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REVIEW

REM sleep loss–induced elevated noradrenaline could predispose an individual to psychosomatic disorders: a review focused on proposal for prediction, prevention, and personalized treatment

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Abstract
Historically and traditionally, it is known that sleep helps in maintaining healthy living. Its duration varies not only among individuals but also in the same individual depending on circumstances, suggesting it is a dynamic and personalized physiological process. It has been divided into rapid eye movement sleep (REMS) and non-REMS (NREMS). The former is unique that adult humans spend the least time in this stage, when although one is physically asleep, the brain behaves as if awake, the dream state. As NREMS is a pre-requisite for appearance of REMS, the latter can be considered a predictive readout of sleep quality and health. It plays a protective role against oxidative, stressful, and psychopathological insults. Several modern lifestyle activities compromise quality and quantity of sleep (including REMS) affecting fundamental physiological and psychopathosomatic processes in a personalized manner. REMS loss–induced elevated brain noradrenaline (NA) causes many associated symptoms, which are ameliorated by preventing NA action. Therefore, we propose that awareness about personalized sleep hygiene (including REMS) and maintaining optimum brain NA level should be of paramount significance for leading physical and mental well-being as well as healthy living. As sleep is a dynamic, multifactorial, homeostatically regulated process, for healthy living, we recommend addressing and treating sleep dysfunctions in a personalized manner by the health professionals, caregivers, family, and other supporting members in the society. We also recommend that maintaining sleep profile, optimum level of NA, and/or prevention of elevation of NA or its action in the brain must be seriously considered for ameliorating lifestyle and REMS disturbance–associated dysfunctions.

Keywords Biomarkers · Healthy sleep · Neuropathology · Noradrenaline · Predictive preventive personalized medicine · REMS · Sleep loss · Sleep quality

Introduction

Traditional wisdom has suggested that "*sound sleep reflects a healthy body, while a disturbed sleep reflects a troubled mind*". It appears to be appropriate and applicable even today on our daily routine to lead healthy life [1]. Sleep is a reversible physiological state, where the consciousness remains in a subdued state. It is a constitutive part of life where the body is relaxed; although the brain is responsive to autonomic stimuli, the threshold of responsiveness to voluntary stimuli is higher. As a matter of fact, optimum sleep can be regarded as an indispensable physiological process necessary for preserving the good health and well-being of an individual; however, its detailed mechanism of action is unknown. Insufficient sleep activates sleep-inducing mechanism(s) as part of homeostatic response that stimulates a compensatory increase in its intensity and duration [2].

Sleep and wakefulness are subjective phenomena, which have been objectively classified based on the electrophysiological signals recorded from the scalp, eye, and neck muscles. The use of such objective criteria not only rejected the earlier passive theory of appearance of sleep but also established that

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sleep is a non-homogenous, active state. Based on such criteria, sleep has been objectively classified into rapid eye movement sleep (REMS) and non-REMS (NREMS). REMS is a unique physiological process expressed in all vertebrates studied so far, including humans, who spend the least amount of time in REMS. It plays an important role in maintaining the most physiological processes; it has been suggested to maintain the house-keeping function of the brain [3]. Disturbed REMS is among the common symptoms reported in almost all psychosomatic, neurological, cardiovascular and respiratory, metabolic dysfunctions and acute as well as chronic pathological conditions including Alzheimer's (AD) and Parkinson's (PD) diseases, mood disorders, depression, narcolepsy, epilepsy, cognitive impairment, trauma, infections, immune dysfunction, fever, trauma, hypertension, diabetes, endocrine, and other metabolic disorders [4–14] (Fig. 1).

Interactions among the cholinergic REM-ON neurons, the noradrenaline (NA)-ergic REM-OFF neurons, and the GABA-ergic neurons in the brainstem form the basic scaffold for the regulation of REMS [15]. The NA-ergic neurons are continuously active and cease activity during REMS, while they continue firing during REMS loss [3]. Upon REMS deprivation (REMSD), the level of NA increases in the brain [16] and that has been shown to induce many REMS loss–associated acute and chronic effects, e.g., hypertension, lack of concentration, confusion, irritability, hyperglycemia, memory loss, psychosomatic disorders, etc. [17–24]. Sleep (including REMS) plays an important role in regulating appetite [25], oxidative stress [26], energy conservation, lethargy [27], behavioral and emotional stability [28], reproduction [29], metabolism [30, 31], cognition [32], endocrine [33], immune function [34], thermoregulation [35], etc. (Table 1). Many of these deficiencies could be due to lack of quality sleep, which should be suspected in case of not maintaining the general health, daytime sleepiness, lack of concentration, psychological dysfunctions, reduced performance, etc. [47].

Sleep quality and sleep monitoring

Sleep quality has been referred to as a "complex phenomenon that is difficult to define and measure objectively" [48]. The sleep quality index is often evaluated by interviewing or asking subjects (or patients) to answer questionnaire about their sleep quality and daily life experiences, for example, the level of tiredness upon waking and through the day, motivation to get up from sleep in the morning, alertness through the day, clear headedness, concentration while working (including driving) throughout the day, sleep onset latency, and frequency of awakening at night [49, 50]. Subsequently, for confirmation and quantification of sleep loss, one's sleep is monitored by polysomnography. Sleep monitoring by polysomnography is usually done through the night that analyzes snoring, breathing, heart rate, sleep interruptions, sleep

