

GENERAL OVERVIEW ON SLEEP MEDICATION

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ABSTRACT

There are many medications that cross the blood-brain barrier affecting the central nervous system and converting the normal patterns of sleep and wakefulness. Some drugs are used to treat special sleep disorders but others can induce sleep disorders (e.g. periodic limb movements during sleep, restless leg syndrome, parasomnia, insomnia) or exacerbate them (e.g. obstructive or central sleep apnea). The most frequent classes of agents used in sleep medicine are: benzodiazepines, nonbenzodiazepines receptor agonists, melatonin and melatonin receptor agonists, antiepileptic drugs, antidepressants, atypical antipsychotics, central stimulants and dopamine agonists.

Keywords: sleep medication, sleep quality, sleep macrostructure, REM and NREM sleep, excessive daytime sleepiness, benzodiazepines, nonbenzodiazepines receptor agonists, melatonin and melatonin receptor agonists, antiepileptic drugs, antidepressants, atypical antipsychotics, central stimulants, dopamine agonists, analgesics, orexin antagonists, insomnia, parasomnia, epilepsy, restless leg syndrome, periodic leg movements in sleep, narcolepsy, hypersomnia

The prevalence of sleep disorders (more than 80 different disorders) is augmenting in our societies where constant exposure to artificial light (television, computers, mobile-phones), interactive activities, socioeconomic pressure and needs drive us into a 24-hour society (“a world that never sleeps”), where the link between work and social time is broken and the sleep health can be compromised. Insomnia and excessive daytime sleepiness are the most common symptoms in sleep medicine practice and sometimes we need medication to improve at least the quality of life of these patients, if we cannot remove the cause of them.

Any medication that passes through the blood-brain barrier has the potential to alter the quality and/or architecture of sleep. *Sleep quality* is the degree to which restful and restorative sleep is maintained during the night and a subjective assessment about the way the individual feels refreshed on waking and on functioning throughout the day. We objectively appreciate the sleep quality with: latency until sleep onset (SO), wakefulness after sleep

onset (WASO) and the duration of sleep (usually on polysomnographic recordings). *Sleep architecture* represents the macrostructure of sleep. Sleep is cyclical, with each cycle composed several non-REM sleep stages (N1, N2 and N3) and rapid eye movement (REM), assessed primarily by electroencephalography (EEG) patterns during polysomnography. Each sleep drug can modify the sleep quality and the sleep macrostructure/microstructure and the ideal sleep pill should increase the sleep quality and maintain the physiologic sleep cycles. In this article, we are going to review the most frequent drugs used in sleep disorders.

Benzodiazepines

Benzodiazepines (Diazepam, Lorazepam, Midazolam, Alprazolam, Clonazepam) and nonbenzodiazepine receptor agonists (Zolpidem, Zaleplon, Eszopiclone) are commonly prescribed sedative-hypnotic medications used to treat insomnia.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and ex-

erts its effects via ionotropic and metabotropic receptors. GABA_A and GABA_C receptors are linked directly to chloride ion channels, whereas GABA_B receptors are G protein coupled. Many drugs that cause sleep or loss of consciousness enhance transmission at the GABA_A receptor. Benzodiazepines facilitate GABA-mediated inhibition of cell firing by binding to a subunit of the GABA_A receptor complex called the benzodiazepine receptor (1,2,3).

They improve sleep quality by decreasing the sleep latency (SL), increasing the total sleep time (TST) and decreasing WASO (2). The sleep architecture does not always remain the same: for example, the benzodiazepine can be a suppressor of N3 sleep and at high doses of REM sleep (1). They reduce N1 (which is a positive effect) but increase N2 and the spindle activity during this sleep stage (the frequency and amplitude of sleep spindles) (6,7). Benzodiazepines can depress respiration and should be used cautiously in patients with sleep apnea or hypoventilation (1,2). They reduce the severity of symptoms in patients with restless legs syndrome (3).

The action duration of benzodiazepine is important in deciding when to use them: *short-acting agents* (Alprazolam, Midazolam, Triazolam, Oxazepam), *intermediate-acting agents* (Clonazepam, Lorazepam) and *long-acting agents* (half-life values usually exceed 24 hours: Diazepam, Clobazam, Flurazepam) (1,2).

