Exploring the association between melatonin and nicotine dependence (Review)

VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1], PAGONA SKLAPANI[2], NIKOLAOS TRAKAS[2], RUSSEL J. REITER[3] and DEMETRIOS A. SPANDIDOS[4]

[1]Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, 11527 Athens, Greece; [2]Department of Biochemistry, Sismanogleio Hospital, 15126 Athens, Greece; [3]Department of Cell Systems and Anatomy, UT Health Science Center, San Antonio, TX 78229, USA; [4]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion, Greece

Received April 10, 2024; Accepted July 19, 2024

DOI: 10.3892/ijmm.2024.5406

Abstract. Due to the addictive qualities of tobacco products and the compulsive craving and dependence associated with their use, nicotine dependence continues to be a serious public health concern on a global scale. Despite awareness of the associated health risks, nicotine addiction contributes to numerous acute and chronic medical conditions, including cardiovascular disease, respiratory disorders and cancer. The nocturnal secretion of pineal melatonin, known as the 'hormone of darkness', influences circadian rhythms and is implicated in addiction-related behaviors. Melatonin receptors are found throughout the brain, influencing dopaminergic neurotransmission and potentially attenuating nicotine-seeking behavior. Additionally, the antioxidant properties of melatonin may mitigate oxidative stress from chronic nicotine exposure, reducing cellular damage and lowering the risk of nicotine-related health issues. In addition to its effects on circadian rhythmicity, melatonin acting via specific neural receptors influences sleep and mood, and provides neuroprotection. Disruptions in melatonin signaling may contribute to sleep disturbances and mood disorders, highlighting the potential therapeutic role of melatonin in addiction and psychiatric conditions. Melatonin may influence neurotransmitter systems involved in addiction, such as the dopaminergic, glutamatergic, serotonergic and endogenous opioid systems. Preclinical studies suggest the potential of melatonin in modulating reward processing, attenuating drug-induced hyperactivity and reducing opioid withdrawal symptoms. Chronotherapeutic approaches targeting circadian rhythms and melatonin signaling show promise in smoking cessation interventions. Melatonin supplementation during periods of heightened nicotine cravings may alleviate withdrawal symptoms and reduce the reinforcing effects of nicotine. Further research is required however, to examine the molecular mechanisms underlying the melatonin-nicotine association and the optimization of therapeutic interventions. Challenges include variability in individual responses to melatonin, optimal dosing regimens and identifying biomarkers of treatment response. Understanding these complexities could lead to personalized treatment strategies and improve smoking cessation outcomes.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: vaso_georgakopoulou@hotmail.com

Key words: melatonin, nicotine dependence, circadian rhythms, addiction, smoking

Contents

1. Introduction

Nicotine dependence, a pervasive and challenging addiction, continues to exact a significant toll on public health globally (1). Despite intensive research being made into the mechanisms

underlying nicotine addiction and its associated health consequences, effective strategies for its prevention and interruption remain elusive (2). In recent years, emerging evidence has shed light on the potential interplay between nicotine dependence and the neuroendocrine hormone, melatonin (3).

The addictive qualities of tobacco products fuel the complex condition known as nicotine dependence, which is characterized by compulsive cravings and physiological or psychological dependence on nicotine. The addictive nature of nicotine stems from its ability to activate the brain's reward pathways, particularly the mesolimbic dopaminergic system, leading to feelings of pleasure and reinforcement of addictive behavior (4). Despite widespread awareness of the health risks associated with smoking, nicotine dependence remains a formidable public health challenge, contributing to a myriad of acute and chronic medical conditions, including cardiovascular disease, respiratory disorders and cancer (5,6).

Melatonin, often referred to as the 'hormone of darkness', is primarily synthesized nocturnally by the pineal gland and plays a crucial role in regulating circadian rhythms (7). The suprachiasmatic nucleus (SCN) of the hypothalamus responds to environmental light-dark cycles by tightly controlling melatonin secretion. Traditionally recognized for its role in promoting sleep onset and regulating the sleep-wake cycle, the influence of melatonin extends far beyond circadian rhythms (8). Emerging research has highlighted the diverse physiological roles of melatonin, including its antioxidant, immunomodulatory and neuroprotective properties (9-12).

The potential association between melatonin and nicotine dependence has attracted increasing attention in the scientific community. Preclinical investigations have offered fascinating revelations regarding the interplay of melatonin and nicotine dependence (13,14). Melatonin receptors are widely distributed throughout the brain, including areas implicated in the reward pathway and addiction-related behaviors. In animal models, evidence suggests that melatonin may modulate the reinforcing effects of nicotine by influencing dopaminergic neurotransmission and attenuating nicotine-seeking behavior (15).

Additionally, the antioxidant properties of melatonin may provide defense against the oxidative stress that chronic nicotine exposure causes, minimizing cellular damage and lowering the risk of nicotine-related health issues (16). Moreover, the role of melatonin in regulating mood and stress responses may influence susceptibility to nicotine addiction and affect smoking behavior (17).

The present comprehensive review synthesizes the existing literature on the association between melatonin and nicotine dependence, provides a critical analysis of the current evidence of this association, and identifies areas for future research. By elucidating the intricate interplay between melatonin and nicotine, the present review aims to provide guidelines for an improved understanding of nicotine addiction and to pave the way for innovative approaches to smoking cessation and health consequences.

2. Melatonin and its diverse physiological roles

Melatonin, a molecule nocturnally produced and released by the pineal gland and by numerous other cells, where its synthesis is neither circadian nor released, has long fascinated researchers due to its diverse physiological roles (18). Initially recognized for its involvement in regulating circadian rhythms, the influence of melatonin extends far beyond sleep-wake cycles and other 24-h rhythms (19). The synthesis of melatonin commences with the conversion of tryptophan into serotonin, catalyzed by the enzyme, tryptophan hydroxylase. Subsequently, serotonin undergoes two enzymatic reactions, mediated by serotonin-*N*-acetyltransferase and acetylserotonin-*O*-methyltransferase, to form melatonin. The SCN located in the hypothalamus exerts precise control over the synthesis and release of melatonin in accordance with environmental light-dark cycles (20,21).

Melatonin plays a pivotal role in synchronizing the circadian rhythms of the body. As darkness falls, the SCN signals the pineal gland to increase melatonin production, promoting sleep onset and regulating the sleep-wake cycle (22). Conversely, exposure to light inhibits melatonin secretion, promoting chronodisruption and wakefulness. Perturbations in the melatonin rhythm, such as those experienced during shift work or jet lag, can lead to sleep disturbances and impaired cognitive function (23).

Beyond its role in circadian rhythms, melatonin exhibits potent antioxidant properties. It scavenges free radicals, neutralizes oxidative stress and protects cells from damage. The ability of melatonin to traverse cellular membranes and accumulate in various organelles underscores its effectiveness as an antioxidant. Moreover, melatonin stimulates the activity of antioxidant enzymes, further enhancing cellular defense mechanisms against oxidative damage (24,25).

Emerging evidence suggests that melatonin plays a crucial role in modulating the immune system. Melatonin receptors are present on immune cells, enabling melatonin to regulate immune responses. Melatonin enhances the production of immune cells, such as natural killer cells and T-lymphocytes, strengthening the defense of the body against pathogens. Additionally, melatonin exhibits anti-inflammatory properties, mitigating excessive immune activation and tissue damage (26-28).

Melatonin exerts neuroprotective effects, safeguarding the brain against various insults. It regulates neurotransmitter release, modulates neuronal excitability and promotes neuronal survival. The antioxidant properties of melatonin, many of which are receptor-independent, counteract neurotoxicity induced by oxidative stress, reducing the risk of developing neurodegenerative disorders, such as Alzheimer's and Parkinson's disease. Moreover, melatonin enhances neuroplasticity, facilitating learning and memory processes (29-32).

In addition to these well-established roles, melatonin affects reproductive function in both males and females. In females, melatonin influences ovulation and protects the placenta from molecular damage, while in males, it modulates spermatogenesis and testosterone production. Melatonin receptors are present in reproductive tissues, highlighting their direct involvement in reproductive processes. Furthermore, the antioxidant properties of melatonin protect the gametes of both sexes from oxidative damage, ensuring reproductive success (33-35). The diverse physiological roles of melatonin are, in part, illustrated in Fig. 1.