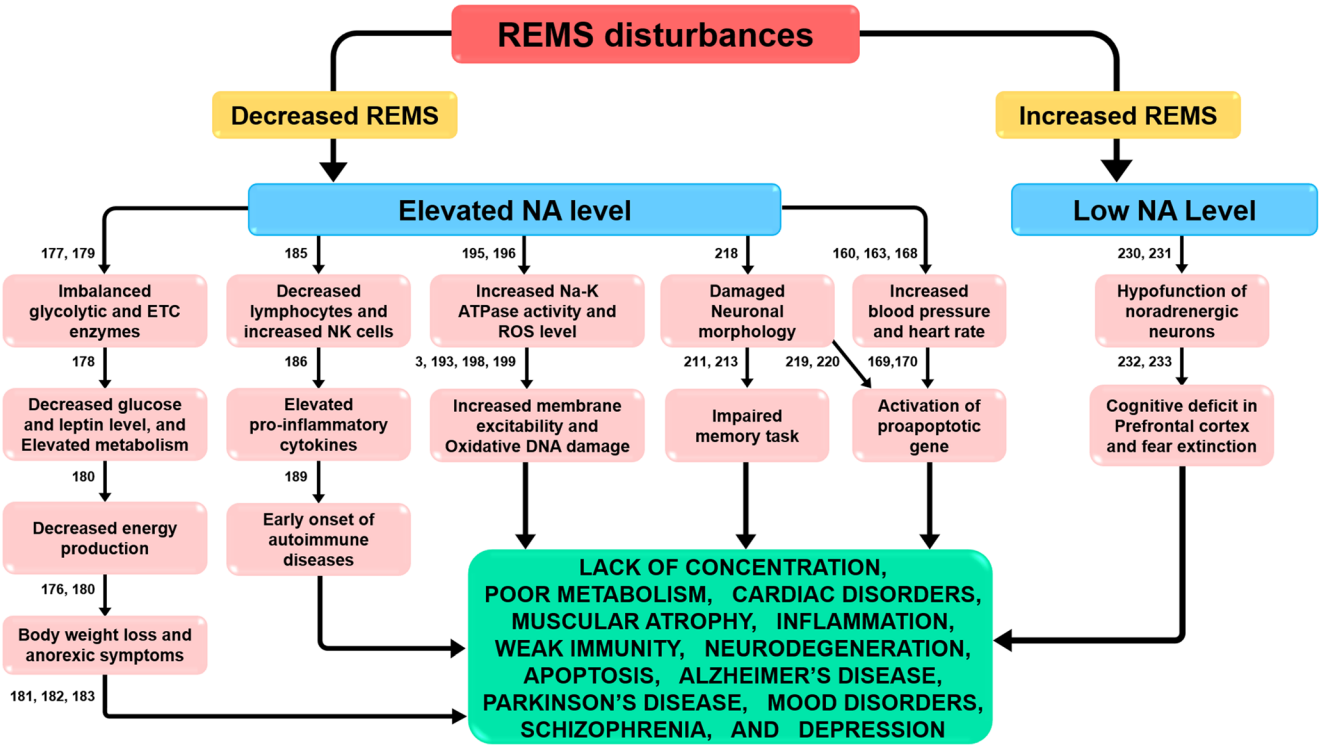

Fig. 1 REMS loss increases the level of noradrenaline (NA), which then affects several systems and induces several symptoms. The numbers correspond to the citation in the reference list. Abbreviations: ETC electron transport chain, NK cells natural killer cells, ROS reactive oxygen species, DNA deoxyribonucleic acid

Table 1 Recovery from diseases upon improvement in sleep quality. The numbers in parentheses show the cited article in the reference list

Disorders	Effect upon sleep improvement	References
Cardiovascular dysfunctions	Lowers the increased heart rate observed upon REMSD and lowers the chances of cardiovascular risks	[36]
Metabolic disorders	Glucose level recovered back to normal level, recovery in fatigue	[37]
Impaired immunity	Increase in counts of lymphocytes, leukocytes, and natural killer cells after sleep recovery	[38, 39]
Oxidative stress	Normalized level of superoxide and stress hormones	[40]
Defective blood-brain barrier	Progressive recovery of damaged blood-brain barrier	[41, 42]
Neurodegeneration	Improvement of neuronal morphology in brain; sufficient duration of recovery normalizes visual motor task, memory task, and cognitive performances; however, short duration sleep recovery is not effective	[43, 44]
Schizophrenia	Improvement in sleep in individuals lessen the psychotic experiences, delusions, and anxiety	[45, 46]

phases including REMS, blood oxygenation, leg movements, etc. Of late, instead of polysomnography, several wearable devices have been designed to record several parameters including physical activity, rest, sleep, breathing, heart rate, and blood pressure among others throughout the day and night when people can perform one's daily routine except while taking bath [51]. The sleep and activity profile are then correlated with other clinical symptoms and behavior of the subject/patient for deciding on the treatment [52, 53].

Role of psychosocial environment

As sleep loss affects many physiological processes, no single process is the primary beneficiary of sleep. In keeping pace with the modern lifestyle, we are constantly exposed to various psychosocial-environmental challenges, which are potentially capable to adversely affect our quality and quantity of sleep. Various psychosocial-environmental factors constantly interact with and often challenge our physiological processes affecting our health. If those factors, which are in dynamic equilibrium, either singly or synergistically overcome the dynamic threshold level to become stressful, various systems in the body react in a non-physiological manner to express acute symptoms. The silver lining is as the intensity of the input factors and the reactions of the body systems are dynamically active, changes in one or more of them may be suitably compensated by that of the others, resulting in reasonable maintenance of one's health. However, if the stressful input(s) becomes more intense and/or lasts longer so that the cumulative inputs are stronger than the threshold, there may be sustained and/or organic changes in the body's reacting systems resulting in chronic disorders. In this schema, sleep (which affects almost all the systems in the body) plays a significant role possibly acting as a sink by redistributing and keeping the output of the systems under control.

In addition to natural environmental factors, our interactions with family, friends, coworkers, and other acquaintances are also an important part of the psychosocial environment. A study demonstrated that emotional support from family, friends, and neighbors and quality sleep were negatively associated with insomnia and related symptoms like anxiety, depression, and suicidality [54], suggesting enjoying quality sleep should be a priority to lead a healthy life. Alcohol abuse and suicidality are among the possible obstructions to healthy sleep. Chronic exposure to alcohol increases latency of sleep onset and fragmentation of sleep [55], and chronic sleep disruption has been significantly correlated with an increased risk of suicidal thoughts, its attempt, and committing suicide [56, 57]. Therefore, providing personalized attention towards maintenance of overall healthy sleep habit is likely to offer protection for leading healthy living, and consequently, a record of personal sleep profile is likely to predict disorder-increation even before other signs and symptoms get expressed.

Unless consciously aware and careful, one may unknowingly become victim of sleep disturbances, which may tend to knock the body out of its homeostatic balance, resulting in disturbed physiology and disease condition(s). Although sleep loss/disturbance may affect most of the systems in the body, all the systems do not get affected equally and at the same time. Often the early acute signs are impairment of attention [58], concentration [59], and cognition [60]. Several factors like genetic make-up, age, gender, lifestyle, and psychosocial and environmental conditions (which include socio-economic status, eating habits, work environment, exercise, habitat, etc.), which affect an individual's sleep profile, affect the susceptibility and vulnerability of an individual to several disease(s) [61–65]. The penetrance and expression of symptoms often vary depending on the loss of quality and quantity of total sleep and/or REMS. Normally, as NREMS precedes and is a prerequisite for appearance of REMS, by-and-large estimation of REMS practically could be of prognostic, preventive, and personalized-predictive importance of multifactorial pathological conditions. Many of the associated symptoms have been proposed as part of predictive, preventive, and personalized medicine (PPPM) [66, 67], and recording and analysis of sleep profile might precede (may be non-specifically) appearance of other classically known symptoms, which may be added.

Personalized susceptibility

Disturbed sleep–related health problems are common; circadian misalignment is often seen in shift workers, nursing personnel, truck and train drivers, frequent travelers particularly due to ignoring circadian shifts and time-zones, etc. Gross estimation is that about one-third of the adult population in developed countries experience insufficient sleep, which can be due to work pressure at schools or offices, leading to increased weekend catching-up with the lost sleep [68]. The weekend sleep recovery process has become a common practice which may tend to overcome sleepiness and other sleep loss–related symptoms. Notwithstanding, the sleep recovery would not only depend on the quantity of lost sleep; more importantly, it would depend on the person's sensitivity as well as predisposition.

At individual level, the quality and quantity of sleep (including REMS) have been reported to vary with gender and age of the subjects (among other factors). For example, women are more vulnerable to sleep disorders associated with daytime sleepiness and fatigue than are men. Also, sleep latency is longer in women than in men, and older women report about 20 min of less sleep per day than men [69]. Women are at about 40% increased risk of developing insomnia compared with men [70], and depression is more associated with sleep apnea in women than in men [71]. The ability of the brain to initiate and maintain sleep reduces with aging. Newborn human babies spend about 80% of the time in REMS, which gradually reduces with advancing age, and in adults, it occupies about 20% of the total sleep time [72]. Many older people complain of deteriorated sleep quality to various degrees as expressed by increased sleep latency, reduced sleep duration, increased sleep fragmentation, excessive daytime sleepiness, poor performance efficiency, and other disturbed sleep–related symptoms.

