule, melatonin is capable of autocrine, paracrine and endocrine signalling; and it permeates several body compartments to exert effects on a variety of functions such as diurnal/seasonal rhythms, reproduction, neurobehaviour, antioxidant defense and general immunity.

Over the years, exogenous melatonin and melatonin analogues have been known to have an established role in the management of a range of sleep disorders. However, melatonin's therapeutic application is not limited to the central nervous system; and research has continued to shed light on the potential use of melatonergic drugs for the management of an increasing number of disorders/diseases including respiratory ailments such as asthma, pneumonias, chronic obstructive airway diseases, pleural cavity diseases, vascular pulmonary disease, and even lung cancer[63] Melatonin administration had also been shown to be protective against intestinal ischaemic-reperfusion injury in young male Sprague-Dawley rats[64] and Wistar albino rats[65].

From the foregoing, it is obvious that due to its unique chemical characteristics and diverse effects, melatonin may be useful in the management of several human diseases/disorders including those of the central nervous system such as drug addiction. Therefore, a better understanding of melatonin's role in addiction might open a new door in addiction management.

Melatonin and drug addiction

The roles played by circadian rhythm/gene abnormalities in the development or entrainment of addiction–related behaviours, or in potentiating changes in neurohormone, neuromodulator or neurotransmitter levels which result in the development of addiction are well-documented[24]. Melatonin's role in the entrainment of circadian rhythms is also well-documented. Observations that alcohol consumption altered the circadian profile of melatonin production in alcohol-dependent humans and alcohol drinking rodents[66,67] have also increased interests in the importance of melatonin in addiction[23].

Studies by Uz *et al*[68], and Kurtuncu *et al*[69] demonstrated loss of diurnal variation in cocaine-induced locomotor sensitisation and cocaine-induced place-preference respectively, in melatonin-deficient pinealectomised mice, suggesting that the cocaine-induced diurnal variations were mediated by melatonin[68,69]. There have also been reports suggesting that (drug-induced) hypothermic responses to injections of morphine, nicotine or ethanol varied with the light-dark cycle[70]. There have been suggestions that disturbances in sleep observed after months of abstinence in humans with alcohol-dependence could be linked to delayed peak of melatonin's nocturnal rise and lower melatonin levels[68,71]. Studies in rodents have also demonstrated similar alterations[67], further buttressing the role of the melatonergic system in drug addiction.

The effects of exogenous melatonin in modulating behavioural responses to specific drugs of abuse have also been studied. Vengeliene *et al*[23] demonstrated that administration of melatonin modulates alcohol-seeking or wanting and/or relapse-like drinking behaviours[23]. Results of *in vitro* electrophysiological studies have also shown that in cerebellar neurons, nicotine-stimulated currents decreased with application of increasing concentrations of melatonin[72]. Markus *et al*[73] also reported nocturnal elevations of melatonin-mediated nicotine-induced glutamate release by cerebellar neurons[73]. Finally, studies have demonstrated that melatonin is able to modulate the reinforcing or relapsing effects of certain drugs of abuse[23,24].

Melatonin receptors and drug addiction

Melatonin exerts its effects on behaviours and physiological functions largely *via* the melatonin (MT) receptors 1 and 2[74,75]. Also, while research has continued to demonstrate the possible roles that melatonin may play in drug addiction, including modulation of the development of dopaminergic behaviours, like drug-seeking behaviours or psychostimulant-induced diurnal locomotor sensitisation; the contributions of melatonin receptors, especially as it relates to specific drugs, are still being evaluated[23]. Research has demonstrated the presence of the MT1 receptor subtype in a number of brain regions, including areas like the prefrontal cortex, hippocampus, nucleus accumbens and amygdala which have been associated with regulating the effects of addictive drugs or behaviours[76,77]. Uz *et al*[76] studied the expression pattern of MT1 receptors in the dopaminergic system of the human and rodent brain, and observed the presence of MT1 receptor in these regions of the post-mortem human brain; while in the mouse brain, they observed a diurnal variation (high protein levels and low mRNA at night) in the expression of the mouse MT1 receptor in the dopaminergic system[76]. A few studies have also observed an increase in melatonin receptor-related cyclic AMP in the mesolimbic dopaminergic system[62]. In another study, prolonged treatment with antidepressants and cocaine was associated with alteration in the content of melatonin receptor mRNA, with the effects of these drugs on MT1/MT2 mRNAs being brain region-specific[78]; however, prolonged cocaine use did not alter MT2 receptor expression[78,79]. There have been reports suggesting that genetic deletion of MT1 and MT2 receptors abolished the development and expression of methamphetamine-induced locomotor sensitisation[79], and methamphetamine-induced reward[80] in melatonin-expressing C3H/HeN mice. Uz *et al*[68] however reported that MT1, and not MT2 receptor was required for cocaine-induced locomotor sensitisation in rodents. In another study by Hutchinson *et al*[81], this time comparing the differences in locomotor sensitisation observed following a single dose of methamphetamine in low melatonin-expressing C57BL/6 wild-type and MT1 knockout mice, to melatonin-proficient C3H/HeN mice; it was reported that methamphetamine pre-treatment induced locomotor sensitisation during the light period in C3H and C57 wild-type mice. A diminution in magnitude of sensitisation in C57 mice in the dark period, and a complete abrogation in the MT1 receptor knockout (MT1KO) mice was observed; buttressing the role of MT1 receptors in the possible management of drug addiction[81]. On the other hand, MT2 receptors have been linked to the modulation of hippocampal-dependent long-term potentiation; with a few studies demonstrating loss of long-term potentiation in transgenic mice deficient of MT2 receptors[82]. There were also reports of loss of experience–dependent short term latency to enter the closed arm on the second day of elevated plus maze exposure; a feature which suggests that MT2 receptors may play an important role in modulating memory processes and hippocampal synaptic plasticity[82]. These properties may prove useful in the management of addiction-related neuroplasticity.

MELATONIN AND THE PHARMACOLOGIC MANAGEMENT OF DRUG ADDICTION

Information garnered from years of research into the aetiopathogenesis of addiction point to the conclusion that drug-dependence is a multifactorial behavioural and biological disorder, which is amenable to medical treatment. The current treatment protocol for drug

use disorders involves the use of psychosocial and pharmacological interventions[5]. The main goals of management include: (1) reduction of drug use and drug craving; (2) improvement of general wellbeing and functioning of the individual; and (3) decreasing the risk of the development of complications and/or recurrence[5]. However, currently-available treatment options remain inadequate, with varying addiction relapse rates, depending on the drugs involved[83,84]. Thankfully, advances in science and research are opening new vistas for possible therapeutic interventions, and as such, current research interests are directed at developing or discovering new treatments options like the use of melatonin (a regulator of the circadian rhythm and potent antioxidant) that could be beneficial in reducing craving/withdrawal period and preventing relapse.