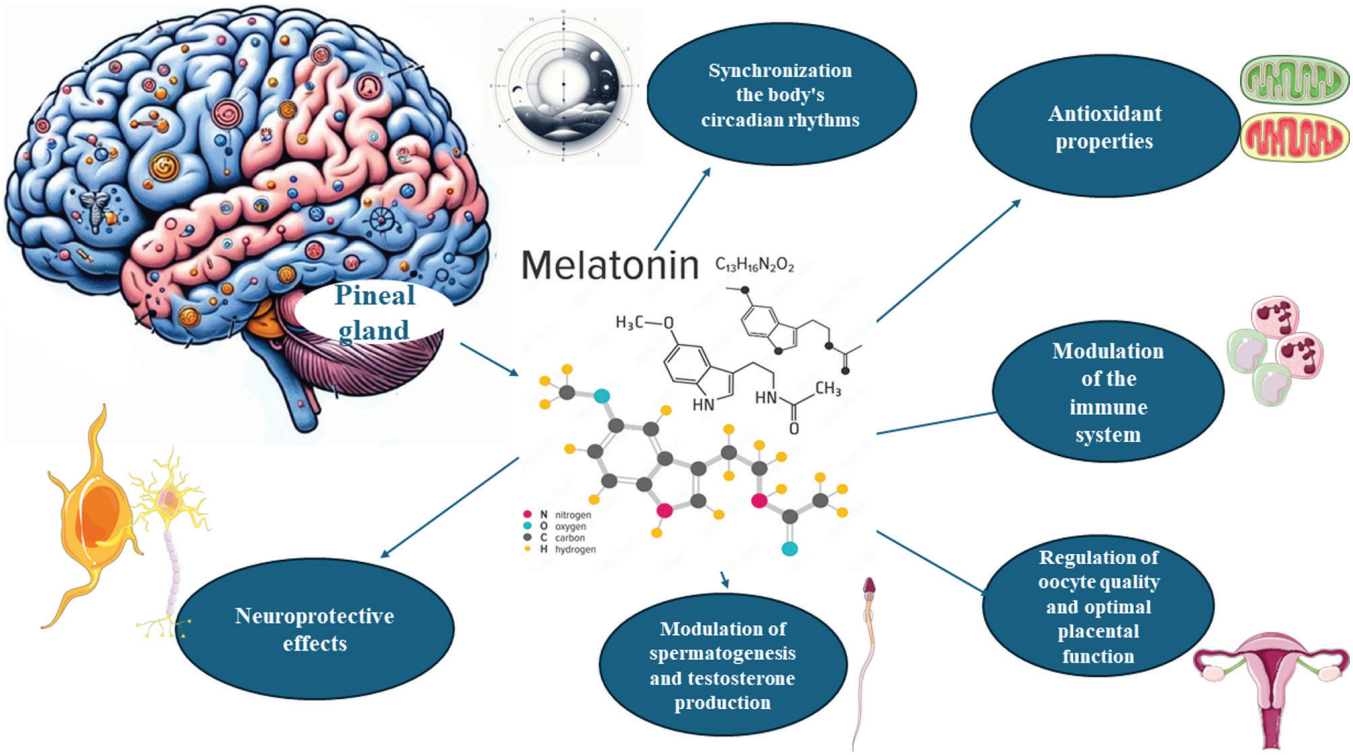

Figure 1. The diverse physiological roles of melatonin. Parts of this image were derived from the free medical site http://smart.servier.com/ (accessed on April 5, 2024) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

3. Overview of nicotine dependence and its impact on health

Nicotine addiction: Mechanisms and pathophysiology. Nicotine addiction stems from the pharmacological effects of nicotine on the reward pathways of the brain. Upon inhalation or ingestion, nicotine swiftly penetrates the blood-brain barrier and attaches to nicotinic acetylcholine receptors (nAChRs) in the mesolimbic dopaminergic system (36). This engagement prompts the discharge of neurotransmitters, predominantly dopamine, fostering sensations of pleasure and reinforcing addictive conduct. Chronic nicotine exposure leads to neuroadaptations, altering the reward circuitry of the brain and perpetuating addiction (37).

Nicotine addiction: Behavioral and psychological factors. Beyond its pharmacological effects, a number of behavioral and psychological factors affect nicotine dependence. Smoking behavior often becomes intertwined with daily routines, social interactions, and coping mechanisms, reinforcing the habituation process. Additionally, individuals may use tobacco products to alleviate stress, manage negative emotions, or enhance cognitive performance, further solidifying nicotine dependence (38). Environmental cues associated with smoking, such as seeing cigarette advertisements or being in social settings where smoking is prevalent, can trigger cravings and perpetuate addiction to this dangerous molecule (39).

Health consequences of nicotine dependence. The inhalation of tobacco smoke exposes the body to a toxic cocktail of chemicals, including carcinogens and harmful gases, which damage vital organs and systems. Smoking is a leading cause of preventable mortality worldwide, accounting for a significant burden of disease attributable to cardiovascular disease, respiratory disorders, and various types of cancer. Moreover, nicotine dependence increases the risk of developing comorbid conditions, such as hypertension, diabetes and mental health disorders (40-51).

Cardiovascular effects. Nicotine exerts profound cardiovascular effects, contributing to the development and progression of cardiovascular disease. It stimulates the sympathetic nervous system, leading to an increased heart rate, blood pressure and vasoconstriction (40). Chronic nicotine exposure promotes atherosclerosis, thrombosis and endothelial dysfunction, predisposing individuals to coronary artery disease, myocardial infarction and stroke (41). Furthermore, the pro-inflammatory and pro-thrombotic properties of nicotine exacerbate vascular pathology, exacerbating cardiovascular morbidity and mortality (42).

Respiratory complications. Tobacco smoke contains numerous respiratory irritants and carcinogens that inflict extensive damage on the respiratory system. The inhalation of tobacco smoke damages airway epithelial cells, impairs mucociliary clearance and induces inflammation, predisposing individuals to chronic obstructive pulmonary disease, emphysema and bronchitis (43). Moreover, nicotine dependence increases the risk of developing respiratory infections and exacerbates pre-existing respiratory conditions, leading to respiratory failure and premature death (44).

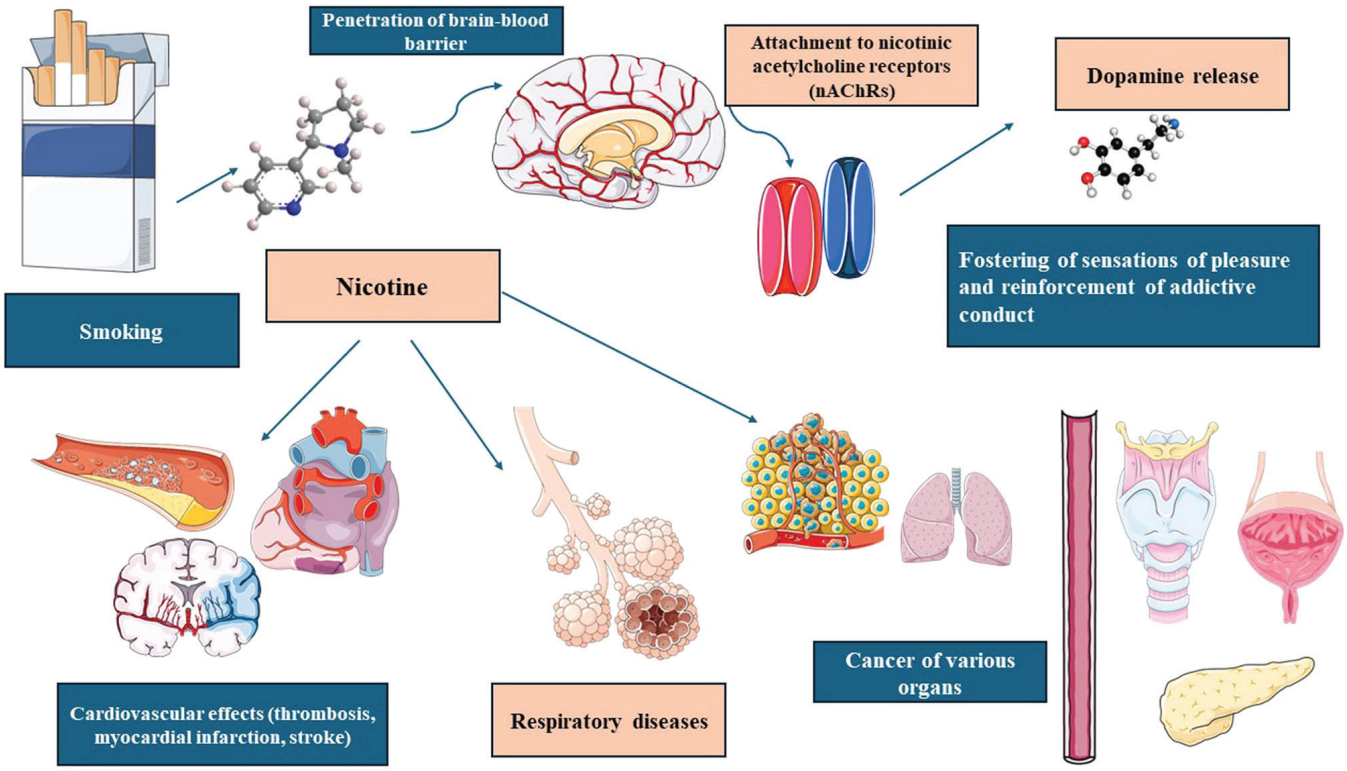

Figure 2. Overview of nicotine dependence and its impact on health. Parts of this image were derived from the free medical site http://smart.servier.com/ (accessed on April 5, 2024) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

Cancer risk. Perhaps the most well-known consequence of nicotine dependence is its association with cancer (45). Tobacco smoke comprises >7,000 compounds; these include carcinogens, such as polycyclic aromatic hydrocarbons and nitrosamines, which instigate and advance oncogenic pathways (46). Smoking stands as the primary cause behind lung cancer, responsible for the majority of cases globally. Moreover, tobacco consumption also escalates the likelihood of developing cancers of the pharynx, oral cavity, larynx, bladder, esophagus, cervix and pancreas (47). Additionally, exposure to secondhand smoke poses a significant cancer risk to non-smokers (48).