The discussions above offer sufficient ground to infer that it is not prudent to trade off sleep for apparent longer working hours keeping in mind the acute and chronic pathophysiological effects associated with direct and indirect costs involved in terms of loss of man-hours, efficiency, material, and finances at personal and at national levels. Despite significant advancement in medical and allied sciences, many questions related to healthy living, particularly related to sleep, REMS loss, and associated disorders, remain unanswered. Experimentally, this issue has been addressed by inducing sleep loss and studying its effects on various behavioral, systemic, cellular, and molecular parameters. However, one of the most important experimental limitations is that as REMS appears only after a period of NREMS, it is almost impossible to induce exclusive loss of NREMS beyond a few hours (depending on the experimental species, circumstances, predisposition, etc.) and to have appropriate control for a meaningful study to arrive at a conclusion. Thus, attempting to induce NREMS loss or total sleep loss effectively induces comparable results, depending on the duration of deprivation. On the other hand, selective REMS loss can be achieved to a reasonable extent. Although there are a few experimental limitations, the advantages are that adequate control experiments may be conducted. The experimental animals can also be deprived of REMS by about 85% [73]; thus, the advantages outweigh the limitations. Earlier, we have discussed in detail the advantages, disadvantages, and limitations of various methods of total sleep deprivation and REMSD. It has been concluded that as of now, experimental REMSD with its various controls is the most effective method to understand the function of REMS, which has advanced our knowledge significantly [74]; however, its detailed mechanism of action is unknown.

Based on current knowledge and our expertise, we expect that REMSD would affect its generating mechanism in the brain and vice versa, which would induce a change in the level of neurotransmitter, and the latter would play a major role in inducing REMSD-associated effects. It is also possible that any factor or input that would affect REMS mechanism or the neurotransmitter(s) might affect the REMS. Accordingly, in this review, we address the following: (a) how REMS maintains optimum level of NA in the brain, which is necessary for the well-being of an individual; (b) REMS loss–associated elevated NA affects physiological processes and induces associated pathophysiological changes; (c) based on these discussions, finally, we would conclude that healthy sleep habit (which includes REMS), by maintaining the level of NA in the brain, prevents imbalances and instabilities among physiological processes and retains physiological equilibrium resulting in healthy and quality life; (d) based on these facts, we recommend that for quality and healthy living, maintenance of record of personalized sleep hygiene and habit should be made a part of national education policy (particularly for training of the health workers and clinicians), and it should be added to the list of clinical history recording of patients [66].

Mechanisms of REMS regulation

Brain areas regulating REMS

To understand better the disturbance in the regulation of REMS, it is important that we describe briefly the basic scaffold of its neural regulation. REMS is characterized by simultaneous presence of desynchronized EEG, rapid eye movements, and muscle atonia. Transection, stimulation, and lesion studies showed that the pontine area is most crucial for the regulation of REMS [75, 76]. Transection made rostral or caudal to the pons showed that characteristic REMS signature signals were expressed only in the portion of the brain which remained connected with the pons [77, 78]. It was therefore concluded that "*the pons is both necessary and sufficient to generate the basic phenomenon of*

REMS" [79]. Interactions of the neurons in the locus coeruleus (LC) and the laterodorsal and pedunculopontine-tegmentum (LDT/PPT) form the basic scaffold that plays a pivotal role in REMS regulation. The neurons from other brain regions like the perifornical area, preoptic area in the hypothalamus [80, 81], basal ganglia [82], nucleus accumbens, ventral tegmental area, amygdala [83], basal forebrain, and the prefrontal cortex [84, 85] modulate REMS possibly through these scaffold nuclei in the brain stem [86].

Based on the firing rate during REMS, the neurons have been classified as REM-ON (active during REMS) or REM-OFF (silent during REMS) [87–89]. The acetylcholine (ACh)-ergic neurons in LDT/PPT become active or increase firing (REM-ON), while the NA-ergic neurons in the LC cease firing (REM-OFF) during REMS. Among the aminergic neurons, isolated reports have shown that the serotonergic neurons in the dorsal raphe also often behaves like REM-OFF type [90–92], while dopaminergic neurons in the substantia nigra do not show a definite trend [93]. Isolated reports have indicated that some of the GABA-ergic neurons in the brainstem also behave like that of REM-ON type [94]. The REM-ON neurons are further classified as phasic and tonic types depending on whether they are active in bursts in association with the phasic appearance of eye movements and/or ponto-geniculo-occipital waves or tonically active throughout the muscle atonia. Although most REM-OFF neurons are usually monoaminergic, isolated reports of possibility of non-monoaminergic REM-OFF neurons have also been proposed [95]. The NA-ergic neurons in the LC cease firing during REMS, and they continue firing during experimental REMSD, while the REM-ON neurons show the opposite behavior [96]. This suggested that possibly the cessation of the LC REM-OFF neurons is a pre-requisite for the withdrawal of inhibition from the REM-ON neurons in the LDT/PPT, resulting in REMS generation [15]. Consistent research over two decades using electrical and chemical stimulation, inhibition of neurons, and behavioral, cellular, neurochemical, and molecular studies [3, 97–107] have confirmed this contention, which has led to construct a comprehensive model of neuronal connections for REMS regulation [15]. These findings from in vivo studies have been used to reconstruct a mathematical model, results of which are complementary [108]. The latter holds prognostic potential as well as it allows predicting neuroanatomical connections associated with normal and abnormal REMS.

LC neurons, their neurotransmitters, and REMS regulation

The LC neurons provide efferent projections to and receive afferent inputs from neurons all over the brain [109]; therefore, the LC neurons may be influenced directly or indirectly by most parts of the brain. These neuro-chemo-anatomical connections support as well as explain why sleep and REMS are affected (increased or decreased) in altered physiological states even before a full-blown disease sets in; REMS disturbance affects most physiological processes [109], while all psychosomatic dysfunctions and disorders are associated with disturbed sleep/REMS [110–113]. The neuronal function(s) depends on the release of neurotransmitters. As we have seen above that LC NA-ergic REM-OFF neurons occupy the pivotal position for REMS regulation and dysregulation, it is expected that disturbed REMS is likely to modulate the level of NA in the brain and vice versa. Further, for confirmation at least as a proof of principle, it needs to be shown if the REMSD-associated changes are mediated by elevated level of NA in the brain.

It has been reported that the level of NA indeed decreased in LC [16] and plasma [114] during REMS as compared with wakefulness, while it increased during REMSD. Upon REMSD, NA and GABA levels increased and decreased in all brain regions except hippocampus, and there was reciprocal relation between them [16]. It was proposed that one of the functions of REMS is to maintain low level of NA in the brain, which then maintains brain excitability and serves housekeeping functions of the brain [3]. Agonist and antagonist studies investigated the effects of various neurotransmitters on the firing of LC neurons. Infusion of GABA-antagonist, picrotoxin [115], baclofen [116], and bicuculine [117] into the LC decreased, while GABA and its agonist, muscimol, into the LC increased [98, 116, 118] the expression of REMS. ACh-ergic perfusion of the LC decreased [119], Orexin (Orx)-ergic agonist into the LC reduced [120], while knockdown of Orx-ergic receptors in the LC increased REMS [121].