The ability of melatonin to mitigate different aspects of addiction neurobiology has been examined extensively. Studies have reported the efficacy of melatonin supplementation in the control of drug-seeking behaviour, opiate withdrawal/ relapse[24], behavioural sensitisation[84,85], regulation of the sleep and or circadian rhythm disorders[86], neuroplasticity, and prevention of: Mitochondrial-induced autophagy, apoptosis, oxidative stress and neurotoxic injury[84] in brain areas linked to reward and emotionality.

Melatonin, withdrawal syndrome and relapse

Prolonged use or abuse of drugs (such as opioids) by humans have been linked to the development of physical dependence and/or addiction, which is usually associated with alterations in brain biochemistry and hormone levels; and disruption of the sleep/wake cycle[87-89]. Also, sudden clearance or reduction in the plasma concentration of opioids of abuse results in withdrawal symptoms, including circadian rhythm disturbances like insomnia, jitteriness and restlessness[90,91]. Studies in animals have reported that chronic morphine administration resulted in a reduction in total activity within a 24 h period, and a dampening of the circadian amplitude in locomotor activity rhythm[92,93]. Abrupt withdrawal of morphine administration in rats has also been associated with sustained disruption of the circadian rhythms in locomotor activity, and alterations in plasma melatonin, β-endorphin, corticosterone, adenocorticothrophic hormone, and orexin concentrations[93-95]. Studies have also reported evidence of anxiety-related behaviour following cocaine withdrawal[96].

The possible effects of melatonin on withdrawal symptoms have also been examined; and while there is a dearth of clinical trials, studies in rodents have demonstrated its effectiveness. Zhdanova and Giorgetti[96] assessed the effects of melatonin supplementation on cocaine-induced anxiety-like behaviour and nucleus accumbens cyclic adenine monophosphate (AMP) levels in rats. In their study, melatonin (200 ng/mL) was administered in drinking water (at night) to groups of rats that had been exposed to repeated cocaine administration (15 mg/kg *i.p.*), or during its withdrawal. Results showed that melatonin caused a reduction in anxiety-like behaviour in a defensive withdrawal paradigm, 48 h after the last injection of cocaine[96]. Melatonin pretreatment also attenuated the augmentation of cAMP levels in the nucleus accumbens following acute administration of cocaine. These results suggest that a low-dose night-time melatonin treatment was effective in militating against symptoms of cocaine-withdrawal in rats[96]. Bondi *et al*[97] conducted a single-centre, randomised, double-blind, placebo-controlled, parallel-group trial to assess the effect of melatonin (5 mg) compared to placebo as adjuvant treatment (alongside behavioural and pharmacotherapy) on weekly self-reported severity of depression, anxiety, stress, and insomnia complaints in recovering substance use disorder subjects males (aged 18 years or older) who were at a residential program. Results showed no significant differences were observed for baseline characteristics; although the frequency of reported adverse events was higher in the melatonin group[97]. The authors were of the opinion although the diversity of medication regimens and behavioural interventions provided increase the complexity of assessing melatonin's efficacy with regards to the measured outcome, there is insufficient evidence to demonstrate melatonin's benefits as an adjuvant in addiction recovery[97].

The use of melatonin for its antioxidant effects during recovery from drug abuse has also been studied. The naloxone-induced heroine withdrawal syndrome has been associated with derangement in antioxidant enzymes and bio-elements which are essential for the maintenance of life[98]. Cemek *et al*[98] examined the effect of melatonin supplementation on the levels of antioxidant enzymes and bio elements in naloxone induced heroine withdrawal syndrome and reported a reversal in heroine withdrawal related alteration in glutathione, catalase levels, and the levels of bio elements (iron, manganese, magnesium, aluminium, calcium and copper). The researchers concluded that exogenous melatonin could be effective in militating bio element and antioxidant enzyme derangements in heroine withdrawal syndrome[98].

A very powerful challenge to drug addiction treatment is the high incidence of drug- use relapse during abstinence[99]. However, years of extensive clinical and preclinical research on drug-use relapse[100,101] have done little to reduce relapse rates[83,102]. Reports from a number of studies have reported that drug-use relapse is usually triggered by acute exposure to the self-administered drug[103], stress[102], the presence of drug-related cues and contexts[104], and protracted periods of withdrawal or exposure to cure that have been previously associated with withdrawal[105]. Extensive research work has led to the identification of possible cellular, neurotransmitter, and/or receptor mediated mechanisms that increase the risk of relapse to drug-use with the intent of identifying novel pharmacological treatment options[106-108]. Takahashi *et al*[24] assessed

the effects of melatonin supplementation (administered at either 25 or 50 mg/kg body weight) on cocaine self-administration and relapse-like behaviours in male Sprague-Dawley rats (which had been exposed to long-term cocaine self-administration training). Behavioural parameters measured included the motivation for cocaine self-administration in the break point test, relapse-like behaviour in the cue-induced reinstatement test, sucrose preference and distance travelled in the open field. Results showed a reduction in the cocaine-seeking behaviour and the desire to self-administer cocaine. The researchers concluded that melatonin supplementation could be beneficial in reducing relapse[24].

Melatonin, addiction-related behavioural sensitisation, neuroplasticity and neurotoxicity

Chronic intermittent use of cocaine and a number of other psychostimulants have been associated with the development of a progressive, long-lasting enhancement of psychomotor effects which have been referred to as cocaine or psychostimulant sensitisation. Studies have demonstrated that behavioural sensitisation to psychostimulants is associated with an increase in nitric oxide synthase[109]. While examining the effect of melatonin on cocaine-induced behavioural sensitisation in rats, Sircar[85] reported that: (1) acute or repeated melatonin injections on its own did not affect locomotor behaviour in rats; (2) acute melatonin pre-exposure augmented the acute locomotor effects of cocaine; and (3) repeated melatonin pre-exposure prevented the development of cocaine induced behavioural sensitisation, while a single injection of melatonin did not halt behavioural sensitisation in rats already sensitised to cocaine. Sircar[85] concluded that while melatonin supplementation increased cocaine's acute behavioural effects and prevented the development of cocaine's behavioural sensitisation, it had no effect in militating fully-developed cocaine behavioural sensitisation[85]. Itzhak *et al*[110] studied the effects of melatonin supplementation on the development of methamphetamine (METH)-induced behavioural sensitisation and reported that pre-treatment with melatonin at 10 mg/kg body weight prevented the development of METH-induced depletion of dopamine and/or its metabolites and depletion of dopamine transporter binding sites. It also attenuated METH-induced behaviours and diminished METH-induced hyperthermia, although it did not reverse fully-developed METH–induced behavioural sensitisation[110]. Feng *et al*[84] also examined the effects of melatonin on morphine-induced behavioural sensitisation and reported that pre-treatment with melatonin prevented the development of morphine-induced behavioural sensitisation and analgesic tolerance; effects which were dose-dependent[84].