Their use comes with several side effects: daytime sleepiness, poor motor coordination, increase in falls, cognitive impairment, confusion and risk of dependency (4). Patients typically develop tolerance to these agents and with chronic use, higher dosages may be required. Discontinuation of the treatment can induce a rebound insomnia and a rebound of REM sleep (3).

Benzodiazepines can be used as antiepileptic drugs, especially in patients with frequent nocturnal seizures (Clonazepam in childhood epilepsies or pharmaco-resistant epilepsies, Clobazam in Lennox-Gastaut syndrome and Landau-Kleffner syndrome, Lorazepam or Diazepam iv. in status epilepticus) (5). They are not usually the first choice for seizure prevention and they tend to be additional anticonvulsive treatment. On the other hand, they tend to increase the percent of N2 which is the main stage of sleep when seizures appear (5).

Clonazepam is the first line treatment in patients with REM sleep behavior disorder (RBD) but should be used with caution in patients with dementia, gait problems or concomitant sleep apnea (8,10). It is the second line treatment in refractory restless leg syndrome (RLS) (9). It can be also used for sleep starts, hypnagogic foot tremor, propriospinal myoclonus at sleep onset and excessive fragmentary myoclonus (when it is the sole abnormality in patients with EDS) (1,3).

Nonbenzodiazepine receptor agonists

Apparently, the nonbenzodiazepine receptor agonists (Zolpidem, Zaleplon, Eszopiclone), acting via the GABA_A receptor complex (at a different site than the benzodiazepines) do not affect the amount of N3 and do not affect breathing during sleep (1,11). They decrease sleep latency and WASO and they might have minimal effect on REM sleep (12). Tolerance and withdrawal effects are not so frequent as for the benzodiazepines (13).

They are indicated for short-term management of insomnia and small doses are recommended for older patients. Adverse effects may include impaired alertness and motor coordination. Compared to conventional benzodiazepines, they are not muscle relaxants, anticonvulsants or anxiolytics. The usual dose of Zolpidem (the most used drug of this category) is 5-10 mg/day and women are seemingly slower metabolizers of Zolpidem than men (13).

The American Geriatrics Society (AGS) Beers Criteria identifies Zolpidem as a potentially inappropriate medication for the elderly due to concerns for the adverse effects mentioned and the risk for delirium, falls and fractures (14).

There is conflicting evidence as to whether Zolpidem is associated with rebound insomnia (1,3). Another concern to clinicians is the occurrence of complex sleep-related behaviors (CSBs) (15). The use of Zolpidem, Zopiclone and Zaleplon has been associated with certain CSBs, including sleepwalking with object manipulation (e.g., cooking, cleaning), sleep conversations (on the telephone or in person), sleep eating, sleep driving, sleep shopping, and sleep sex (15,16).

Melatonin and melatonin receptor agonists

Considering the function of suprachiasmatic nucleus in circadian rhythm regulation, melatonin and

melatonin agonists can be used as a treatment for circadian rhythm sleep disorders and insomnia. *Melatonin* (a pineal gland hormone, released mostly during darkness) binds to all three types of melatonin receptors and as a drug, it is a good chronobiotic agent used for phase shifting circadian rhythm (a first-line treatment for this sleep problems) (1-3). Melatonin increases sleep propensity when taken in the evening and can produce a phase delay when administered in the morning (17).

Ramelteon (a melatonin receptor agonists) binds to melatonin receptors type 1 and 2 (MT1 and MT2), inhibiting the activity of suprachiasmatic nucleus in promoting wake. It has no direct sedative effects. In contrast to Melatonin, it has lower sensitivity for MT3. It is used for the treatment of sleep onset insomnia (18,19).

Antiepileptic agents

By their many mechanisms of action (blocking the voltage-dependent sodium channels, blocking the glutamate receptors, stimulating GABA-ergic effects, inhibiting GABA degradation, modulating calcium channels, decreasing potassium efflux, inhibiting the glutamate release etc.), antiepileptic drugs (AED) can modify sleep, with beneficial or detrimental effects (5).