Activation of LC neurons in rats by continuous low-frequency, mild electrical stimulation [100] reduced REMS, while upon recovery, there was a rebound increase in REMS. Recently, it has been shown that optogenetic stimulation of LC neurons reduced REMS and enhanced wakefulness [122]. These findings confirm that cessation of LC neurons is a pre-requisite for the appearance of REMS, and their activation results in REMS loss [107]. Stimulation of histaminergic [123], serotonergic [124], and Orx-ergic [125, 126] neurons increased wakefulness along with reduced REMS. The effects were expected to be due to activation of LC-neuronal projections [127–130]. Dopamine may modulate REMS; however, its detailed mechanism, particularly in relation to LC neurons, is not known [131]. The GABA-ergic neurons from the substantia nigra act presynaptically onto the LC NA-ergic terminals to regulate NA release over PPT ACh-ergic neurons and promote REMS initiation [108, 132]. The LC neurons also project onto the ACh-ergic and Orx-ergic neurons and, in turn, modulate physiological processes and REMS [83]. Infusion of serotonin into the LC inhibited the basal neuronal discharge, and the effect appears to be mediated by glutamatergic innervations [103, 130]. Thus, modulation of REMS by several neurotransmitters appears to be mediated

at least by acting on the LC neurons and factor(s) which would affect LC neurons and would affect REMS. Additionally, as the LC neurons receive inputs from across the body and the brain, which are person specific, we propose that maintenance of REMS needs to be made part of preventive as well as personalized treatment protocols for healthy living. Further, subject to confirmation, higher level of NA might be suggestive of disturbed REMS.

Risk factors and causes of sleep disorders

Sleep (including REMS) is vital for maintaining normal physiological processes; its deficit and/or disturbances cause short- and long-term health consequences. Several factors, including genetic and environmental, contribute to influencing an individual's susceptibility to sleep disorders [133, 134]. Sleep loss has been positively associated with cardiovascular and respiratory disorders, diabetes, obesity and metabolic disorders, depression, and Alzheimer's, Parkinson's, and neurodegenerative diseases [113]. Several components, like lifestyle changes (food habit, exercise, shift work etc.), environmental factors (light, noise, temperature, family/partner support etc.), drugs/chemicals of abuse (nicotine, caffeine, alcohol etc.), acute and chronic psychosomatic disturbances, and various pathophysiological and diseased conditions, contribute to sleep disruption. The altered level of NA has been observed in most of the cases [23, 135–161] (Table 2). Greater reliance on longer working hours, shift work, increased time spent on electronic accessories (television, internet, games, chatting, etc.) have encroached into our sleep time affecting quality and quantity of sleep, misalignment of circadian rhythm, and other comorbidities [167]. Advancing age, gender, and obesity are some of the risk factors of obstructive sleep apnea [162, 168]. It has been reported that adults with insomnia have higher levels of cortisol and adrenocorticotropic hormone [169] apparently suggesting a person's sleep and insomnia record could be considered a non-invasive readout of a person's pathophysiological state and stress level. Since quality and quantity of sleep (inverse of insomnia) are highly dynamic and individualistic expressions, they can serve as reliable personalized parameter for not only prevention and prediction but also for treatment and prognosis of recovery of an individual from acute as well as chronic diseases.

Preventive role of REMS in maintaining normal physiology and associated biomarkers

Circulatory system

Cardiovascular system (CVS) is responsible for transport (import as well as export) of vital molecules including oxygen, nutrients, lymphocytes, etc. throughout the body. It also mediates the absorption and excretion of toxic molecules to and out of the body. As insufficient sleep disturbs cardiovascular functioning, it may lead to several pathological symptoms and conditions [163], severity of which would depend on several factors including susceptibility and chronicity of exposure. In humans, sleep deprivation (SD) has been reported to be an important risk and predisposing factor for CVS disorders compromising longevity [170–172]. For example, patients who suffer from insomnia showed significantly dampened parasympathetic activation and increased sympathovagal imbalance [173] (Table 2). Kakadzic and Dement showed that REMSD induces a significant increase in the heart rate [174] and increased apoptosis of the heart muscles [175]. Additionally, there was lower basal cardiac function and less tolerance to myocardial ischemic-reperfusion injury induced by increased level of nitric oxide and apoptosis [175, 176] (Table 3). Upon REMSD, pain-associated exaggeration of blood pressure and increased heart rate responsiveness has been reported [196]. REMSD also has been shown to cause endothelial dysfunction and increased risk for hypertension [197, 198]; post-ischemic recovery of both systolic and diastolic functions is also affected [199]. In addition to the elevation of heart rate, REMSD also leads to increased respiratory rate [164]. Although sustained and chronic REMS loss affect CVS in otherwise healthy individual, acute REMS loss predisposes susceptible and vulnerable subjects, who may be affected by factors which may not affect otherwise normal subject (may be synergistic effect). As it is not easy to predict the predisposition (a dynamic factor) of an individual, advising maintenance of personal sleep profile (routine/diary) should be practiced by all, more stringently by the otherwise normal elderly as preventive, while by the patients as prognostic value.

A fundamental, dynamic property of the neurons is its excitability that affects the functions and responsiveness of the brain. LC NA-ergic neurons project all over the brain modulating the latter's excitability and influencing voluntary as well as involuntary physiological processes, including the CVS. Also, NA is an important factor for the regulation of autonomic processes (Table 2). The (over) activation of NA-ergic neurons projecting rostrally from the brainstem is responsible for NA spill-over and that might mediate REMS disturbance-associated sympathetic nervous system activation–induced heart failure [200]. In vivo studies have shown that high dose of NA has a cytotoxic and apoptotic effect on cardiac fibroblast by the activation of caspase-3 and downregulation of the antiapoptotic gene [177, 178] (Table 3). The NA-induced effects were confirmed by the fact that NA-ergic blockers reduced the effects [201]. The dysregulation of CVS-functioning upon REMSD (or vice versa) can subsequently affect other physiological systems and processes. Additionally, recovery from sleep loss has been shown to

Table 2 Several factors including social, environmental, lifestyle, habits, and some disorders affecting sleep-including REMS and NA levels. The numbers in parentheses show the cited article in the reference list