The development of long-lasting addiction-related behavioural dysfunction and structural deficits in the brain have been linked to alterations in the methylation processes for purine metabolism/serotonin pathways[111], oxidative stress-induced autophagy[84], mitochondrial mediated apoptosis[112,113], alteration in mitochondrial DNA copy number in distinct brain regions[81], and neurotoxicity[84,114]. Li *et al*[95] also reported that protracted opiate withdrawal in rats was associated with the disruption of the circadian rhythm of hormones (adrenocorticotropin, orexin and corticosterone), leading to the induction of neurobiological changes which may worsen the risk of relapse[95].

Feng *et al*[84] examined the ability of melatonin to militate against the deleterious effects of opiate addiction and reported that melatonin was able to reverse morphine induced mitochondrial dysfunction and oxidative stress, in cultured cells. They also demonstrated that melatonin reversed morphine-induced autophagy and changes in mitochondrial DNA copy number in cultured cells and neurons[84]. *In vivo* studies using a mouse model of morphine addiction demonstrated that melatonin also counteracted morphine–induced autophagic effects and decrease in mitochondrial DNA copy number in the hippocampus[84].

Melatonin in the management of drug-addiction related sleep and circadian rhythm disorders

Sleep and circadian rhythm disorders have been well-defined in a number of substances use disorders, including those of marijuana[115], alcohol[52,116,117], nicotine[118], benzodiazepines[86,119] and cocaine[51]. Also, results from a number of rodent studies have reported interactions between alcohol and homeostatic mechanisms[120] and/or circadian systems[121-123]. Treatment options for insomnias in drug addiction are limited, largely because traditional hypnotics that target benzodiazepine receptors are associated with abuse potential, withdrawal effects, and the potential for overdose. Melatonin supplement has been found particularly valuable in the management of circadian rhythm disorders[124], in the treatment of insomnias in subjects with chronic schizophrenia[125], in the elderly[126,127], and among children with sleep onset insomnia[128]. However, its benefits in addiction-related sleep and/or circadian rhythm disorders are still being evaluated. A double-blind cross-over control study that examined melatonin's ability in militating sleep difficulties associated with benzodiazepine (BDZ) withdrawal reported that while melatonin did not increase the likelihood of BDZ discontinuation, it improved sleep quality, especially in subjects who continued to use BDZ[86].

Its use in alcohol addicts have been supported by studies that have reported low plasma melatonin levels in this group of substance users[66,129]. Other studies have examined the efficacy of melatonin analogs in militating addiction-related sleep disorders. Brower *et al*[116] examined the ability of the melatonin receptor agonist ramelteon to attenuate insomnia in recovering alcoholics, and reported an improvement in sleep quality and quantity. Another study using ag-

omelatine (a melatonergic agonist at MT1 and MT2 receptors, and a 5-HT2C antagonist approved for use as an antidepressant) reported improved sleep in alcohol-dependent subjects with insomnia; with participants reporting improved subjective sleep quality after 6 wk of administration[130].

CONCLUSION

To date, melatonin and its analogs have continued to show promise in the management of drug addiction. However, the use of melatonin may be limited by its short half-life and an additive sedative effect when used alongside BDZs and other drugs such as morphine; also, its safety in the younger age groups are still being debated. Despite these, evidences from both animal and human studies continue to show the potentials of melatonin and its analogs in the management of drug addiction. Therefore, research must continue to focus on the applications of melatonergic agents in drug addiction management, especially, beyond their established use for associated sleep disorders.