Mental health effects. Nicotine dependence is closely intertwined with mental health, exacerbating symptoms of anxiety, depression and stress. While individuals may initially use tobacco products as a coping mechanism for stress relief or mood enhancement, chronic nicotine exposure disrupts neurotransmitter balance and exacerbates psychiatric symptoms. Moreover, nicotine dependence is highly prevalent among individuals with mental health disorders, contributing to resistance to treatment and poorer clinical outcomes (49-51). An overview of nicotine dependence and its impact on health is illustrated in Fig. 2.

4. Melatonin receptors and their distribution in the brain

Likely central to numerous of the actions of melatonin are its receptors, which are distributed throughout the brain and peripheral tissues.

Types of melatonin receptors. Melatonin exerts its effects via two main types of membrane receptors: Melatonin receptor type 1 (MT1) and melatonin receptor type 2 (MT2), both belonging to the G protein-coupled receptor family. MT1 receptors are predominantly coupled to inhibitory G proteins (Gi/o), while MT2 receptors can activate both inhibitory (Gi/o) and stimulatory (Gs) G proteins. These receptors exhibit distinct, yet overlapping expression patterns, mediating diverse physiological responses to melatonin (52).

Distribution in the brain. Melatonin receptors are widely distributed throughout the brain, encompassing various regions involved in circadian regulation, sleep-wake cycles, mood modulation and neuroendocrine function. In the hypothalamus, MT1 and MT2 receptors are localized in the SCN, the master circadian pacemaker, where they regulate the timing of melatonin secretion and synchronize biological rhythms with the light-dark cycle. Additionally, melatonin receptors are found in the hypothalamic-pituitary axis, where they function in the modulation of pituitary hormone secretion related to reproductive function (53).

Circadian regulation. The SCN serves as the central hub for circadian regulation, integrating photic and non-photic cues to entrain circadian central and peripheral clocks. Melatonin receptors within the SCN play a crucial role in transducing melatonin signals and modulating neuronal activity, thereby influencing the timing of sleep onset, body temperature and hormone secretion. Disruptions in melatonin receptor signaling, such as those observed in circadian rhythm disorders or shift work, can lead to sleep disturbances and the desynchronization of biological rhythms (54-56).

Sleep-wake regulation. Beyond its role in circadian rhythms, melatonin influences sleep-wake cycles by modulating the activity of sleep-promoting and wake-promoting pathways in the brain. Melatonin receptors are densely expressed in the hypothalamic nuclei, such as the ventrolateral preoptic nucleus (VLPO) and the orexinergic neurons in the lateral hypothalamus, which regulate sleep onset and maintenance. The activation of MT1 receptors in the VLPO promotes sleep by inhibiting arousal systems, while MT2 receptors modulate the sensitivity of orexin neurons to sleep-promoting signals (57,58).

Mood modulation. Emerging evidence suggests a role for melatonin receptors in mood modulation and affective disorders. Melatonin receptors are distributed in limbic structures implicated in emotional regulation, including the hippocampus, amygdala and prefrontal cortex (PFC) (59). The dysregulation of melatonin receptor signaling has been implicated in mood disorders, such as depression and bipolar disorder. The modulation of melatonin receptors may offer a novel therapeutic approach for mood stabilization and the management of mood disorders (60).

Neuroprotective effects. Melatonin exerts neuroprotective effects against oxidative stress, inflammation and neurodegeneration, mediated in part by its receptors. Melatonin receptors are expressed in neuronal populations vulnerable to oxidative damage, such as the hippocampus and substantia nigra (61). The activation of melatonin receptors enhances antioxidant defenses, reduces neuronal apoptosis and promotes neurogenesis, thereby mitigating the progression of neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's diseases (62,63).

Therapeutic implications. The widespread distribution of melatonin receptors in the brain as well as its receptor-independent actions underscore the potential importance of melatonin as a therapeutic treatment for a wide range of neurological and psychiatric disorders. Agonists and antagonists targeting melatonin receptors have been explored for their efficacy in sleep disorders, mood disorders and neurodegenerative diseases. The selective modulation of melatonin receptor subtypes may offer personalized treatment strategies with improved efficacy and reduced side-effects (64,65).

5. Potential influence of melatonin on neurotransmitter systems related to addiction

Dopaminergic system. The dopaminergic system, particularly that involved in the mesolimbic pathway, is integral to the reinforcement of rewarding behaviors and the development of addiction. Dopamine release in the nucleus accumbens (NAc) mediates the pleasurable effects of drug abuse and reinforces drug-seeking behavior (66). Melatonin receptors, particularly MT1 and MT2 receptors, are expressed in dopaminergic neurons and modulate dopamine release in response to various stimuli (67). Preclinical studies have demonstrated that the administration of melatonin attenuates dopamine release induced by psychostimulants, such as cocaine and amphetamines, suggesting a potential role in modulating reward processing and addiction vulnerability (68,69).

Glutamatergic system. The glutamatergic system plays a crucial role in addiction, mediating synaptic plasticity and long-term potentiation within the reward circuitry. Glutamate release in the NAc and PFC contributes to drug-induced neuroadaptations and craving behavior (70). Melatonin receptors are expressed in glutamatergic neurons, where they modulate glutamate release and synaptic transmission (71). Preclinical studies have shown that melatonin attenuates glutamate-induced excitotoxicity and reduces drug-seeking behavior in mouse HT22 hippocampal neurons and in mouse retinal ganglion cells (72,73). Furthermore, melatonin may modulate glutamate receptor expression and function, thereby influencing synaptic plasticity and addiction-related behaviors (74).

GABAergic system. Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the brain, plays a critical role in addiction by modulating the activity of dopaminergic neurons and regulating reward-related behaviors. GABAergic interneurons in the NAc and ventral tegmental area exert inhibitory control over the mesolimbic dopaminergic pathway (75,76). Melatonin receptors are expressed in GABAergic neurons, where they modulate GABA release and neuronal excitability. Preclinical studies suggest that melatonin administration enhances GABAergic transmission and attenuates drug-induced hyperactivity in animal models of addiction, highlighting its potential as a modulator of GABAergic signaling in addiction (77).

Serotonergic system. The serotonergic system, is involved with the raphe nuclei, modulates mood, impulsivity and reward processing, rendering it a key target in addiction research. Serotonin receptors are widely distributed throughout the brain, including regions implicated in addiction such as the NAc and PFC (78). Melatonin receptors are also expressed in serotonergic neurons, where they modulate serotonin synthesis, release and reuptake. Preclinical studies have suggested that melatonin may influence serotonergic neurotransmission and mood regulation, thereby affecting addiction vulnerability and comorbid mood disorders (79,80).

Endogenous opioid system. The endogenous opioid system, encompassing mu, delta and kappa opioid receptors, plays a crucial role in mediating the rewarding effects of drugs and natural reinforcers (81). Opioid receptors are densely expressed in the mesolimbic system, where they modulate dopamine release and reward processing (82). Melatonin receptors interact with the endogenous opioid system to modulate opioid receptor expression and opioid-induced analgesia. Preclinical studies have suggested that melatonin may attenuate opioid withdrawal symptoms and reduce opioid self-administration in animal models of addiction, underscoring its potential as a modulator of the opioid system in addiction (83,84). The diverse actions of melatonin on neurotransmitter systems related to addiction are summarized in Fig. 3.

6. Interplay between melatonin-regulated circadian rhythms and nicotine cravings

Circadian regulation of nicotine cravings. Circadian rhythms, orchestrated by melatonin in the SCN, play a central role