	Factors	Symptoms	Changes in NA levels	References
Environmental and Lifestyle changes	Light: Usage of light and electronic appliances/gadgets prior to and during sleep	Affects sleep onset, sleep quality	Increased, in LC and paraventricular hypothalamus	[138, 139, 149]
	Noise: Fragmented sleep because of noisy appliances or noisy environment	Daytime sleepiness, insomnia	Increased, in Serum and Urine	[146, 150, 151]
	Temperature: Extreme temperature disfavors sleep depth	Sleep disruption, especially REM sleep loss	Increased NA level in blood	[20, 147]
	Family/social support: Lack of family emotional support, childhood trauma	Psychological symptoms like anxiety, depression, suicidality, further effects sleep quality	Deficiency in NA and 5-hydroxytryptamine (5-HT)	[159]
	Food habit: Eating heavy food in night may lead to indigestion and affects sleep	Indigestion, frequent awakening, and insomnia	Increased level in plasma	[143–145, 147, 148]
	Shift work: Variable shifts timing in work	Circadian misalignment, insomnia or excessive sleepiness	Increased blood level of NA and cortisol	[149, 160]
Disorders	Cardio-respiratory: Asthma, cough, sputum production	Sleep disturbance, increased insomnia	Increased level	[71, 162–164]
	Stress, anxiety, and depression: Daily work stress, conditional anxiety	Light and brief episodes of sleep, difficult to achieve restful sleep, loss of interest and appetite, apathy, and suicidal thoughts	Extreme level of NA	[23, 71, 161, 165]
	Alzheimer's: Aging, lifestyle, family history, genetics, and head injuries	loss of interest and appetite, dementia, and sleep/REMS disturbances	Decreased level in many brain areas (difference in depressed and non-depressed AD patients) but Increased level in CSF	[4, 19, 21, 158, 166]
	Parkinson's: Exposure toxins, environmental factors, and genetic mutation	Impairs motor skills, sleep difficulties, cognitive problems	Loss of LC neurons and decreased level of NA in brain	[156, 157]
Drugs/Chemicals abuse	Caffeine: Consumption during bedtime induces alertness, temporarily blocks adenosine receptor	Maintain alertness, decreases sleep quality	Level of noradrenaline increases in brain	[141, 142, 155]
	Alcohol: Excessive drinking leads to increased awakening, sleep fragmentation	Increase in sleep-onset latency	Decrease in level of NA (however the release of NA is dependent on alcohol dose)	[142, 154]
	Nicotine: Intake (smoking) during sleep time lead to alertness	Maintain alertness, decreases sleep quality	Increases level of noradrenaline, inhibits monoamine oxidase in brain	[142, 152, 153]

LC locus coeruleus, *AD* Alzheimer's disease, *NA* noradrenaline, *CSF* cerebrospinal fluid

Table 3 Changes observed in biomolecules in association with altered sleep including REMS. The numbers in parentheses show the cited article in the reference list

Biomolecules studied	Effect on the biomolecules	Tissue sample	Associated disorders	References
Caspase-3	Activation of caspase-3 and downregulation of antiapoptotic gene	Brain	Oxidative DNA damage, ROS-induced carcinogenesis, neurodegeneration	[177, 178]
Reactive oxygen species (ROS)	ROS level increases, increased apoptosis			[179–181]
Na-K ATPase	Increased activity of Na-K ATPase and increased membrane excitability			[182, 183]
Corticosterone	Increased level	Plasma		[184]
Leucocyte	Increased leucocyte count	Plasma	Higher titer of antinuclear antibodies, worsen immune functions, Early onset of Autoimmune and inflammatory diseases, modulate blood-brain barrier	[184]
Lymphocytes	Decreased number of lymphocytes			[184]
Natural killer (NK) cells	Increased number of NK cells			[185]
Cytokines	Elevation of pro-inflammatory cytokines (IL-6)	Plasma		[186]
Complement C3	Increased level	Serum		[184]
Immunoglobulin-M (IgM)	Increased level			[184]
Immunoglobulin-A (IgA)	Decreased level			[187]
Nitric oxide	Higher expression of nitric oxide synthase and increased apoptosis in heart muscles	Heart ventricle	Myocardial ischemic-reperfusion injury, cardiac disorders	[175, 176]
Hexokinase	Increased activity	Brain	Decreased energy production, body weight loss, lethargy, skeletal muscular atrophy, anorexia	[188]
Glucose-6-phosphatase	Decreased activity			[188]
Glucose, glucose-6-phosphate, and pyruvate	Significant fall in their levels	Brain (cerebral frontal lobe)		[189]
Succinate-CoQ reductase	Decreased in the activity	Brain (mitochondria of hippocampus and striatum)		[190]
CoQH2-cytochrome c reductase				[190]
Cytochrome c oxidase		Brain (mitochondria of the prefrontal cortex, cerebral cortex, cerebellum, hippocampus, and striatum)		[190]
Citrate synthase	Increased activity	Brain (prefrontal cortex)		[190]
Leptin	Decreased level	Plasma	Anorexia, depression, and Alzheimer's disease	[189, 191–193]
Gut microbiota	Found in blood	Plasma	Inflammation and damage in the blood-brain barrier	[194, 195]
Noradrenaline (NA)	Increased release of NA in different brain areas	Brain, plasma, urine, and cerebrospinal fluid (CSF)	Associated with most of the disease mentioned above	[4, 16, 19, 21, 96, 158, 166]
Gamma amino butyric acid (GABA)	Increased level	Brain		[16]
Acetylcholine	Decreased level	Brain		[96]

normalize the increased heart rate and reduces the chances of cardiovascular risk [36] (Table 1). Therefore, we propose that at personal level, REMS disturbance must be consciously and carefully prevented to avoid as well as recover from CVS dysfunction where sympathetic tone is already disturbed. Also, for prevention, one must enjoy adequate sleep (NREMS as well as REMS) to lead healthy living.

Bioenergetics

Sleep, being an essential and natural process, has a fundamental role in the regulation of energy balance of the body. Chronic and acute sleep loss leads to energy balance disturbances [202–204]. Animals upon REMSD have been shown to have a progressive loss of body weight and show hypoglycemic symptoms [205]. REMSD has a major impact on glucose metabolism and mitochondrial electron transport chain and subsequently on the generation of energy in the form of adenosine tri-phosphates (ATPs). The hexokinase (a glycolytic enzyme) activity has been found to be increased upon REMSD; however, glucose-6-phosphatase (a gluconeogenic enzyme) activity was decreased in the brain [188], and these effects may be mediated through NA. These changes in enzyme activities may help in explaining a significant fall in glucose level, glucose 6-phosphate, and pyruvate as observed in cerebral frontal lobe upon REMSD [189]. A study on rats has shown that REMSD caused a significant decrease in the activity of complex II (i.e., succinate-CoQ reductase) and III (i.e., $CoQH_2$-cytochrome *c* reductase) in the mitochondria of hippocampus and striatum [190]. The activity of complex IV (i.e., cytochrome c oxidase) was also decreased in the mitochondria of the prefrontal cortex, cerebral cortex, cerebellum, hippocampus, and striatum; however, citrate synthase (Kreb's cycle enzyme) activity was increased in the prefrontal cortex [190]. On the other hand, the oxygen consumption increased upon REMSD, which represent elevated metabolic rate, while serum leptin level decreased and remained suppressed upon REMSD [189]. Studies have also shown that low leptin level in plasma is associated with anorexia, depression, and Alzheimer's disease [191–193]. Yujra et al. have shown that REMSD causes skeletal muscular atrophy and defects in masticatory muscles [206] (Table 3). Thus, REMS loss may reduce energy production and increase energy consumption, which might explain at least some of the REMSD-associated muscular weakness, lethargy, and tiredness. REMS loss has a global impact on energy metabolic pathways, from digestion to electron transport chain (ETC). Since metabolism is significantly affected by REMS loss, maintaining sleep routine and compensation of lost sleep would bring the metabolism to optimum level and prevent dysregulation. Thus, along with other measures, optimizing sleep (including REMS) of individuals is likely to maintain physiological homeostasis leading to better health and help recovery from sickness. Improved sleep has been shown to help glucose metabolism and recovery from fatigue [37] (Table 1). Importantly, as these effects would be significantly influenced by the person's predisposition and acclimatization, maintaining proper sleep profiling is strongly recommended to lead healthy living. In other words, it can be suggested that altered sleep and REMS might prove to be of predictive and prognostic value for disturbances in the metabolic machinery (enzymes and biomolecules), while as a corollary, improved sleep/REMS quality should serve as a prognostic value [189, 205].