REFERENCES

1 **Zhou Y**, Zhao M, Zhou C, Li R. Sex differences in drug addiction and response to exercise intervention: From human to animal studies. *Front Neuroendocrinol* 2016; **40**: 24-41 [PMID: 26182835 DOI: 10.1016/j.yfrne.2015.07.001]
2 **Wakefield JC**. DSM-5 substance use disorder: how conceptual missteps weakened the foundations of the addictive disorders field. *Acta Psychiatr Scand* 2015; **132**: 327-334 [PMID: 25968656 DOI: 10.1111/acps.12446]
3 **Gardner EL**. Addiction and brain reward and antireward pathways. *Adv Psychosom Med* 2011; **30**: 22-60 [PMID: 21508625 DOI: 10.1159/000324065]
4 **Jones JD**, Comer SD. A review of pharmacogenetic studies of substance-related disorders. *Drug Alcohol Depend* 2015; **152**: 1-14 [PMID: 25819021 DOI: 10.1016/j.drugalcdep.2015.03.003]
5 **UNODC: United Nations Office on Drugs and Crimes**. International Standards for the Treatment of Drug Use Disorders-Draft for Field Testing 2016. Available from: URL: https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_59/ECN72016_CRP4_V1601463.pdf
6 **Burns L**. World Drug Report 2013 United Nations Office on Drugs and Crime. *Drug Alcohol Rev* 2014; **33**: 216-216 [DOI: 10.1111/dar.12110]
7 **Wingo T**, Nesil T, Choi JS, Li MD. Novelty Seeking and Drug Addiction in Humans and Animals: From Behavior to Molecules. *J Neuroimmune Pharmacol* 2016; **11**: 456-470 [PMID: 26481371 DOI: 10.1007/s11481-015-9636-7]
8 **Jadidi N**, Nakhaee N. Etiology of drug abuse: a narrative analysis. *J Addict* 2014; **2014**: 352835 [PMID: 25247105 DOI: 10.1155/2014/352835]
9 **Volkow ND**, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med* 2016; **374**: 363-371 [PMID: 26816013 DOI: 10.1056/NEJMra1511480]
10 **Volkow ND**, Morales M. The Brain on Drugs: From Reward to Addiction. *Cell* 2015; **162**: 712-725 [PMID: 26276628 DOI: 10.1016/j.cell.2015.07.046]
11 **Demers CH**, Bogdan R, Agrawal A. The Genetics, Neurogenetics and Pharmacogenetics of Addiction. *Curr Behav Neurosci Rep* 2014; **1**: 33-44 [PMID: 25045619 DOI: 10.1007/s40473-013-0004-8]
12 **Volkow ND**, Muenke M. The genetics of addiction. *Hum Genet* 2012; **131**: 773-777 [PMID: 22562404 DOI: 10.1007/s00439-012-1173-3]
13 **Logan RW**, Williams WP 3rd, McClung CA. Circadian rhythms and addiction: mechanistic insights and future directions. *Behav Neurosci* 2014; **128**: 387-412 [PMID: 24731209 DOI: 10.1037/a0036268]
14 **Falcón E**, McClung CA. A role for the circadian genes in drug addiction. *Neuropharmacology* 2009; **56** Suppl 1: 91-96 [PMID: 18644396 DOI: 10.1016/j.neuropharm.2008.06.054]
15 **Conroy DA**, Hairston IS, Arnedt JT, Hoffmann RF, Armitage R, Brower KJ. Dim light melatonin onset in alcohol-dependent men and women compared with healthy controls. *Chronobiol Int* 2012; **29**: 35-42 [PMID: 22217099 DOI: 10.3109/07420528.2011.636852]
16 **Lynch WJ**, Girgenti MJ, Breslin FJ, Newton SS, Taylor JR. Gene profiling the response to repeated cocaine self-administration in dorsal striatum: a focus on circadian genes. *Brain Res* 2008; **1213**: 166-177 [PMID: 18452895 DOI: 10.1016/j.brainres.2008.02.106]
17 **Trujillo JL**, Roberts AJ, Gorman MR. Circadian timing of ethanol exposure exerts enduring effects on subsequent ad libitum consumption in C57 mice. *Alcohol Clin Exp Res* 2009; **33**: 1286-1293 [PMID: 19389184 DOI: 10.1111/j.1530-0277.2009.00954.x]
18 **Webb IC**. Circadian Rhythms and Substance Abuse: Chronobiological Considerations for the Treatment of Addiction. *Curr Psychiatry Rep* 2017; **19**: 12 [PMID: 28188587 DOI: 10.1007/s11920-017-0764-z]
19 **Roberts DC**, Brebner K, Vincler M, Lynch WJ. Patterns of cocaine self-administration in rats produced by various access conditions under a discrete trials procedure. *Drug Alcohol Depend* 2002; **67**: 291-299 [PMID: 12127200 DOI: 10.1016/S0376-8716(02)00083-2]
20 **Abarca C**, Albrecht U, Spanagel R. Cocaine sensitization and reward are under the influence of circadian genes and rhythm. *Proc Natl Acad Sci USA* 2002; **99**: 9026-9030 [PMID: 12084940 DOI: 10.1073/pnas.142039099]
21 **Jansen HT**, Sergeeva A, Stark G, Sorg BA. Circadian discrimination of reward: evidence for simultaneous yet separable food- and drug-entrained rhythms in the rat. *Chronobiol Int* 2012; **29**: 454-468 [PMID: 22475541 DOI: 10.3109/07420528.2012.667467]
22 **Mohawk JA**, Pezuk P, Menaker M. Methamphetamine and dopamine receptor D1 regulate entrainment of murine circadian oscillators. *PLoS One* 2013; **8**: e62463 [PMID: 23626822 DOI: 10.1371/journal.pone.0062463]
23 **Vengeliene V**, Noori HR, Spanagel R. Activation of Melatonin Receptors Reduces Relapse-Like Alcohol Consumption. *Neuropsychopharmacology* 2015; **40**: 2897-2906 [PMID: 25994077 DOI: 10.1038/npp.2015.143]
24 **Takahashi TT**, Vengeliene V, Spanagel R. Melatonin reduces motivation for cocaine self-administration and prevents relapse-like behavior in rats. *Psychopharmacology* (Berl) 2017; **234**: 1741-1748 [PMID: 28246896 DOI: 10.1007/s00213-017-4576-y]
25 **World Health Organization**. Neuroscience of psychoactive drug use and dependence. WHO, Geneva Switzerland 2004: 1-286. Available from: URL: https://www.naabt.org/documents/Neuroscience%20of%20psychoactive.pdf
26 **Carter A**, HalL W, Capps B, Daglish M. Neurobiological research on addiction: A review of the scientific, public health and social policy Implications for Australia. 2009: 1-241. Available from: URL: https://www.nationaldrugstrategy.gov.au/
27 **Hyman SE**, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci* 2006; **29**: 565-598 [PMID: 16776597 DOI: 10.1146/annurev.neuro.29.051605.113009]
28 **Goldstein RZ**, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002; **159**: 1642-1652 [PMID: 12359667 DOI: 10.1176/appi.ajp.159.10.1642]
29 **Koob GF**, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. *Science* 1997; **278**: 52-58 [PMID: 9311926 DOI: 10.1126/science.278.5335.52]
30 **Koob GF**, Le Moal M. Addiction and the brain antireward system. *Annu Rev Psychol* 2008; **59**: 29-53 [PMID: 18154498 DOI: 10.1146/annurev.psych.59.103006.093548]
31 **Kreek MJ**, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend* 1998; **51**: 23-47