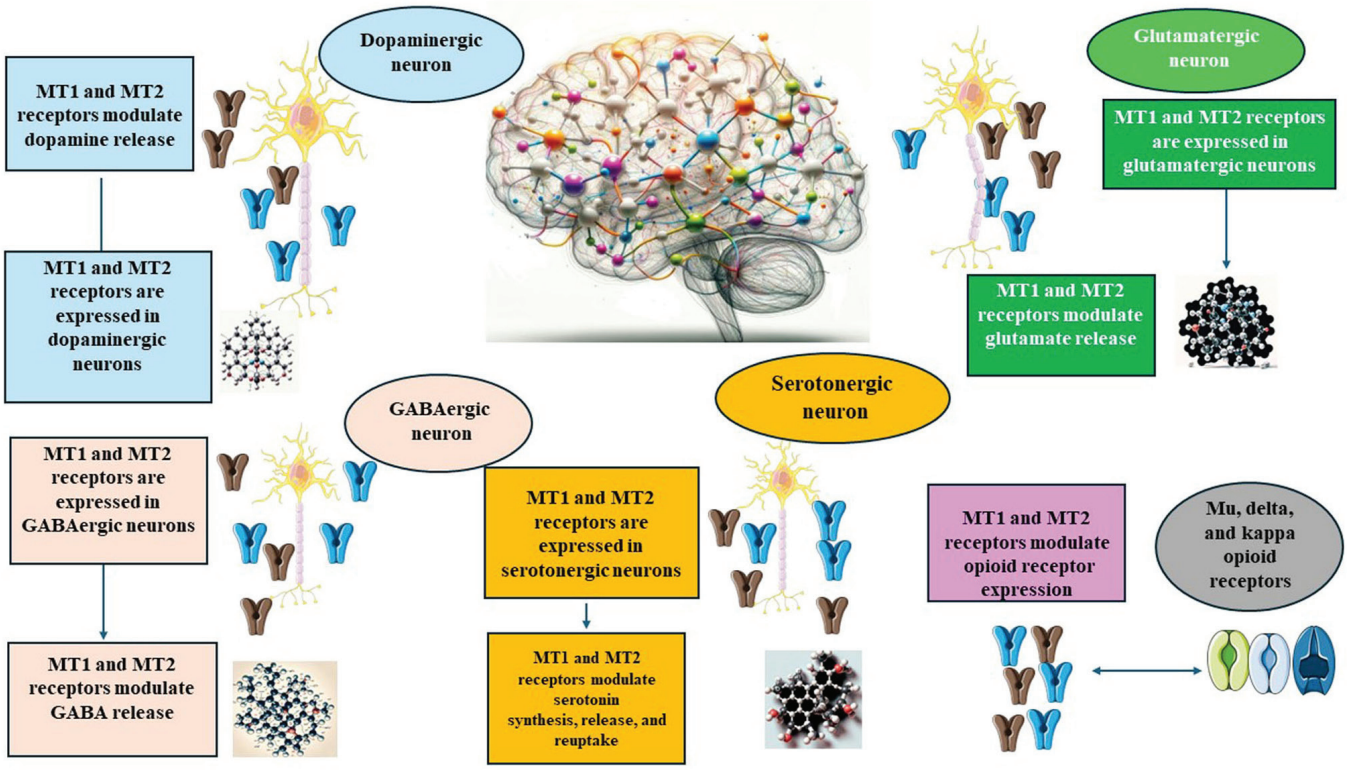

Figure 3. Potential influence of melatonin on neurotransmitter systems related to addiction. GABA, gamma-aminobutyric acid; MT1 and MT2, melatonin receptor types 1 and 2. Parts of this image derived from the free medical site http://smart.servier.com/ (accessed on April 5, 2024) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

in regulating various physiological processes, including sleep-wake cycles, hormone secretion and metabolism (85). Nicotine cravings and withdrawal symptoms often exhibit diurnal variations, with heightened cravings observed during periods of nicotine deprivation and reduced cravings during smoking or nicotine administration (86). The circadian regulation of nicotine cravings may be attributed, in part, to the influence of melatonin on reward-related pathways and neurotransmitter systems implicated in addiction (87).

Circadian disruptions and nicotine cravings. Disruptions to circadian rhythms, such as those experienced during shift work, jet lag, or chronic sleep disturbances, can exacerbate nicotine cravings and increase vulnerability to nicotine addiction (88). Shift workers, in particular, often exhibit alterations in melatonin secretion and circadian rhythms, which may contribute to heightened nicotine cravings and impaired nicotine dependence treatment outcomes. Strategies aimed at restoring circadian rhythmicity, such as light therapy or melatonin supplementation, may mitigate nicotine cravings and improve smoking cessation outcomes in individuals with circadian disruptions (89).

Chronotherapeutic approaches to nicotine addiction. Chronotherapeutic interventions targeting circadian rhythms and melatonin signaling hold promise for the treatment of nicotine addiction. Chronotherapy involves the timed administration of medications or behavioral interventions to align treatment efficacy with endogenous circadian rhythms (90). Melatonin supplementation or melatonin receptor agonists may be useful if administered during periods of heightened nicotine cravings to attenuate withdrawal symptoms and reduce the reinforcing effects of nicotine (13). Additionally, timed exposure to bright light or other circadian entrainment strategies may help normalize circadian rhythms and alleviate nicotine cravings in individuals with circadian disruptions (87).

7. Association between disrupted circadian rhythms and increased vulnerability to nicotine dependence

There is mounting evidence to suggest a compelling association between disrupted circadian rhythms and an increased vulnerability to nicotine dependence. Studies have consistently reported a higher prevalence of smoking among individuals with irregular sleep patterns or those engaged in shift work, indicating a potential interplay between circadian disruptions and nicotine addiction (91,92).

One proposed mechanism for this potential interaction involves the influence of circadian genes on nicotine metabolism. Genes involved in regulating circadian rhythms also modulate the metabolism of nicotine and other substances. Genetic variations in these circadian genes may affect the response of an individual to nicotine, potentially altering their susceptibility to developing dependence (93,94).

Moreover, circadian disruptions can exert profound effects on brain regions implicated in addiction, such as the mesolimbic dopaminergic system. This neural circuitry underpins reward processing and reinforcement learning which play pivotal roles in addictive behaviors. By distrupting the normal

functioning of this system, circadian disturbances may amplify the rewarding effects of nicotine, thereby heightening the risk of dependence (95).

8. Potential role of melatonin in mitigating withdrawal symptoms during smoking cessation

Understanding nicotine withdrawal. Nicotine, the primary psychoactive component in tobacco, exerts its addictive effects through the activation of nAChRs. Prolonged exposure to nicotine leads to neuroadaptations, resulting in dependence and subsequent withdrawal symptoms upon cessation. These symptoms can manifest as cravings, irritability, anxiety, a depressed mood and sleep disturbances, posing significant barriers to successful smoking cessation (96,97).

Exploring the effects of melatonin on nicotine withdrawal. Published preclinical and clinical studies have shed light on the potential therapeutic effects of melatonin in mitigating nicotine withdrawal symptoms. Melatonin administration attenuates nicotine withdrawal-induced anxiety-like behaviors and craving-related responses, suggesting a modulatory role in the reward circuitry of the brain (17). Furthermore, the antioxidant properties of melatonin may mitigate the oxidative stress associated with chronic exposure to nicotine, potentially ameliorating neuroinflammatory processes implicated in withdrawal symptoms (98). Additionally, the interactions of melatonin with neurotransmitter systems, including dopamine and GABA, could contribute to its anti-withdrawal effects by modulating neurotransmission in key brain regions involved in addiction (99).

9. Insights from studies on melatonin supplementation in nicotine withdrawal protocols

Research on melatonin supplementation in nicotine withdrawal protocols has yielded promising results. For example, clinical trials on humans have also shown the potential benefits of melatonin supplementation during smoking cessation. A randomized controlled trial found that smokers receiving melatonin supplementation experienced reduced withdrawal symptoms compared to those given a placebo. Specifically, melatonin-treated individuals reported lower levels of craving, irritability and sleep disturbances, suggesting a therapeutic role for melatonin in mitigating nicotine withdrawal symptoms (17).

Melatonin supplementation may also improve sleep quality during smoking cessation, which addresses one of the most commonly reported withdrawal symptoms (100). Sleep disturbances often exacerbate other withdrawal symptoms and increase the risk of relapse. By promoting improved sleep, melatonin supplementation could enhance overall cessation outcomes and reduce the likelihood of relapse (89).

The safety profile and tolerability of melatonin render it an attractive adjunctive therapy for smoking cessation. Unlike some pharmacotherapies, melatonin is a naturally occurring molecule with few adverse effects, making it suitable for long-term use (101,102). Additionally, melatonin supplements are readily available over-the-counter and inexpensive, providing convenient access to individuals seeking support during smoking cessation (103).

10. Consideration of potential therapeutic interventions targeting melatonin for nicotine dependence

Potential therapeutic interventions targeting melatonin for nicotine dependence offer promising avenues for enhancing smoking cessation outcomes. Several approaches could be explored.

Melatonin supplementation can reduce nicotine withdrawal symptoms and improve sleep quality among smokers attempting to quit (17). Further research is required however, to optimize dosing regimens, treatment durations and the timing of melatonin administration to maximize therapeutic efficacy.

Developing selective agonists targeting melatonin receptors may offer more specific and potent therapeutic effects compared to melatonin supplementation alone. These compounds could modulate neural circuits implicated in nicotine addiction and withdrawal, potentially reducing cravings and reinforcing the effects of nicotine (104).

Combining melatonin-based interventions with existing pharmacotherapies for smoking cessation, such as nicotine replacement therapy (NRT) or bupropion, may produce synergistic effects and improve treatment outcomes. These combined approaches could target both the physiological and behavioral aspects of nicotine dependence, providing a comprehensive approach to smoking cessation (105).

Integrating melatonin-based interventions with behavioral therapies, such as cognitive behavioral therapy (CBT) may enhance the efficacy of smoking cessation interventions. CBT addresses maladaptive behaviors and cognitive processes associated with nicotine addiction, while melatonin supplementation could target underlying neurobiological mechanisms contributing to craving and withdrawal symptoms (106).

Light therapy, which usually involves exposure to bright artificial light exposure at specific times of the day, modulates circadian rhythms and melatonin secretion (107). Incorporating light therapy as an adjunctive treatment for nicotine dependence may help regulate sleep-wake cycles and improve mood, potentially reducing nicotine cravings and withdrawal symptoms.