Carbamazepine may increase slow wave sleep and but decreases REM sleep and there are studies which demonstrated the initial administration of Carbamazepine leading to an increased number of sleep stages shifts and increasing fragmentation of REM sleep (20,21). In the Gigli's study (initiation of CBZ treatment in seven patients with temporal lobe epilepsy), it seems that disruption of REM sleep was present only in the acute phase of drug administration. Looking for REM sleep disorders, in our own practice, we met a patient with severe nightmares after the initiation of Carbamazepine (monotherapy for seizures).

Valproate's effects are variable, with some patients showing sleep stabilization and others showing increased arousals (20,22).

Gabapentin increases REM sleep and slow wave sleep duration and decreases the awakenings and the N1 stage (20,22). It is the only AED shown to be effective for periodic limb movements in sleep (1,3).

Somnolence was reported in 30% of patients taking *Pregabalin* and this adverse effect seems to

be mild or moderate in intensity, occurring within the first two weeks of therapy initiation (24).

Mildly detrimental effects on sleep are possible for *Ethosuximide* because it increases N1 and decreases N3 (20,22).

Lamotrigine has been reported to cause insomnia and the insomnia appeared to be dose-related (23). On the other hand, drowsiness is one of the most frequent side-effects and is dose-dependent too, probably because it increases REM sleep and decreases the amount of slow-wave sleep (15).

Epileptic patients taking *Levetiracetam* proved to develop a sleep consolidation (increase in total sleep time spent in NREM stages) while volunteers were less alert and sleepier on waking (26).

Add-on trials reported a higher frequency of somnolence in patients receiving *Topiramate* (29) while other studies showed no daytime sleepiness on starting doses of 200mg/d (28). This drug can be a second-line treatment for sleep-related eating disorder (27) (SSRIs are the first line).

Subjective somnolence was reported in patients taking *Vigabatrin* in the first 4-6 weeks after drug initiation (30). The Vigabatrin-administered kindled rats showed an increase in total sleep time due to an increase in total N1 sleep stage (31).

Lacosamide 300 mg/day had no effect on objective or subjective sleep parameters in healthy subjects and was generally well tolerated (32,33).

For patients with frequent nocturnal seizures, AEDs can also stabilize sleep by decreasing seizures and interictal epileptiform discharges. Newer generation of AEDs generally tend to cause less disturbance of the sleep cycle and greater stabilization of sleep architecture.

Antidepressants

Antidepressant agents may influence sleep: some are sedating and some are stimulating.

The tricyclic agents (TCA) act by blocking the serotonin and norepinephrine transporters. Tertiary amines (Amitriptyline, Clomipramine, Doxepin, Imipramine) induce excessive daytime somnolence (EDS) and impairment of cognitive and psychomotor performances. They can be used in insomniac patients (34). Secondary amines (Desipramine, Protriptyline) are activating antidepressants by increasing the sleep latency and WASO with a lower sleep efficiency (35). TCAs can be used to treat re-

sistant insomnia but they can cause abnormal dreams. Sudden drug withdrawal can produce REM sleep rebound and insomnia.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants. SSRIs (Paroxetine, Fluoxetine, Sertraline, Escitalopram) block the reabsorption (reuptake) of the serotonin in the brain. They can cause EDS (Paroxetine, Fluvoxamine) or insomnia (Citalopram, Fluoxetine) (1,2,3). SSRIs can precipitate or worsen periodic limb movements of sleep and restless legs syndromes and the effect might be dose-dependent (36,37). They can also increase other movement disorders during sleep and REM sleep behavior disorder (RBD) and can amplify the electromyographic activity during REM sleep (38). Abnormal slow eye movements during sleep has been observed after ingestion of Fluoxetine (“Prozac eyes”) (39).

Venlafaxine is a *serotonin and norepinephrine reuptake inhibitor (SNRI)* used as antidepressant and anxiolytic, but also for the treatment of episodes of cataplexy. It can cause insomnia or EDS and may increase the periodic leg movements of sleep (37). Status cataplecticus (a rare manifestation of narcolepsy with cataplexy episodes recurring for hours or days, without a refractory period, in the absence of emotional triggers) can be developed after abrupt onset of Venlafaxine (40,41). Orexins excite neurons of the locus coeruleus and dorsal raphe nucleus; drugs that increase noradrenergic and serotonergic transmitters suppress cataplexy (66,67). But then, treatment of cataplexy with antidepressants may trigger or exacerbate RBD symptoms.