[PMID: 9716928 DOI: 10.1016/S0376-8716(98)00064-7]
32 **Koob G**, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry* 2007; **164**: 1149-1159 [PMID: 17671276 DOI: 10.1176/appi.ajp.2007.05030503]
33 **Koob GF**, Le Moal M. Neurobiology of addiction. 1st ed. New York: Academic Press, 2006
34 **Wise RA**. Dopamine, learning and motivation. *Nat Rev Neurosci* 2004; **5**: 483-494 [PMID: 15152198 DOI: 10.1038/nrn1406]
35 **Volkow ND**, Li TK. Drug addiction: the neurobiology of behaviour gone awry. *Nat Rev Neurosci* 2004; **5**: 963-970 [PMID: 15550951 DOI: 10.1038/nrn1539]
36 **Wise RA**. Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotox Res* 2008; **14**: 169-183 [PMID: 19073424 DOI: 10.1007/BF03033808]
37 **Di Chiara G**. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res* 2002; **137**: 75-114 [PMID: 12445717 DOI: 10.1016/S0166-4328(02)00286-3]
38 **van Ree JM**, Gerrits MA, Vanderschuren LJ. Opioids, reward and addiction: An encounter of biology, psychology, and medicine. *Pharmacol Rev* 1999; **51**: 341-396 [PMID: 10353987]
39 **Feltenstein MW**, See RE. Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. *Behav Brain Res* 2006; **174**: 1-8 [PMID: 16920204 DOI: 10.1016/j.bbr.2006.06.039]
40 **Brauer LH**, De Wit H. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacol Biochem Behav* 1997; **56**: 265-272 [PMID: 9050084 DOI: 10.1016/S0091-3057(96)00240-7]
41 **Goodman A**. Neurobiology of addiction. An integrative review. *Biochem Pharmacol* 2008; **75**: 266-322 [PMID: 17764663 DOI: 10.1016/j.bcp.2007.07.030]
42 **Heinz A**, Reimold M, Wrase J, Hermann D, Croissant B, Mundle G, Dohmen BM, Braus DF, Schumann G, Machulla HJ, Bares R, Mann K. Correlation of stable elevations in striatal mu-opioid receptor availability in detoxified alcoholic patients with alcohol craving: a positron emission tomography study using carbon 11-labeled carfentanil. *Arch Gen Psychiatry* 2005; **62**: 57-64 [PMID: 15630073 DOI: 10.1001/archpsyc.62.1.57]
43 **Williams TM**, Daglish MR, Lingford-Hughes A, Taylor LG, Hammers A, Brooks DJ, Grasby P, Myles JS, Nutt DJ. Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study. *Br J Psychiatry* 2007; **191**: 63-69 [PMID: 17602127 DOI: 10.1192/bjp.bp.106.031120]
44 **Zubieta JK**, Gorelick DA, Stauffer R, Ravert HT, Dannals RF, Frost JJ. Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med* 1996; **2**: 1225-1229 [PMID: 8898749 DOI: 10.1038/nm1196-1225]
45 **Kalivas PW**, Lalumiere RT, Knackstedt L, Shen H. Glutamate transmission in addiction. *Neuropharmacology* 2009; **56** Suppl 1: 169-173 [PMID: 18675832 DOI: 10.1016/j.neuropharm.2008.07.011]
46 **Hochhauser M**. Chronobiological Factors in Drug Abuse. A. J. Schecter (ed.). Drug Dependence and Alcoholism. New York: Plenum Press, 1981: 855-864
47 **Hasler BP**, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. *Sleep Med Rev* 2012; **16**: 67-81 [PMID: 21620743 DOI: 10.1016/j.smrv.2011.03.004]
48 **Garmabi B**, Vousooghi N, Vosough M, Yoonessi A, Bakhtazad A, Zarrindast MR. Effect of circadian rhythm disturbance on morphine preference and addiction in male rats: Involvement of period genes and dopamine D1 receptor. *Neuroscience* 2016; **322**: 104-114 [PMID: 26892296 DOI: 10.1016/j.neuroscience.2016.02.019]
49 **Doyle SE**, Feng H, Garber G, Menaker M, Lynch WJ. Effects of circadian disruption on methamphetamine consumption in methamphetamine-exposed rats. *Psychopharmacology* (Berl) 2015; **232**: 2169-2179 [PMID: 25543849 DOI: 10.1007/s00213-014-3845-2]
50 **Parekh PK**, Ozburn AR, McClung CA. Circadian clock genes: effects on dopamine, reward and addiction. *Alcohol* 2015; **49**: 341-349 [PMID: 25641765 DOI: 10.1016/j.alcohol.2014.09.034]
51 **Schierenbeck T**, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev* 2008; **12**: 381-389 [PMID: 18313952 DOI: 10.1016/j.smrv.2007.12.004]
52 **Brower KJ**. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health* 2001; **25**: 110-125 [PMID: 11584550]
53 **Baker TB**, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev* 2004; **111**: 33-51 [PMID: 14756584 DOI: 10.1037/0033-295X.111.1.33]
54 **Thompson PM**, Gillin JC, Golshan S, Irwin M. Polygraphic sleep measures differentiate alcoholics and stimulant abusers during short-term abstinence. *Biol Psychiatry* 1995; **38**: 831-836 [PMID: 8750043 DOI: 10.1016/0006-3223(95)00070-4]
55 **Morgan PT**, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing effects of modafinil on sleep in chronic cocaine users. *Am J Psychiatry* 2010; **167**: 331-340 [PMID: 20080983 DOI: 10.1176/appi.ajp.2009.09050613]
56 **Bolla KI**, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR, Allen RP, David PM, Cadet JL. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med* 2010; **11**: 882-889 [PMID: 20685163 DOI: 10.1016/j.sleep.2010.02.013]
57 **Fraschini F**, Cesarani A, Alpini D, Esposti D, Stankov BM. Melatonin influences human balance. *Biol Signals Recept* 1999; **8**: 111-119 [PMID: 10085472 DOI: 10.1159/000014578]
58 **Reiter RJ**. Melatonin: clinical relevance. *Best Pract Res Clin Endocrinol Metab* 2003; **17**: 273-285 [PMID: 12787552 DOI: 10.1016/S1521-690X(03)00016-2]
59 **Hardeland R**, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin-a pleiotropic, orchestrating regulator molecule. *Prog Neurobiol* 2011; **93**: 350-384 [PMID: 21193011 DOI: 10.1016/j.pneurobio.2010.12.004]
60 **Ekmekcioglu C**. Melatonin receptors in humans: biological role and clinical relevance. *Biomed Pharmacother* 2006; **60**: 97-108 [PMID: 16527442 DOI: 10.1016/j.biopha.2006.01.002]
61 **Jockers R**, Maurice P, Boutin JA, Delagrange P. Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new? *Br J Pharmacol* 2008; **154**: 1182-1195 [PMID: 18493248 DOI: 10.1038/bjp.2008.184]
62 **Pandi-Perumal SR**, Trakht I, Srinivasan V, Spence DW, Maestroni GJ, Zisapel N, Cardinali DP. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. *Prog Neurobiol* 2008; **85**: 335-353 [PMID: 18571301 DOI: 10.1016/j.pneurobio.2008.04.001]
63 **Habtemariam S**, Daglia M, Sureda A, Selamoglu Z, Gulhan MF, Nabavi SM. Melatonin and Respiratory Diseases: A Review. *Curr Top Med Chem* 2017; **17**: 467-488 [PMID: 27558675 DOI: 10.2174/1568026616666160824120338]
64 **Ateş B**, Yılmaz HR, Selamoğlu Z, Iraz M, Yılmaz İ. Melatonin' in İntestinal İskemi-Reperfüzyonda 6-Fosfoglukonat Dehidrogenaz Aktivitesi Üzerine Etkisi. *Süleyman Demirel Üniversitesi Tıp Fakültesi Dergisi* 2004; **11**: 8-11
65 **Tas U**, Ayan M, Sogut E, Kuloglu T, Uysal M, Tanriverdi HI, Senel U, Ozyurt B, Sarsilmaz M. Protective effects of thymoquinone and melatonin on intestinal ischemia-reperfusion injury. *Saudi J Gastroenterol* 2015; **21**: 284-289 [PMID: 26458854 DOI: 10.4103/1319-3767.166203]
66 **Kühlwein E**, Hauger RL, Irwin MR. Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. *Biol Psychiatry* 2003; **54**: 1437-1443 [PMID: 14675809 DOI: 10.1016/S0006-3223(03)00005-2]
67 **Peres R**, do Amaral FG, Madrigrano TC, Scialfa JH, Bordin S, Afeche SC, Cipolla-Neto J. Ethanol consumption and pineal melatonin daily profile in rats. *Addict Biol* 2011; **16**: 580-590 [PMID: 21635669 DOI: 10.1111/j.1369-1600.2011.00342.x]
68 **Uz T**, Javaid JI, Manev H. Circadian differences in behavioral sensitization to cocaine: putative role of arylalkylamine N-acetyltransferase. *Life Sci* 2002; **70**: 3069-3075 [PMID: 12138020 DOI: 10.1016/S0024-3205(02)01559-X]
69 **Kurtuncu M**, Arslan AD, Akhisaroglu M, Manev H, Uz T. Invol-