Immunity

Sleep disturbance disbalances conjoint physiological processes and that may compromise homeostatic processes, including immunity in the body. REMSD has been reported to decrease the percentage of T-lymphocytes and induced a significant increase in natural killer (NK) cells in plasma [185]. This may provoke major changes in the immune system by inducing inflammation. The plasma levels of pro-inflammatory cytokines and markers get significantly elevated in REMS-deprived rats [186]. REMSD leads to increased complement C3 (in serum), corticosterone concentration, spleen weight, total leukocyte counts, and decreased lymphocyte count in plasma. However, the production of a certain class of immunoglobulin, the IgM, increased in the serum [184]. In another study, serum IgA levels decreased during the entire period of REMSD in human volunteers [187]. REMSD exhibits an early onset of an autoimmune disease in mice which resembles systemic lupus erythematosus in humans. The disease onset was reflected by exhibiting high titers of antinuclear antibodies [207] (Table 3). Taken together, the immune responses are improved by REMS, while REMSD-associated worsening of immune function could underlie or aggravate inflammatory and autoimmune diseases, which may be improved by maintaining healthy sleep profile. As many of the immune effects could be modulated and/or induced by NA [18, 208], subject to confirmation, at least some of the REMSD-associated altered immune responses could be due to elevated level of NA.

Thus, sleep loss, including REMS loss, compromises immune responses, which further aggravates the existing disease and/or onset of person-specific autoimmune diseases. The sleep loss–related aggravation may be supported by the fact that recovery of lost sleep has been shown to improve or reset the impaired immune functions as evidenced by regaining towards normal counts of leucocyte, lymphocyte, and NK cells, while reducing the levels of pro-inflammatory cytokines [38, 39] (Table 1). As recent studies have correlated compromised immunity with disturbed sleep, we propose that conscious efforts are needed to spread awareness among both the patients as well as healthy population to maintain healthy sleep hygiene. Although details need to be worked out, personalized sleep monitoring could be used as a predictive and

prognostic measure to maintain good health and to recover from diseases associated with compromised immunity; additionally, optimum personal sleep habit would prevent disbalance or maintain homeostasis of personal immunity and immune responses.

Oxidative stress, membrane potential, and brain excitability

REMSD altered neuronal excitability; some reported increase, while other decreased excitability. These may be explained as REMSD could be either a cause or effect of increased neuronal excitability. REMSD indeed increased neuronal depolarization [209], which is likely to cause increased brain excitability. Upon REMSD, neuronal excitability was severely reduced in CA1 neurons, and the production of long-term potentiation of synaptic strength was inhibited [210]. In pyramidal cells of layer V/VI of the medial prefrontal cortex, the miniature excitatory postsynaptic current amplitude was slightly reduced, and intrinsic membrane excitability was increased [182]. REMSD increased the Na-K ATPase enzyme activity in the rat brain; the pons and the medulla (where the REMS regulatory REM-ON and REM-OFF neurons are located) were the first sites to be affected [183]. REMSD induced ROS generation and caused oxidative DNA damage, apoptosis, and ROS-induced carcinogenesis [179–181]. The REMSD-associated increased membrane potential, ROS generation, and apoptosis have been shown to be mediated by the elevated level of NA in the brain [3, 209, 211] (Table 3). Normalized levels of superoxides and stress hormones have been reported upon sleep recovery, which signals the necessity of quality sleep [40] (Table 1). Collectively, loss of NREMS and REMS would affect the brain excitability, which in turn would affect physiological processes and homeostasis. Therefore, the time spent in quality and quantity of sleep is likely to act as a buffer to mitigate the adverse effects including apoptosis. It would also re-align excitability of the neurons in the brain and maintain homeostasis. Thus, the quantity of disturbed REMS (and total sleep for that matter) should be of prognostic value. As a corollary, we expect that enjoying optimum REMS should offer protection and prevent an individual from future disorders. Further, as mechanism of action, we know that many of these changes would be modulated by level of NA in the brain [16, 74, 109].

Blood-brain barrier

Endothelial cells, pericytes, astroglia, and microglia are the major constituents of the blood-brain barrier (BBB). It selectively transports molecules and protects the brain from potentially toxic blood-borne molecules, which may modulate reactivity and induce apoptosis of the neuronal and glial cells. REMS restriction has been shown to increase the caveolae and permeability of the BBB, which has been shown to be restored rapidly and effectively even upon a brief period of sleep recovery [212]. In another study, it was observed that in the hippocampus, the number of pinocytic vesicles had been increased by threefold when animals were subjected to REMSD, which suggests the possibility of compromised integrity of the BBB [41]. Additionally, sleep loss leads to an increase in pro-inflammatory mediators (IL-6) in plasma, which affect the tight junction proteins and promote changes in cellular components of the BBB, particularly in brain endothelial cells [213] (Table 3). Gut microbiota has been detected in blood after sleep loss, which causes induction of inflammation, and the BBB becomes sensitive to these microbiotas [194, 195]. The effect of NA (acting through α-adrenoceptor) on BBB permeability has been studied by stereotactic injection of NA in the rat's cerebral ventricle. It increased the BBB permeability, which eventually increased the pinocytic activity of endothelial cells in cerebrum [214]. Therefore, REMSD-associated BBB permeability may also be mediated by the elevated level of NA, which needs to be studied. These isolated findings may be supported by the fact that improved sleep has been reported to induce progressive recovery in permeability of BBB [41, 42] (Table 1). In conclusion, a compromised BBB is commonly reported in sleep-deprived subjects. As infiltration of pathogens and toxins into the brain is related to BBB permeability, sleep loss might facilitate the process. Thus, on one hand, for prevention and protection from diseases particularly where the brain may be affected due to compromised BBB, the public at large must be educated about ensuring optimum quality and quantity of sleep. On the other hand, while treating, patients must be advised maintaining proper sleep habit and hygiene for effective treatment of all disorders and comorbidities. Disturbed sleep should ring the initial warning bell of anticipating possible future disorder(s), and thus, it should serve as an important predictor. Therefore, we strongly recommend that in addition to other steps [67], taking care of personal sleep habit and hygiene should be considered as a priority by all, the healthy persons, the patients, and the caregivers for maintaining healthy living and for effective recovery.