Promoting healthy lifestyle habits that support optimal circadian rhythms, such as regular sleep patterns, regular exercise and avoiding exposure to artificial light at night, may complement melatonin-based interventions for smoking cessation. These lifestyle modifications could enhance the efficacy of melatonin supplementation and promote long-term smoking abstinence (108).

Considering individual differences in melatonin secretion patterns, circadian rhythms and genetic variations may inform personalized treatment strategies for nicotine dependence (87). Tailoring interventions based on biomarkers predictive of treatment response could optimize therapeutic outcomes and minimize adverse effects.

Developing strategies to sustain melatonin-based interventions beyond the initial phase of smoking cessation is crucial for preventing relapse. Long-term maintenance approaches, such as gradual tapering of melatonin supplementation or intermittent dosing schedules, may help maintain stable circadian rhythms and support sustained smoking abstinence.

11. Identification of gaps in current knowledge

While research on the association between melatonin and nicotine dependence has provided valuable insight, several gaps in current knowledge warrant further investigation. Although preclinical studies have suggested that melatonin may modulate nicotine-seeking behavior and withdrawal symptoms through its interactions with neurotransmitter systems (68,69,72,73,77,79,80,83,84), the specific mechanisms underlying these effects remain incompletely understood. Further research is required to elucidate the molecular pathways and neural circuits involved in the effects of melatonin on nicotine dependence. Additionally, longitudinal studies tracking changes in melatonin secretion patterns over time, particularly during nicotine withdrawal and smoking cessation attempts, are required in order to better understand the temporal dynamics of melatonin dysregulation in relation to nicotine addiction.

There is a lack of research examining individual differences in melatonin responsiveness and circadian rhythms in relation to nicotine dependence. Investigating factors, such as age, sex, genetic variations and comorbidities that may influence the effects of melatonin on smoking behavior could help identify subgroups of smokers who may benefit most from melatonin-based interventions.

Some challenges remain in the integration of melatonin supplementation into nicotine withdrawal protocols. Variability in individual responses to melatonin, optimal dosing regimens and the potential for interactions with other medications necessitate further research. Additionally, the long-term efficacy of melatonin supplementation in maintaining smoking abstinence requires investigation in larger, longitudinal studies.

There is a need to identify biomarkers and predictors of treatment response to melatonin supplementation in nicotine dependence. Biomarkers associated with melatonin dysregulation or circadian disruption could serve as potential targets for personalized treatment strategies and may help stratify individuals based on their likelihood of responding to melatonin-based interventions.

12. Considering individual differences in treatment effects

Genetic variations. Genetics play a crucial role in how individuals metabolize and respond to melatonin. Polymorphisms in genes related to melatonin receptors (MT1 and MT2) and circadian rhythm regulation can affect the efficacy of melatonin in treating nicotine dependence. For instance, variations in the genes encoding for melatonin receptors may influence receptor sensitivity, thereby altering the effectiveness of melatonin in modulating nicotine cravings and withdrawal symptoms (109). Genetic testing can identify these polymorphisms, allowing for the customization of melatonin doses and treatment regimens to match the genetic profile of an individual (110). Personalized approaches based on genetic testing could enhance treatment efficacy and reduce the risk of adverse effects, offering a more targeted and effective intervention for nicotine dependence.

Age. Age is another critical factor influencing the effectiveness of melatonin in treating nicotine dependence. Melatonin production decreases with age, which may necessitate adjustments in dosage for older individuals to achieve therapeutic effects. Moreover, age-related changes in circadian rhythms and sleep patterns could affect how melatonin is metabolized and utilized by the body (111). Younger individuals may require different dosing schedules compared to older adults to align treatment with their specific circadian patterns. Tailoring melatonin supplementation according to age can optimize its effectiveness, improving treatment outcomes across different age groups.

Sex. Sex differences can also affect how individuals respond to melatonin treatment. Hormonal variations between males and females can influence circadian rhythms and melatonin metabolism. For example, fluctuations in estrogen levels during the menstrual cycle can affect melatonin levels, and its effects on sleep and mood (112). Research suggests that women may experience different nicotine withdrawal symptoms and cravings compared to men, which could influence their response to melatonin treatment (113). By considering these sex-specific differences, clinicians could develop more effective treatment protocols that address the unique needs of males and females, potentially improving adherence and outcomes.

Comorbid conditions. The presence of comorbid conditions, such as psychiatric disorders, cardiovascular diseases, or metabolic syndromes, can influence the effectiveness and safety of melatonin treatment for nicotine dependence. For instance, individuals with depression or anxiety may have altered melatonin signaling pathways, affecting the overall treatment response (114). Tailoring melatonin supplementation to account for these comorbid conditions involves a comprehensive assessment of the health status of a patient and the careful monitoring of the treatment progress.

Lifestyle factors. Lifestyle factors, including sleep patterns, diet and exposure to light, significantly affect the effectiveness of melatonin treatment. For instance, individuals with irregular sleep patterns or those exposed to high levels of artificial light at night may experience disruptions in their circadian rhythms, affecting the therapeutic potential of melatonin (115). Lifestyle modifications, such as improving sleep hygiene, reducing evening light exposure and maintaining a regular sleep schedule, can enhance the effectiveness of melatonin treatment.

13. Methodological challenges in studying the melatonin-nicotine association

Studying the association between melatonin and nicotine presents several methodological challenges, which researchers have to consider to obtain robust and reliable findings.

Measurement of melatonin levels. Accurately measuring melatonin levels presents a challenge due to its episodic release, its short half-life in the blood and its unique nocturnal elevation which requires darkness (116,117).

The majority of studies rely on indirect measures, such as salivary melatonin or urinary melatonin metabolite samples to monitor its circulating concentrations, which may

not capture fluctuations accurately. Additionally, factors, such as smoking-related changes in metabolism and excretion rates may make measuring melatonin in smokers more challenging (118,119).

Assessment of nicotine exposure. Quantifying nicotine exposure in study participants can be challenging, particularly in observational studies or clinical trials where self-reported smoking status may be unreliable. Biomarkers, such as cotinine levels in blood or urine can provide objective measures of nicotine exposure, but may not capture variations in nicotine intake over time accurately (120).

Accounting for circadian rhythms. Melatonin secretion follows a circadian rhythm, with levels peaking at night and minimal during the day (121). Studies investigating the melatonin-nicotine association should account for these circadian variations when assessing melatonin levels and nicotine effects. Failure to consider circadian rhythms adequately could confound the study results and obscure true associations between melatonin and nicotine dependence.

Control of confounding variables. Numerous confounding factors, such as age, sex, genetics, lifestyle factors (e.g., sleep patterns, diet) and comorbidities (such as psychiatric disorders), may affect smoking behavior and melatonin secretion (122,123). Failure to control for these confounders adequately can introduce bias and limit the validity of study findings.

Longitudinal study designs. Investigating the temporal association between melatonin levels and nicotine dependence requires longitudinal study designs that follow participants over time. However, longitudinal studies are resource-intensive and may face challenges, such as participant attrition, loss of follow-up and changes in smoking behavior during the study, which complicates data analysis and interpretation (124).

Experimental manipulation. Conducting experimental studies to investigate the effects of melatonin manipulation on nicotine dependence faces ethical and practical challenges. Ethical considerations, such as ensuring informed consent may limit the ability to administer melatonin or manipulate melatonin levels in human participants, while animal models may not fully recapitulate the complex neurobiological and behavioral aspects of nicotine addiction in humans (125).

Generalizability of findings. Limited search examining the melatonin-nicotine association has been conducted in controlled laboratory settings or specific population groups, which may limit the generalizability of findings to broader populations of smokers (17). Ensuring the diversity and representativeness of study samples is crucial for extrapolating findings to real-world settings (126).

14. Detailed discussions on clinical trial designs and practical challenges

Clinical trial designs. Randomized controlled trials are the gold standard for evaluating the efficacy of melatonin in reducing nicotine dependence. Participants are randomly assigned to receive melatonin or a placebo. Key considerations include an adequate sample size, randomization, double-blinding and clear outcome definitions, such as reduced nicotine cravings and withdrawal symptoms, with long-term follow-up (127).

Crossover trials involve participants receiving both treatment and placebo at different times, reducing variability by serving as their own control. Key considerations are adequate washout periods and randomized order of treatments (128). Factorial designs test multiple interventions simultaneously, such as melatonin with CBT or NRT, assessing interaction effects and managing increased design complexity.

Practical challenges and solutions in real-world applications. Ensuring participant adherence to the melatonin regimen and study protocols is a significant challenge, particularly during long-term follow-up. Solutions include thorough education on adherence and study benefits, automated reminders via text messages or phone calls, and support systems, such as peer groups or regular check-ins.

Accurately measuring nicotine dependence and withdrawal symptoms, along with capturing subjective outcomes such as cravings and mood changes, presents another challenge. Solutions involve using validated scales and questionnaires, incorporating biomarkers such as cotinine levels, and requesting that participants keep daily diaries.

Variability in individual responses to melatonin, influenced by genetics, age and circadian rhythms, necessitates a tailored approach. Effective strategies include the development of personalized treatment plans, conducting subgroup analyses to identify populations that benefit most, and optional genetic testing to explore correlations between genetic markers and treatment response.