vement of the pineal gland in diurnal cocaine reward in mice. *Eur J Pharmacol* 2004; **489**: 203-205 [PMID: 15087244 DOI: 10.1016/j.ejphar.2004.03.010]

70 **Williams RL**, Soliman KF, Mizinga KM. Circadian variation in tolerance to the hypothermic action of CNS drugs. *Pharmacol Biochem Behav* 1993; **46**: 283-288 [PMID: 8265682 DOI: 10.1016/0091-3057(93)90354-V]

71 **Drummond SP**, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcohol Clin Exp Res* 1998; **22**: 1796-1802 [PMID: 9835298 DOI: 10.1097/00000374-199811000-00026]

72 **Lax P**. Melatonin inhibits nicotinic currents in cultured rat cerebellar granule neurons. *J Pineal Res* 2008; **44**: 70-77 [PMID: 18078451 DOI: 10.1111/j.1600-079X.2007.00481.x]

73 **Markus RP**, Santos JM, Zago W, Reno LA. Melatonin nocturnal surge modulates nicotinic receptors and nicotine-induced [3H]glutamate release in rat cerebellum slices. *J Pharmacol Exp Ther* 2003; **305**: 525-530 [PMID: 12606693 DOI: 10.1124/jpet.102.045625]

74 **Onaolapo OJ**, Onaolapo AY. Melatonin, adolescence, and the brain: An insight into the period-specific influences of a multifunctional signaling molecule. *Birth Defects Res* 2017; **109**: 1659-1671 [PMID: 29251845 DOI: 10.1002/bdr2.1171]

75 **Onaolapo OJ**, Onaolapo AY. Chapter 4. Melatonin Receptors, Behaviour and Brain Function. Lore Correia and Germaine Mayers (Eds) in Melatonin: Medical Uses and Role in Health and Disease 2018: 133-158

76 **Uz T**, Arslan AD, Kurtuncu M, Imbesi M, Akhisaroglu M, Dwivedi Y, Pandey GN, Manev H. The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. *Brain Res Mol Brain Res* 2005; **136**: 45-53 [PMID: 15893586 DOI: 10.1016/j.molbrainres.2005.01.002]

77 **Noori HR**, Spanagel R, Hansson AC. Neurocircuitry for modeling drug effects. *Addict Biol* 2012; **17**: 827-864 [PMID: 22978651 DOI: 10.1111/j.1369-1600.2012.00485.x]

78 **Imbesi M**, Uz T, Yildiz S, Arslan AD, Manev H. Drug- and region-specific effects of protracted antidepressant and cocaine treatment on the content of melatonin MT(1) and MT(2) receptor mRNA in the mouse brain. *Int J Neuroprot Neuroregener* 2006; **2**: 185-189 [PMID: 18389085]

79 **Hutchinson AJ**, Hudson RL, Dubocovich ML. Genetic deletion of MT(1) and MT(2) melatonin receptors differentially abrogates the development and expression of methamphetamine-induced locomotor sensitization during the day and the night in C3H/HeN mice. *J Pineal Res* 2012; **53**: 399-409 [PMID: 22672659 DOI: 10.1111/j.1600-079X.2012.01010.x]

80 **Clough SJ**, Hutchinson AJ, Hudson RL, Dubocovich ML. Genetic deletion of the MT1 or MT2 melatonin receptors abrogates methamphetamine-induced reward in C3H/HeN mice. *Physiol Behav* 2014; **132**: 79-86 [PMID: 24813704 DOI: 10.1016/j.physbeh.2014.04.049]

81 **Hutchinson AJ**, Ma J, Liu J, Hudson RL, Dubocovich ML. Role of MT1 melatonin receptors in methamphetamine-induced locomotor sensitization in C57BL/6 mice. *Psychopharmacology* (Berl) 2014; **231**: 257-267 [PMID: 23934259 DOI: 10.1007/s00213-013-3228-0]

82 **Zahn PK**, Lansmann T, Berger E, Speckmann EJ, Musshoff U. Gene expression and functional characterization of melatonin receptors in the spinal cord of the rat: implications for pain modulation. *J Pineal Res* 2003; **35**: 24-31 [PMID: 12823610 DOI: 10.1034/j.1600-079X.2003.00047.x]

83 **Sinha R**. New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep* 2011; **13**: 398-405 [PMID: 21792580 DOI: 10.1007/s11920-011-0224-0]

84 **Feng YM**, Jia YF, Su LY, Wang D, Lv L, Xu L, Yao YG. Decreased mitochondrial DNA copy number in the hippocampus and peripheral blood during opiate addiction is mediated by autophagy and can be salvaged by melatonin. *Autophagy* 2013; **9**: 1395-1406 [PMID: 23800874 DOI: 10.4161/auto.25468]

85 **Sircar R**. Effect of melatonin on cocaine-induced behavioral sensitization. *Brain Res* 2000; **857**: 295-299 [PMID: 10700581 DOI: 10.1016/S0006-8993(99)02460-9]