Neurodegeneration and cognition

The percentage of REMS remains stable in normal aging; however, it is reduced in Alzheimer's patients [166, 215]. Sleep plays a crucial role in brain development, memory consolidation after the acquisition of information, and cognition [216, 217]. Total sleep loss and/or REMSD leads to impaired concentration, decision-making, mood disturbances, psychomotor vigilance performance, anxiety-like behavior, and working memory dysfunction [79, 218–221] (Fig. 2). At least some of these effects could be due to changes in neuroinflammation, microglial activation, neuronal apoptosis, and a significant reduction in glucocorticoid-induced neurogenesis [43, 222–224]. Several studies have demonstrated that REMSD drastically impaired object-recognition test [225, 226],

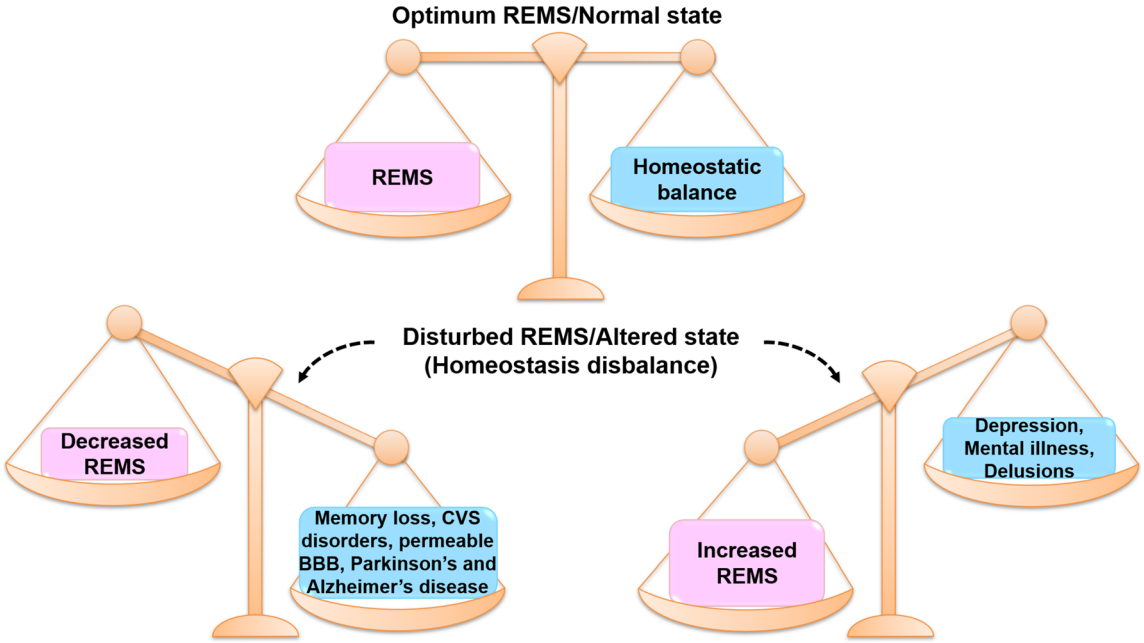

Fig. 2 This figure shows that the optimum level of REMS maintains physiological homeostasis. Both increased and decreased REMS disbalance the said homeostasis, which results in dysregulation and disorder (pathological condition). Decreased or increased REMS induces different sets of disorders depending on various factors including susceptibility and surrounding conditions. Abbreviations: CVS cardiovascular system, BBB blood-brain barrier

decreased motivation for food reward [227], and decreased break-point for sucrose pellet reinforcement [228]. REMSD affects CA1 cholinergic muscarinic receptors, which may be responsible for REMSD-associated amnesia [229] and emotional responsiveness. In a human study, REMSD-induced enhanced emotional reactivity has been found in the visual emotional reactivity task [230], which could be due to the enhanced activity of the brain regions involved in emotional processing, such as occipital and temporal areas and the ventrolateral prefrontal cortex [230] (Table 3). Thus, accumulation of the factors due to aging-associated gradual REMS loss could predispose aging-associated memory as well as other deficits and neurodegenerative disorders. Several studies have shown that sufficient recovery of sleep is positively associated with improvement in damaged neuronal morphology, memory, and cognitive performances [43, 44] (Table 1). Analysis of sleep profile could prove to be of predictive and prognostic value for taking appropriate steps at personal level at all ages, more so for the aged population.

Psychiatric ailments and REMS

Depression

Depression is a common mental health disorder that co-exists with other physical and psychiatric comorbidities. REMS may influence emotions, and disturbed REMS causes emotional distress [28]. There is a strong correlation between altered REMS density, REMS latency, and the onset of depression [165]. Reduced REMS latency, increased duration of REMS, and increased frequency of eye movements are some of the characteristic clinical symptoms of patients with major depressive disorder. Most of the antidepressants target REMS, and thus, REMS suppression might be a key mechanism underlying antidepressant treatment [231]. Depression-associated changes in REMS has been proposed to be mediated by complex interplay of NA-ergic, serotonergic, and cholinergic systems. Reduced activity of the monoaminergic neurons has been traditionally accepted as the cause of depression [232–235]. Antidepressants inhibit re-uptake of the monoamine neurotransmitters, inhibit monoamine oxidase (which degrades NA), and/or antagonize the inhibitory presynaptic NA-ergic auto-receptors [23]. These factors enhance the availability of NA and NA-mediated neurotransmission resulting in amelioration of depressive symptoms. Thus, we propose conducting suitable study to confirm that keeping a record of experiencing quantum of REMS is likely to help in assessing the depth of depression and vice versa, or that the quantity of REMS may have a prognostic value associated with improvement from depression, or that record of optimum REMS might help to protect an individual from depression if the REMS or associated problems are identified and addressed early enough.

Schizophrenia

Schizophrenia is characterized by hallucinations, delusions, and cognitive impairments [236–238]. Deficiency of

GABA-ergic neuronal functioning with or without associated dysregulation of other neurotransmitters is thought to be one of the important correlates of this disorder [239–242]. Decreased expression of the glutamic acid decarboxylase-1 gene, which encodes for the 67-kDa glutamate decarboxylase enzyme and is involved in the synthesis of GABA, is commonly seen in schizophrenic postmortem brains [243, 244]. A few studies have reported alterations in slow-wave sleep, along with reduced REMS latency and REMS density [245, 246]. Most of the patients with schizophrenia report abnormal sleep pattern, which includes insomnia, obstructive sleep apnea, restless leg syndrome, or periodic limb movement disorder [247]. Treatment with antipsychotic drugs is associated with an increase in total sleep time and sleep efficiency and is often associated with increased REMS latency [247]. It has been proposed that cholinergic hyperactivity (muscarinic super-sensitivity) could be responsible for the shortened REMS latency in schizophrenic patients [248], while some evidence suggests that schizophrenic patients are at high risk of sleep-related breathing disorder [245]. Mannaa and Walker [249] have proposed that schizophrenia is like a dream-attack of REMS while awake; however, the detailed mechanism needs further study. These contentions may be supported by the report that improvement in sleep in individuals lessens the symptoms associated with psychotic experiences, delusions, and anxiety [45, 46] (Table 1). Thus, due to the clinical association of disturbed sleep in schizophrenia, personalized intervention to improve quality and quantity of sleep and REMS should be seriously considered during assessment of patients [67].

REMS mechanisms for dream episodes

Appearance of vivid dreams is among the most intriguing and fascinating phenomenon yet unexplained aspect of sleep. Dreaming is governed by elements of apparently sleeping brain, which are less responsive to external stimuli. In other words, dreaming may be termed as a cognitive phenomenon of the *subconscious mind (!)*, and it is the *activity of the brain, by the brain and for the brain*. The field is still open for neurobiological explanation of why and how we dream and what purpose it serves. It has been proposed that the brain interprets the activity of the neuronal network that results into thought during waking, while possibly a similar phenomenon during sleep results into dreaming, which helps memory consolidation. Although both states, REMS or NREMS, can provide the framework for the expression of dreams, usually, subjects report most dreams (at least those we remember upon waking) during REMS.