Addressing environmental and social factors that influence smoking behavior, such as stress and exposure to smoking cues, is critical. Integrating melatonin with holistic interventions, combining it with behavioral therapies such as CBT, and engaging community resources and support networks provide a supportive environment for smoking cessation.

15. Future research directions and conclusions

Future research in the field of melatonin and nicotine dependence is required to explore several promising directions as outlined herein to advance our understanding and improve treatment strategies.

Novel therapeutic targets. Identifying novel therapeutic targets within the melatonergic system and circadian clock machinery could lead to the development of more specific and potent interventions for nicotine dependence. Investigating the role of melatonin receptors, clock genes, and other components of the circadian system in nicotine addiction may uncover new avenues for pharmacological intervention.

Digital health interventions. Leveraging digital health technologies, such as mobile applications, wearable devices and telemedicine platforms could enhance the delivery and accessibility of melatonin-based interventions for smoking

cessation. Further research is required to explore the feasibility and effectiveness of digital interventions in supporting adherence to melatonin supplementation and monitoring treatment outcomes remotely.

In conclusion, the interplay between melatonin and nicotine dependence involves complex neurobiological, physiological and behavioral mechanisms. Understanding this association could provide insight into novel therapeutic strategies for managing nicotine addiction and associated sleep disturbances. However, further research is warranted in order to elucidate the precise mechanisms underlying this interaction and to develop effective interventions for individuals with nicotine dependence.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

DAS and VEG conceptualized the study. VEG, PS, NT, RJR and DAS made a substantial contribution to the interpretation and analysis of the data to be included in the review, and wrote and prepared the draft of the manuscript. RJR and DAS analyzed the data and provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the AI tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Widysanto A, Combest FE, Dhakal A and Saadabadi A: Nicotine addiction (Updated 2023 Aug 8). In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2024.
2. Prochaska JJ and Benowitz NL: Current advances in research in treatment and recovery: Nicotine addiction. Sci Adv 5: eaay9763, 2019.
3. Onaolapo OJ and Onaolapo AY: Melatonin in drug addiction and addiction management: Exploring an evolving multidimensional relationship. World J Psychiatry 8: 64-74, 2018.
4. Picciotto MR and Kenny PJ: Mechanisms of nicotine addiction. Cold Spring Harb Perspect Med 11: a039610, 2021.
5. Zhu J, Nelson K, Toth J and Muscat JE: Nicotine dependence as an independent risk factor for atherosclerosis in the national lung screening trial. BMC Public Health 19: 103, 2019.
6. Trakas N, Georgakopoulou VE, Melemeni D, Damaskos C, Mantzouranis K, Garmpis N, Gkoufa A, Papalexis P, Chlapoutakis S, Sklapani P, *et al*: Association between smoking cessation and alterations in forced expiratory volume in one second (FEV1). A follow-up study from a greek tobacco cessation clinic. Addict Health 14: 87-95, 2022.
7. Masters A, Pandi-Perumal SR, Seixas A, Girardin JL and McFarlane SI: Melatonin, the hormone of darkness: From sleep promotion to ebola treatment. Brain Disord Ther 4: 1000151, 2014.
8. Hardeland R, Madrid JA, Tan DX and Reiter RJ: Melatonin, the circadian multioscillator system and health: The need for detailed analyses of peripheral melatonin signaling. J Pineal Res 52: 139-166, 2012.
9. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z and Reiter RJ: Melatonin as a potent and inducible endogenous antioxidant: Synthesis and metabolism. Molecules 20: 18886-18906, 2015.
10. Reiter RJ, Rosales-Corral SA, Tan DX, Acuna-Castroviejo D, Qin L, Yang SF and Xu K: Melatonin, a full service anti-cancer agent: Inhibition of initiation, progression and metastasis. Int J Mol Sci 18: 843, 2017.
11. Bocheva G, Slominski RM, Janjetovic Z, Kim TK, Böhm M, Steinbrink K, Reiter RJ, Kleszczyński K and Slominski AT: Protective role of melatonin and its metabolites in skin aging. Int J Mol Sci 23: 1238, 2022.
12. Lempesis IG, Georgakopoulou VE, Reiter RJ and Spandidos DA: A mid-pandemic night's dream: Melatonin, from harbinger of anti-inflammation to mitochondrial savior in acute and long COVID-19 (Review). Int J Mol Med 53: 28, 2024.
13. Horton WJ, Gissel HJ, Saboy JE, Wright KP Jr and Stitzel JA: Melatonin administration alters nicotine preference consumption via signaling through high-affinity melatonin receptors. Psychopharmacology (Berl) 232: 2519-2530, 2015.
14. Schiller ED, Champney TH, Reiter CK and Dohrman DP: Melatonin inhibition of nicotine-stimulated dopamine release in PC12 cells. Brain Res 966: 95-102, 2003.
15. Markus RP, Santos JM, Zago W and Reno LA: Melatonin nocturnal surge modulates nicotinic receptors and nicotine-induced [3H]glutamate release in rat cerebellum slices. J Pharmacol Exp Ther 305: 525-530, 2003.
16. Wang Y, Guo D, Wang J, Tian B, Li Y, Sun G and Zhang H: Exogenous melatonin alleviates NO_2 damage in tobacco leaves by promoting antioxidant defense, modulating redox homeostasis, and signal transduction. J Hazard Mater 424: 127265, 2022.
17. Zhdanova IV and Piotrovskaya VR: Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. Pharmacol Biochem Behav 67: 131-135, 2000.
18. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, Rosales-Corral S, Tan DX and Reiter RJ: Extrapineal melatonin: Sources, regulation, and potential functions. Cell Mol Life Sci 71: 2997-3025, 2014.
19. Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B and Hardeland R: Melatonin: Nature's most versatile biological signal? FEBS J 273: 2813-2838, 2006.
20. Xie X, Ding D, Bai D, Zhu Y, Sun W, Sun Y and Zhang D: Melatonin biosynthesis pathways in nature and its production in engineered microorganisms. Synth Syst Biotechnol 7: 544-553, 2022.
21. Zhao D, Yu Y, Shen Y, Liu Q, Zhao Z, Sharma R and Reiter RJ: Melatonin synthesis and function: evolutionary history in animals and plants. Front Endocrinol (Lausanne) 10: 249, 2019.
22. Zisapel N: New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol 175: 3190-3199, 2018.