86 **Peles E**, Hetzroni T, Bar-Hamburger R, Adelson M, Schreiber S. Melatonin for perceived sleep disturbances associated with benzodiazepine withdrawal among patients in methadone maintenance treatment: a double-blind randomized clinical trial. *Addiction* 2007; **102**: 1947-1953 [PMID: 17916225 DOI: 10.1111/j.1360-0443.2007.02007.x]

87 **Dimsdale JE**, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med* 2007; **3**: 33-36 [PMID: 17557450]

88 **Wang Q**, Yue XF, Qu WM, Tan R, Zheng P, Urade Y, Huang ZL. Morphine inhibits sleep-promoting neurons in the ventrolateral preoptic area via mu receptors and induces wakefulness in rats. *Neuropsychopharmacology* 2013; **38**: 791-801 [PMID: 23303062 DOI: 10.1038/npp.2012.244]

89 **Licata SC**, Renshaw PF. Neurochemistry of drug action: insights from proton magnetic resonance spectroscopic imaging and their relevance to addiction. *Ann N Y Acad Sci* 2010; **1187**: 148-171 [PMID: 20201852 DOI: 10.1111/j.1749-6632.2009.05143.x]

90 **Gossop M**, Bradley B, Phillips GT. An investigation of withdrawal symptoms shown by opiate addicts during and subsequent to a 21-day in-patient methadone detoxification procedure. *Addict Behav* 1987; **12**: 1-6 [PMID: 3565107 DOI: 10.1016/0306-4603(87)90002-5]

91 **Pjrek E**, Frey R, Naderi-Heiden A, Strnad A, Kowarik A, Kasper S, Winkler D. Actigraphic measurements in opioid detoxification with methadone or buprenorphine. *J Clin Psychopharmacol* 2012; **32**: 75-82 [PMID: 22198453 DOI: 10.1097/JCP.0b013e31823f91d1]

92 **Hood S**, Cassidy P, Mathewson S, Stewart J, Amir S. Daily morphine injection and withdrawal disrupt 24-h wheel running and PERIOD2 expression patterns in the rat limbic forebrain. *Neuroscience* 2011; **186**: 65-75 [PMID: 21536108 DOI: 10.1016/j.neuroscience.2011.04.045]

93 **Glaser AM**, Reyes-Vázquez C, Prieto-Gómez B, Burau K, Dafny N. Morphine administration and abrupt cessation alter the behavioral diurnal activity pattern. *Pharmacol Biochem Behav* 2012; **101**: 544-552 [PMID: 22386964 DOI: 10.1016/j.pbb.2012.02.015]

94 **Li SX**, Liu LJ, Jiang WG, Lu L. Morphine withdrawal produces circadian rhythm alterations of clock genes in mesolimbic brain areas and peripheral blood mononuclear cells in rats. *J Neurochem* 2009; **109**: 1668-1679 [PMID: 19383088 DOI: 10.1111/j.1471-4159.2009.06086.x]

95 **Li SX**, Liu LJ, Jiang WG, Sun LL, Zhou SJ, Le Foll B, Zhang XY, Kosten TR, Lu L. Circadian alteration in neurobiology during protracted opiate withdrawal in rats. *J Neurochem* 2010; **115**: 353-362 [PMID: 20738730 DOI: 10.1111/j.1471-4159.2010.06941.x]

96 **Zhdanova IV**, Giorgetti M. Melatonin alters behavior and cAMP levels in nucleus accumbens induced by cocaine treatment. *Brain Res* 2002; **956**: 323-331 [PMID: 12445702 DOI: 10.1016/S0006-8993(02)03565-5]

97 **Bondi CD**, Kamal KM, Johnson DA, Witt-Enderby PA, Giannetti VJ. The Effect of Melatonin Upon Postacute Withdrawal Among Males in a Residential Treatment Program (M-PAWS): A Randomized, Double-blind, Placebo-controlled Trial. *J Addict Med* 2018; **12**: 201-206 [PMID: 29351138 DOI: 10.1097/ADM.0000000000000386]

98 **Cemek M**, Büyükokuroğlu ME, Hazman Ö, Bulut S, Konuk M, Birdane Y. Antioxidant enzyme and element status in heroin addiction or heroin withdrawal in rats: effect of melatonin and vitamin E plus Se. *Biol Trace Elem Res* 2011; **139**: 41-54 [PMID: 20180043 DOI: 10.1007/s12011-010-8634-0]

99 **O'Brien CP**. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry* 2005; **162**: 1423-1431 [PMID: 16055763 DOI: 10.1176/appi.ajp.162.8.1423]

100 **Kalivas PW**, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 2008; **33**: 166-180 [PMID: 17805308 DOI: 10.1038/sj.npp.1301564]

101 **Sinha R**, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. *Psychopharmacology* (Berl) 2011; **218**: 69-82 [PMID: 21494792 DOI: 10.1007/s00213-011-2263-y]

102 **Sinha R**. How does stress increase risk of drug abuse and relapse? *Psychopharmacology* (Berl) 2001; **158**: 343-359 [PMID: 11797055 DOI: 10.1007/s002130100917]

103 **Jaffe JH**, Cascella NG, Kumor KM, Sherer MA. Cocaine-induced cocaine craving. *Psychopharmacology* (Berl) 1989; **97**: 59-64 [PMID: 2496428 DOI: 10.1007/BF00443414]

104 **O'Brien CP**, Ehrman RN, Ternes JW. Classical conditioning in human opioid dependence. In: Behavioral analysis of drug dependence (Goldberg S, Stolerman I, eds). Orlando, FL: Academic, 1986: 329-356

105 **Wikler A**. Dynamics of drug dependence. Implications of a conditioning theory for research and treatment. *Arch Gen Psychiatry* 1973; **28**: 611-616 [PMID: 4700675 DOI: 10.1001/archpsyc.1973.01750350005001]

106 **Bossert JM**, Marchant NJ, Calu DJ, Shaham Y. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. *Psychopharmacology* (Berl) 2013; **229**: 453-476 [PMID: 23685858 DOI: 10.1007/s00213-013-3120-y]

107 **Mantsch JR**, Baker DA, Funk D, Lê AD, Shaham Y. Stress-Induced Reinstatement of Drug Seeking: 20 Years of Progress. *Neuropsychopharmacology* 2016; **41**: 335-356 [PMID: 25976297 DOI: 10.1038/npp.2015.142]