Diverse emotional content and vivid description associated with REMS are suggestive of the involvement of multiple brain regions and neurotransmitters. It has been reported that subjects awakened during REMS recalled an emotional and vivid description of dreams as compared with those awakened during NREMS [250]. Several studies have reported a positive role of REMS-associated dreams in memory consolidation, mood regulation, and assimilation of new experiences. A relationship among REMS, dreams, and facial expressions during sleep in newborns, normal adults, and patients (adults) with REMS behavior disorder (RBD) was assessed. It was observed that almost half of the facial expressions were temporally associated with rapid eye movements associated with REMS, and the happy facial expression was associated with a happy dreaming scenario [250]. Half of the RBD patients smiled while one-third laughed mostly during REMS. This high frequency of happy emotional expression during RBD suggests that the RBD model can provide insights into the emotional component of REMS. This can also facilitate the understanding of mood regulation and emotional desensitization during sleep.

Almost all psychological and psychiatric disorders are associated with disturbed REMS, and improvement in sleep quality has been reported to improve depression and hallucination. Some of the psychological symptoms, e.g., hallucinations, RLS, etc., are apparently comparable to REMS-associated behavioral expressions, e.g., dreams. Recent studies also show that the brain areas known to modulate hallucinations also modulate REMS, and experimental REMSD may induce hallucination-like symptoms [251, 252]. Therefore, we propose that a record of sleep profile is likely to have predictive and prognostic value of one's suffering from psychological disorders. Also, appropriate personalized advice to the patients to maintain quality and quantity of sleep should play a significant role in preventing and ameliorating pathophysiological conditions and diseases.

Elevated NA might be the cause of REMS loss–associated effects

We have seen above that acute as well as chronic REMS loss affects most (if not all) physiological processes in the body, and conversely, REMS is affected in most disorders. As a mechanism of action, it has been shown that upon REMSD, at least the level of NA is elevated in the brain, which otherwise is reduced during REMS. Many isolated as well as systematic control and clinical studies have shown that elevated NA is a cause for inducing many of the REMSD-associated symptoms. In support, as a proof of principle, it has been shown that if the NA was not allowed to be synthesized in the brain where REM-OFF neurons are located and then the rats were REMS deprived, the REMSD-associated symptoms were prevented [253]. Notwithstanding, although experimentally we have shown in animal models, it needs to be confirmed in normal humans as well as patients with various

comorbidities before applying the knowledge for treatment on humans. Based on these and other related studies in normally behaving animal models, we reiterate our proposition that through evolution, REMS has evolved to maintain the brain level of NA, which protects as well as maintains the housekeeping function(s) of the brain, while REMSD-associated elevated NA is at least one of the primary factors for inducing REMSD-associated disorders and associated symptoms [3, 211, 224].

Conclusion and recommendations

The importance of sleep in maintaining good health has been emphasized in many ways in ancient literatures of all cultures. REMS is an essential component of sleep, at least in higher animals including humans; the appearance of NREMS precedes and is a pre-requisite for appearance of REMS. An adult spends the least amount of time in REMS, and it may be considered an effective readout of sleep status of an individual. Disturbed REMS is a common symptom in most disorders, and many of the symptoms of those disorders can be seen upon experimental REMSD.

We propose that maintenance of optimum quantity of sleep and REMS should be a priority for leading quality life. Furthermore, subject to confirmation in humans, we recommend that evaluation of daily REMS pattern is likely to prove to be of prognostic and predictive significance for many disorders and overall health of an individual. Appropriate personalized advice on maintaining adequate (optimum) sleep paradigm is likely to have synergistic effect along with or without medication for amelioration of comorbidities with or without sleep disturbance.

Based on our review of the literature and expertise, we expect that conscious attention towards experiencing optimum sleep–including REMS might prevent either or several of the following: for example, falling sick, predicting veracity of many diseases, reduce the dose and length of treatment, facilitate one's recovery from comorbidities and diseases, etc. In fact, even in modern treatment and management of diseases, spending quality time in sleep is being advised in several diseases including viral infections and many psychosomatic disorders, etc. It has been consistently shown in animal studies that the level of NA plays a significant role in regulating REMS, and adequate REMS maintains optimum NA level in the brain. It has been shown that many of the symptoms either associated with diseases where REMS is also affected, or associated with REMSD, are indeed induced by NA. Therefore, subject to confirmation in humans, we propose that REMS loss–associated effects could be ameliorated by reducing the synthesis or elevation of the level of NA and/or by preventing the action of the elevated NA; the former is more desirable though.

As expression of quantity of sleep is a dynamic personalized phenomenon and its disturbance may result in psychosomatic as well as metabolic disturbances (and vice versa) in a person-specific manner, we recommend that personalized sleep issues be essentially considered as a predictive indicator, as well as preventive and protective shield as the case may be. Further, as the effects due to sleep disturbance would affect interpersonal relationships, sleep loss may become a social nuisance, which is not being considered seriously as yet. Hence, awareness about sleep health and sleep hygiene, preferably at personalized level, should be made a part of formal and informal academic courses, curricula, and training at all levels. Such awareness programs among individuals of every section of the society including the primary, middle, and high school students; parents; students for higher studies/trainees; drivers; pilots; nurses; night-shift workers; management bosses; expectant mothers; medical professionals; policymakers; and so on [66], and it should form a part of the national policy. As members of the global society, we appear to be already late in taking up the issue; we must initiate action on a priority basis, comparable to the global concerns raised by other issues, such as environmental pollution, global warming, terrorism, smoking, alcoholism, drug abuse, climatic changes, and so on. Finally, here, we summarize a few recommendations as suggested by many authors in the reviewed literature, for enjoying good sleep, which would encourage healthy living:

- Healthy sleep routine must be practiced by all normal individuals of all ages as well as patients.
- Routine time schedule for going to bed and waking must be maintained. Routine relaxing activity before bedtime (e.g. reading non-serious books and enjoying TV programs) is advisable.
- A quiet, dark, non-cluttered (with unnecessary gadgets e.g. TV, computer, phone, etc.) room with a comfortable bed is needed [136–139].
- Strenuous physical exercise and psychological and emotional stress, which may release excess NA and other stress hormone(s), should be avoided until about at least 4 h prior to going to bed [140, 254].
- Consumption of caffeine, alcohol, nicotine, and other chemicals that interfere with sleep must be avoided within several hours (depending on one's sensitivity) before bedtime [141, 142].
- Stimulatory and high caloric intake should be avoided close to bedtime [143–145].
- We strongly recommend keeping record of sleep profile by every individual.
- Also, maintaining sleep profile should be in-built in the course curriculum of every level of health professionals, administrators, managers, etc.

- Finally, if the sleep disturbances and difficulties do not improve through good sleep practices, consulting a sleep specialist is highly recommended.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations *ACh,* acetylcholine; *AD,* Alzheimer's disease; *GABA,* gamma-aminobutyric acid; *IgA,* immunoglobulin-A; *IgM,* immunoglobulin-M; *LC,* locus coeruleus; *NA,* noradrenaline; *NK cells,* natural killer cells; *NREMS,* non-rapid eye movement sleep; *Orx,* orexin; *PD,* Parkinson's disease; *PPPM,* predictive, preventive, and personalized medicine; *REMS,* rapid eye movement sleep; *RBD,* REMS behavior disorders; *REMSD,* rapid eye movement sleep deprivation

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