23. Blume C, Garbazza C and Spitschan M: Effects of light on human circadian rhythms, sleep and mood. Somnologie (Berl) 23: 147-156, 2019.
24. Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L and Zagrean AM: Melatonin's impact on antioxidative and anti-inflammatory reprogramming in homeostasis and disease. Biomolecules 10: 1211, 2020.
25. Kopustinskiene DM and Bernatoniene J: Molecular mechanisms of melatonin-mediated cell protection and signaling in health and disease. Pharmaceutics 13: 129, 2021.
26. Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernández-Montesinos R, Guerrero JM and Pozo D: The modulatory role of melatonin on immune responsiveness. Curr Opin Investig Drugs 7: 423-431, 2006.
27. Calvo JR, González-Yanes C and Maldonado MD: The role of melatonin in the cells of the innate immunity: A review. J Pineal Res 55: 103-120, 2013.
28. Carrillo-Vico A, Lardone PJ, Alvarez-Sánchez N, Rodríguez-Rodríguez A and Guerrero JM: Melatonin: Buffering the immune system. Int J Mol Sci 14: 8638-8683, 2013.
29. Lee JG, Woo YS, Park SW, Seog DH, Seo MK and Bahk WM: The neuroprotective effects of melatonin: Possible role in the pathophysiology of neuropsychiatric disease. Brain Sci 9: 285, 2019.
30. Won E, Na KS and Kim YK: Associations between melatonin, neuroinflammation, and brain alterations in depression. Int J Mol Sci 23: 305, 2021.
31. Tozihi M, Shademan B, Yousefi H, Avci CB, Nourazarian A and Dehghan G: Melatonin: A promising neuroprotective agent for cerebral ischemia-reperfusion injury. Front Aging Neurosci 15: 1227513, 2023.
32. Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B and Hardeland R: Melatonin in Alzheimer's disease and other neurodegenerative disorders. Behav Brain Funct 2: 15, 2006.
33. Reiter RJ, Tamura H, Tan DX and Xu XY: Melatonin and the circadian system: Contributions to successful female reproduction. Fertil Steril 102: 321-328, 2014.
34. Aversa S, Pellegrino S, Barberi I, Reiter RJ and Gitto E: Potential utility of melatonin as an antioxidant during pregnancy and in the perinatal period. J Matern Fetal Neonatal Med 25: 207-221, 2012.
35. Olcese JM: Melatonin and female reproduction: An expanding universe. Front Endocrinol (Lausanne) 11: 85, 2020.
36. Benowitz NL: Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 49: 57-71, 2009.
37. De Biasi M and Dani JA: Reward, addiction, withdrawal to nicotine. Annu Rev Neurosci 34: 105-130, 2011.
38. Wang Y, Chen X, Gong J and Yan Y: Relationships between stress, negative emotions, resilience, and smoking: Testing a moderated mediation model. Subst Use Misuse 51: 427-438, 2016.
39. Stevenson JG, Oliver JA, Hallyburton MB, Sweitzer MM, Conklin CA and McClernon FJ: Smoking environment cues reduce ability to resist smoking as measured by a delay to smoking task. Addict Behav 67: 49-52, 2017.
40. Roy A, Rawal I, Jabbour S and Prabhakaran D: Chapter 4: Tobacco and cardiovascular disease: A summary of evidence. In: Cardiovascular, Respiratory, and Related Disorders. Prabhakaran D, Anand S, Gaziano TA, Mbanya JC, Wu Y and Nugent R (eds). 3rd edition. The International Bank for Reconstruction and Development/The World Bank, Washington, DC, 2017.
41. Liu CC and Yeh HI: Nicotine: A double-edged sword in atherosclerotic disease. Acta Cardiol Sin 30: 108-113, 2014.
42. Benowitz NL and Burbank AD: Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med 26: 515-523, 2016.
43. Strzelak A, Ratajczak A, Adamiec A and Feleszko W: Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: A mechanistic review. Int J Environ Res Public Health 15: 1033, 2018.
44. Mishra A, Chaturvedi P, Datta S, Sinukumar S, Joshi P and Garg A: Harmful effects of nicotine. Indian J Med Paediatr Oncol 36: 24-31, 2015.
45. Grando SA: Connections of nicotine to cancer. Nat Rev Cancer 14: 419-429, 2014.
46. Caliri AW, Tommasi S and Besaratinia A: Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Rev Mutat Res 787: 108365, 2021.
47. Chang CM, Corey CG, Rostron BL and Apelberg BJ: Systematic review of cigar smoking and all cause and smoking related mortality. BMC Public Health 15: 390, 2015.
48. Kim AS, Ko HJ, Kwon JH and Lee JM: Exposure to secondhand smoke and risk of cancer in never smokers: A meta-analysis of epidemiologic studies. Int J Environ Res Public Health 15: 1981, 2018.
49. El-Sherbiny NA and Elsary AY: Smoking and nicotine dependence in relation to depression, anxiety, and stress in Egyptian adults: A cross-sectional study. J Family Community Med 29: 8-16, 2022.
50. Kutlu MG, Parikh V and Gould TJ: Nicotine addiction and psychiatric disorders. Int Rev Neurobiol 124: 171-208, 2015.
51. Albarrak DA, Alotaibi AB, Alotaibi RF, Alramadhan SH, Bin Muhanna AI, Aldehan AM and Bin Abdulrahman KA: The association between nicotine dependence and mental health in the general population of Saudi Arabia: A cross-sectional analytical study. Int J Gen Med 16: 5801-5815, 2023.
52. Cecon E, Oishi A and Jockers R: Melatonin receptors: Molecular pharmacology and signalling in the context of system bias. Br J Pharmacol 175: 3263-3280, 2018.
53. Doghramji K: Melatonin and its receptors: A new class of sleep-promoting agents. J Clin Sleep Med 3 (Suppl 5): S17-S23, 2007.
54. Healy KL, Morris AR and Liu AC: Circadian synchrony: Sleep, nutrition, and physical activity. Front Netw Physiol 1: 732243, 2021.
55. Sato TK, Yamada RG, Ukai H, Baggs JE, Miraglia LJ, Kobayashi TJ, Welsh DK, Kay SA, Ueda HR and Hogenesch JB: Feedback repression is required for mammalian circadian clock function. Nat Genet 38: 312-319, 2006.
56. Rahman SA, St Hilaire MA, Chang AM, Santhi N, Duffy JF, Kronauer RE, Czeisler CA, Lockley SW and Klerman EB: Circadian phase resetting by a single short-duration light exposure. JCI Insight 2: e89494, 2017.
57. Schwartz MD and Kilduff TS: The neurobiology of sleep and wakefulness. Psychiatr Clin North Am 38: 615-644, 2015.
58. Wright KP, Lowry CA and Lebourgeois MK: Circadian and wakefulness-sleep modulation of cognition in humans. Front Mol Neurosci 5: 50, 2012.
59. Valdés-Tovar M, Estrada-Reyes R, Solís-Chagoyán H, Argueta J, Dorantes-Barrón AM, Quero-Chávez D, Cruz-Garduño R, Cercós MG, Trueta C, Oikawa-Sala J, *et al*: Circadian modulation of neuroplasticity by melatonin: A target in the treatment of depression. Br J Pharmacol 175: 3200-3208, 2018.
60. Boiko DI, Shkodina AD, Hasan MM, Bardhan M, Kazmi SK, Chopra H, Bhutra P, Baig AA and Skrypnikov AM: Melatonergic receptors (Mt1/Mt2) as a potential additional target of novel drugs for depression. Neurochem Res 47: 2909-2924, 2022.
61. Mehraein F, Talebi R, Jameie B, Joghataie MT and Madjd Z: Neuroprotective effect of exogenous melatonin on dopaminergic neurons of the substantia nigra in ovariectomized rats. Iran Biomed J 15: 44-50, 2011.
62. Shukla M, Govitrapong P, Boontem P, Reiter RJ and Satayavivad J: Mechanisms of melatonin in alleviating Alzheimer's disease. Curr Neuropharmacol 15: 1010-1031, 2017.
63. Kim J, Li W, Wang J, Baranov SV, Heath BE, Jia J, Suofu Y, Baranova OV, Wang X, Larkin TM, *et al*: Biosynthesis of neuroprotective melatonin is dysregulated in Huntington's disease. J Pineal Res 75: e12909, 2023.
64. Laudon M and Frydman-Marom A: Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. Int J Mol Sci 15: 15924-15950, 2014.
65. Kostoglou-Athanassiou I: Therapeutic applications of melatonin. Ther Adv Endocrinol Metab 4: 13-24, 2013.
66. Scofield MD, Heinsbroek JA, Gipson CD, Kupchik YM, Spencer S, Smith ACW, Roberts-Wolfe D and Kalivas PW: The nucleus accumbens: Mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol Rev 68: 816-871, 2016.
67. Ekmekcioglu C: Melatonin receptors in humans: Biological role and clinical relevance. Biomed Pharmacother 60: 97-108, 2006.
68. Leeboonngam T, Pramong R, Sae-Ung K, Govitrapong P and Phansuwan-Pujito P: Neuroprotective effects of melatonin on amphetamine-induced dopaminergic fiber degeneration in the hippocampus of postnatal rats. J Pineal Res 64: e12456, 2018.
69. Sae-Ung K, Uéda K, Govitrapong P and Phansuwan-Pujito P: Melatonin reduces the expression of alpha-synuclein in the dopamine containing neuronal regions of amphetamine-treated postnatal rats. J Pineal Res 52: 128-137, 2012.