108 **Dong Y**, Taylor JR, Wolf ME, Shaham Y. Circuit and Synaptic Plasticity Mechanisms of Drug Relapse. *J Neurosci* 2017; **37**: 10867-10876 [PMID: 29118216 DOI: 10.1523/JNEUROSCI.1821-17.2017]

109 **Bhargava HN**, Kumar S. Sensitization to the locomotor stimulant activity of cocaine is associated with increases in nitric oxide synthase activity in brain regions and spinal cord of mice. *Pharmacology* 1997; **55**: 292-298 [PMID: 9413858 DOI: 10.1159/000139541]

110 **Itzhak Y**, Martin JL, Black MD, Ali SF. Effect of melatonin on methamphetamine- and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity and methamphetamine-induced behavioral sensitization. *Neuropharmacology* 1998; **37**: 781-791 [PMID: 9707292 DOI: 10.1016/S0028-3908(98)00067-7]

111 **Patkar AA**, Rozen S, Mannelli P, Matson W, Pae CU, Krishnan KR, Kaddurah-Daouk R. Alterations in tryptophan and purine metabolism in cocaine addiction: a metabolomic study. *Psychopharmacology* (Berl) 2009; **206**: 479-489 [PMID: 19649617 DOI: 10.1007/s00213-009-1625-1]

112 **Cunha-Oliveira T**, Rego AC, Garrido J, Borges F, Macedo T, Oliveira CR. Street heroin induces mitochondrial dysfunction and apoptosis in rat cortical neurons. *J Neurochem* 2007; **101**: 543-554 [PMID: 17250679 DOI: 10.1111/j.1471-4159.2006.04406.x]

113 **Lin X**, Wang YJ, Li Q, Hou YY, Hong MH, Cao YL, Chi ZQ, Liu JG. Chronic high-dose morphine treatment promotes SH-SY5Y cell apoptosis via c-Jun N-terminal kinase-mediated activation of mitochondria-dependent pathway. *FEBS J* 2009; **276**: 2022-2036 [PMID: 19292871 DOI: 10.1111/j.1742-4658.2009.06938.x]

114 **Cunha-Oliveira T**, Rego AC, Oliveira CR. Cellular and molecular mechanisms involved in the neurotoxicity of opioid and psychostimulant drugs. *Brain Res Rev* 2008; **58**: 192-208 [PMID: 18440072 DOI: 10.1016/j.brainresrev.2008.03.002]

115 **Bolla KI**, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, David PM, Verdejo-Garcia A, Benbrook AR. Sleep disturbance in heavy marijuana users. *Sleep* 2008; **31**: 901-908 [PMID: 18548836 DOI: 10.1093/sleep/31.6.901]

116 **Brower KJ**, Conroy DA, Kurth ME, Anderson BJ, Stein MD. Ramelteon and improved insomnia in alcohol-dependent patients: a case series. *J Clin Sleep Med* 2011; **7**: 274-275 [PMID: 21677897 DOI: 10.5664/JCSM.1070]

117 **Roehrs T**, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. *Sleep Med Rev* 2001; **5**: 287-297 [PMID: 12530993 DOI: 10.1053/smrv.2001.0162]

118 **Colrain IM**, Trinder J, Swan GE. The impact of smoking cessation on objective and subjective markers of sleep: review, synthesis, and recommendations. *Nicotine Tob Res* 2004; **6**: 913-925 [PMID: 15801567 DOI: 10.1080/14622200412331324938]

119 **Schreiber S**. [Benzodiazepines--update]. *Harefuah* 1993; **125**: 172-174 [PMID: 7901131]

120 **Clasadonte J**, McIver SR, Schmitt LI, Halassa MM, Haydon PG. Chronic sleep restriction disrupts sleep homeostasis and behavioral sensitivity to alcohol by reducing the extracellular accumulation of adenosine. *J Neurosci* 2014; **34**: 1879-1891 [PMID: 24478367 DOI: 10.1523/JNEUROSCI.2870-12.2014]

121 **Comasco E**, Nordquist N, Göktürk C, Aslund C, Hallman J, Oreland L, Nilsson KW. The clock gene PER2 and sleep problems: association with alcohol consumption among Swedish adolescents. *Ups J Med Sci* 2010; **115**: 41-48 [PMID: 20187847 DOI: 10.3109/03009731003597127]

122 **Spanagel R**, Rosenwasser AM, Schumann G, Sarkar DK. Alcohol consumption and the body's biological clock. *Alcohol Clin Exp Res* 2005; **29**: 1550-1557 [PMID: 16156052 DOI: 10.1097/01.alc.0000175074.70807.fd]

123 **Wang X**, Mozhui K, Li Z, Mulligan MK, Ingels JF, Zhou X, Hori RT, Chen H, Cook MN, Williams RW, Lu L. A promoter polymorphism in the Per3 gene is associated with alcohol and stress response. *Transl Psychiatry* 2012; **2**: e73 [PMID: 22832735 DOI: 10.1038/tp.2011.71]

124 **Cajochen C**, Kräuchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 2003; **15**: 432-437 [PMID: 12622846 DOI: 10.1046/j.1365-2826.2003.00989.x]

125 **Shamir E**, Laudon M, Barak Y, Anis Y, Rotenberg V, Elizur A, Zisapel N. Melatonin improves sleep quality of patients with chronic schizophrenia. *J Clin Psychiatry* 2000; **61**: 373-377 [PMID: 10847313 DOI: 10.4088/JCP.v61n0509]

126 **Garfinkel D**, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995; **346**: 541-544 [PMID: 7658780 DOI: 10.1016/S0140-6736(95)91382-3]

127 **Garfinkel D**, Zisapel N, Wainstein J, Laudon M. Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999; **159**: 2456-2460 [PMID: 10665894 DOI: 10.1001/archinte.159.20.2456]

128 **Smits MG**, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol* 2001; **16**: 86-92 [PMID: 11292231 DOI: 10.1177/088307380101600204]

129 **Wetterberg L**, Aperia B, Gorelick DA, Gwirtzman HE, McGuire MT, Serafetinides EA, Yuwiler A. Age, alcoholism and depression are associated with low levels of urinary melatonin. *J Psychiatry Neurosci* 1992; **17**: 215-224 [PMID: 1489763]

130 **Grosshans M**, Mutschler J, Luderer M, Mann K, Kiefer F. Agomelatine is effective in reducing insomnia in abstinent alcohol-dependent patients. *Clin Neuropharmacol* 2014; **37**: 6-8 [PMID: 24434525 DOI: 10.1097/WNF.0000000000000007]

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