70. Quintero GC: Role of nucleus accumbens glutamatergic plasticity in drug addiction. Neuropsychiatr Dis Treat 9: 1499-1512, 2013.
71. Evely KM, Hudson RL, Dubocovich ML and Haj-Dahmane S: Melatonin receptor activation increases glutamatergic synaptic transmission in the rat medial lateral habenula. Synapse 70: 181-186, 2016.
72. Wang DD, Jin MF, Zhao DJ and Ni H: Reduction of mitophagy-related oxidative stress and preservation of mitochondria function using melatonin therapy in an HT22 hippocampal neuronal cell model of glutamate-induced excitotoxicity. Front Endocrinol (Lausanne) 10: 550, 2019.
73. Wang C, An Y, Xia Z, Zhou X, Li H, Song S, Ding L and Xia X: The neuroprotective effect of melatonin in glutamate excitotoxicity of R28 cells and mouse retinal ganglion cells. Front Endocrinol (Lausanne) 13: 986131, 2022.
74. Jia S, Guo X, Chen Z, Li S and Liu XA: The roles of the circadian hormone melatonin in drug addiction. Pharmacol Res 183: 106371, 2022.
75. Li X and Slesinger PA: $GABA_B$ receptors and drug addiction: Psychostimulants and other drugs of abuse. Curr Top Behav Neurosci 52: 119-155, 2022.
76. Kalsbeek A, Garidou ML, Palm IF, Van Der Vliet J, Simonneaux V, Pévet P and Buijs RM: Melatonin sees the light: Blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. Eur J Neurosci 12: 3146-3154, 2000.
77. Cheng XP, Sun H, Ye ZY and Zhou JN: Melatonin modulates the GABAergic response in cultured rat hippocampal neurons. J Pharmacol Sci 119: 177-185, 2012.
78. Sari Y, Johnson VR and Weedman JM: Role of the serotonergic system in alcohol dependence: From animal models to clinics. Prog Mol Biol Transl Sci 98: 401-443, 2011.
79. Míguez JM, Simonneaux V and Pévet P: Evidence for a regulatory role of melatonin on serotonin release and uptake in the pineal gland. J Neuroendocrinol 7: 949-956, 1995.
80. Micale V, Arezzi A, Rampello L and Drago F: Melatonin affects the immobility time of rats in the forced swim test: The role of serotonin neurotransmission. Eur Neuropsychopharmacol 16: 538-545, 2006.
81. Befort K: Interactions of the opioid and cannabinoid systems in reward: Insights from knockout studies. Front Pharmacol 6: 6, 2015.
82. Fields HL and Margolis EB: Understanding opioid reward. Trends Neurosci 38: 217-225, 2015.
83. Dai X, Cui SG, Li SR, Chen Q and Wang R: Melatonin attenuates the development of antinociceptive tolerance to delta-, but not to mu-opioid receptor agonist in mice. Behav Brain Res 182: 21-27, 2007.
84. El-Shenawy SM, Abdel-Salam OM, Baiuomy AR, El-Batran S and Arbid MS: Studies on the anti-inflammatory and anti-nociceptive effects of melatonin in the rat. Pharmacol Res 46: 235-243, 2002.
85. Van Drunen R and Eckel-Mahan K: Circadian rhythms of the hypothalamus: From function to physiology. Clocks Sleep 3: 189-226, 2021.
86. McLaughlin I, Dani JA and De Biasi M: Nicotine withdrawal. Curr Top Behav Neurosci 24: 99-123, 2015.
87. Logan RW, Williams WP III and McClung CA: Circadian rhythms and addiction: Mechanistic insights and future directions. Behav Neurosci 128: 387-412, 2014.
88. Hasler BP, Smith LJ, Cousins JC and Bootzin RR: Circadian rhythms, sleep, and substance abuse. Sleep Med Rev 16: 67-81, 2012.
89. Cho YM, Kim HR, Kang MY, Myong JP and Koo JW: Fixed night workers and failed smoking cessation. J Occup Med Toxicol 14: 23, 2019.
90. Cardinali DP, Brown GM and Pandi-Perumal SR: Chronotherapy. Handb Clin Neurol 179: 357-370, 2021.
91. Bae MJ, Song YM, Shin JY, Choi BY, Keum JH and Lee EA: The association between shift work and health behavior: Findings from the Korean national health and nutrition examination survey. Korean J Fam Med 38: 86-92, 2017.
92. Short NA, Mathes BM, Gibby B, Oglesby ME, Zvolensky MJ and Schmidt NB: Insomnia symptoms as a risk factor for cessation failure following smoking treatment. Addict Res Theory 25: 17-23, 2017.
93. Perreau-Lenz S and Spanagel R: Clock genes × stress × reward interactions in alcohol and substance use disorders. Alcohol 49: 351-357, 2015.
94. Saad L, Zwiller J, Kalsbeek A and Anglard P: Epigenetic regulation of circadian clocks and its involvement in drug addiction. Genes (Basel) 12: 1263, 2021.
95. Lewis RG, Florio E, Punzo D and Borrelli E: The Brain's reward system in health and disease. Adv Exp Med Biol 1344: 57-69, 2021.
96. Wittenberg RE, Wolfman SL, De Biasi M and Dani JA: Nicotinic acetylcholine receptors and nicotine addiction: A brief introduction. Neuropharmacology 177: 108256, 2020.
97. Jiloha RC: Biological basis of tobacco addiction: Implications for smoking-cessation treatment. Indian J Psychiatry 52: 301-307, 2010.
98. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M and Qin L: Melatonin as an antioxidant: Under promises but over delivers. J Pineal Res 61: 253-278, 2016.
99. Datta PC and King MG: Melatonin: Effects on brain and behavior. Neurosci Biobehav Rev 4: 451-458, 1980.
100. Fatemeh G, Sajjad M, Niloufar R, Neda S, Leila S and Khadijeh M: Effect of melatonin supplementation on sleep quality: A systematic review and meta-analysis of randomized controlled trials. J Neurol 269: 205-216, 2022.
101. Foley HM and Steel AE: Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. Complement Ther Med 42: 65-81, 2019.
102. Motooka Y, Matsui T, Slaton RM, Umetsu R, Fukuda A, Naganuma M, Hasegawa S, Sasaoka S, Hatahira H, Iguchi K and Nakamura M: Adverse events of smoking cessation treatments (nicotine replacement therapy and non-nicotine prescription medication) and electronic cigarettes in the food and drug administration adverse event reporting system, 2004-2016. SAGE Open Med 6: 2050312118777953, 2018.
103. Erland LAE and Saxena PK: Melatonin natural health products and supplements: Presence of serotonin and significant variability of melatonin content. J Clin Sleep Med 13: 275-281, 2017.
104. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M and Dubocovich ML: MT1 and MT2 melatonin receptors: A therapeutic perspective. Annu Rev Pharmacol Toxicol 56: 361-383, 2016.
105. Giulietti F, Filipponi A, Rosettani G, Giordano P, Iacoacci C, Spannella F and Sarzani R: Pharmacological approach to smoking cessation: An updated review for daily clinical practice. High Blood Press Cardiovasc Prev 27: 349-362, 2020.
106. Perkins KA, Conklin CA and Levine MD: Cognitive-behavioral therapy for smoking cessation: A practical guidebook to the most effective treatments (1st edition). Routledge, New York, NY, 2007.
107. Shirani A and St Louis EK: Illuminating rationale and uses for light therapy. J Clin Sleep Med 5: 155-163, 2009.
108. Patterson F, Grandner MA, Malone SK, Rizzo A, Davey A and Edwards DG: Sleep as a target for optimized response to smoking cessation treatment. Nicotine Tob Res 21: 139-148, 2019.
109. Silva ACPE, Santos MJD, Koike BDV, Moreira MSA, Gitai DLG, de Miranda Coelho JAP and de Andrade TG: Melatonin receptor 1B-1193T>C polymorphism is associated with diurnal preference and sleep habits. Sleep Med 53: 106-114, 2019.
110. Sulkava S, Ollila HM, Alasaari J, Puttonen S, Härmä M, Viitasalo K, Lahtinen A, Lindström J, Toivola A, Sulkava R, *et al*: Common genetic variation near melatonin receptor 1A gene linked to job-related exhaustion in shift workers. Sleep 40: zsw011, 2017.
111. Pandi-Perumal SR, Zisapel N, Srinivasan V and Cardinali DP: Melatonin and sleep in aging population. Exp Gerontol 40: 911-925, 2005.
112. Shechter A and Boivin DB: Sleep, hormones, and circadian rhythms throughout the menstrual cycle in healthy women and women with premenstrual dysphoric disorder. Int J Endocrinol 2010: 259345, 2010.
113. Leventhal AM, Waters AJ, Boyd S, Moolchan ET, Lerman C and Pickworth WB: Gender differences in acute tobacco withdrawal: Effects on subjective, cognitive, and physiological measures. Exp Clin Psychopharmacol 15: 21-36, 2007.
114. Repova K, Baka T, Krajcirovicova K, Stanko P, Aziriova S, Reiter RJ and Simko F: Melatonin as a potential approach to anxiety treatment. Int J Mol Sci 23: 16187, 2022.
115. Touitou Y, Reinberg A and Touitou D: Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption. Life Sci 173: 94-106, 2017.

116. English J, Arendt J, Poulton A and Symons AM: Short-term variations of circulating melatonin in the ewe. J Pineal Res 4: 359-366, 1987.
117. Cozzi B, Ravault JP, Ferrandi B and Reiter RJ: Melatonin concentration in the cerebral vascular sinuses of sheep and evidence for its episodic release. J Pineal Res 5: 535-543, 1988.
118. Rzepka-Migut B and Paprocka J: Melatonin-measurement methods and the factors modifying the results. A systematic review of the literature. Int J Environ Res Public Health 17: 1916, 2020.
119. Benloucif S, Burgess HJ, Klerman EB, Lewy AJ, Middleton B, Murphy PJ, Parry BL and Revell VL: Measuring melatonin in humans. J Clin Sleep Med 4: 66-69, 2008.
120. Florescu A, Ferrence R, Einarson T, Selby P, Soldin O and Koren G: Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: Focus on developmental toxicology. Ther Drug Monit 31: 14-30, 2009.
121. Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N and Fougerou C: Melatonin: pharmacology, functions and therapeutic benefits. Curr Neuropharmacol 15: 434-443, 2017.
122. Valentine JA: The transformative role of authentic partnership in the tuskegee public health ethics program. J Healthc Sci Humanit 8: 21-29, 2018.
123. Minichino A, Bersani FS, Calò WK, Spagnoli F, Francesconi M, Vicinanza R, Delle Chiaie R and Biondi M: Smoking behaviour and mental health disorders-mutual influences and implications for therapy. Int J Environ Res Public Health 10: 4790-4811, 2013.
124. Caruana EJ, Roman M, Hernández-Sánchez J and Solli P: Longitudinal studies. J Thorac Dis 7: E537-E540, 2015.
125. Yip C, Han NR and Sng BL: Legal and ethical issues in research. Indian J Anaesth 60: 684-688, 2016.
126. Faber J and Fonseca LM: How sample size influences research outcomes. Dental Press J Orthod 19: 27-29, 2014.
127. Hariton E and Locascio JJ: Randomised controlled trials-the gold standard for effectiveness research: Study design: Randomised controlled trials. BJOG 125: 1716, 2018.
128. Lim CY and In J: Considerations for crossover design in clinical study. Korean J Anesthesiol 74: 293-299, 2021.