Serotonin antagonist and reuptake inhibitors (SARI) block the serotonin receptors and inhibit the reuptake of serotonin, norepinephrine and dopamine. Trazodone is a sedating antidepressant which increases the N3 stage of sleep and decreases the REM stage (42,43). Instead, Nefazodone decreases N3 and increases N2 (44).

Monoamine oxidase inhibitors (MAOI), the first developed type of antidepressants, which inhibit the enzymes involved in the metabolism of norepinephrine, dopamine and serotonin, usually produce insomnia but may also induce EDS. They decrease the total sleep time, increase WASO and decrease REM sleep (45). MAOI's are the most potent REM

inhibitors and REM sleep rebound can occur frequently after drug withdrawal. MAOI (Phenelzine, Selegiline, Tranylcypromine, Rasagiline) can cause abnormal dreams and nightmares.

In conclusion, almost all antidepressant agents suppress REM sleep (increase the REM latency and decrease the amount of REM sleep) but their effect on sleep latency and sleep quality is different and some studies are contradictory.

Atypical antipsychotics

Atypical antipsychotic medications are often used as hypnotics. Whereas the typical antipsychotic medications have only dopaminergic antagonism, the atypical antipsychotic medications have both serotonergic and dopaminergic antagonism. *Quetiapine, Olanzapine, Clozapine, Risperidone* reduce the sleep latency and WASO and increase the total sleep time (46,47,48). In general, they suppress REM sleep and increase N3. Because of their long half-time, diurnal sedation is frequent. Quetiapine and Risperidone might cause or increase periodic leg movements of sleep and restless leg syndrome (49).

Central nervous system stimulants

Medication that stimulates the central nervous system (CNS) has important effects on sleep quality and quantity. *Modafinil, Methylphenidate and Dextroamphetamine* may be used in sleep disorders with somnolence (narcolepsy, hypersomnia etc.) (3,4). They increase sleep latency and wakefulness during sleep period, increase N1 and decrease N3 and REM. Usually patients develop tolerance to these side effects on sleep. Stopping the medication can induce REM rebound and EDS. The amphetamines (Methylphenidate, Dextroamphetamine, Methamphetamine) act by increasing the synaptic availability of norepinephrine and dopamine (1,4). But there are several problems with their use. First, tolerance may develop requiring escalating doses and sometimes “a drug holiday” (several days without medication) may be useful. Second, they increase blood pressure. Third, they induce other side effects: nervousness, irritability, headache, decreased appetite, insomnia, paranoia or hallucinations.

The mechanism of Modafinil remains elusive but it seems to have monoaminergic effects stimulating the histamine, norepinephrine, dopamine,

serotonin and orexin systems (50,51,52). Modafinil may reduce the effectiveness of birth control medications (53). It can be used in somnolence in relation to narcolepsy, idiopathic hypersomnia, periodic limb movement disorder, Parkinson disease, obstructive sleep apnea, multiple sclerosis or myotonic dystrophy (1,4).

Other medications used in narcolepsy and hypersomnia

Sodium oxybate (Gamma-hydroxybutyrate), a GABA precursor, increases sleep continuity and decreases the frequency of cataplexy in persons with narcolepsy (54,55). Gradual and mild improvement in EDS has also been reported with chronic use. Adverse effects include enuresis, parasomnia, headaches, dizziness, vertigo and nausea. Over dosage can result in respiratory depression, confusion, seizures, coma or death. It is usually taken twice each night because it has a very short half-time (using an alarm clock for the second dose is an important inconvenience of this drug). The precise mechanism by which sodium oxybate reduces cataplexy is not known yet. It is contraindicated in patients treated with sedative hypnotics (4).

Pitolisant is a histamine H3 antagonist, a new wake-enhancing drug that increases the histamine release in the brain by blocking presynaptic H3 histamine reuptake, a drug that can improve the EDS in hypersomnia (idiopathic and symptomatic) and narcolepsy (56).

Dopamine agonists

Dopaminergic agonists (*Pramipexol* – D2 and D3 receptor agonist, *Ropinirole* – with high specificity for D3 receptors) represents the first line of sleep treatment in periodic limb movements of sleep (PLMS) and restless leg syndrome (RLS) (57,58,59). The most frequent side effects are nausea and somnolence, which typically decrease over time. *Rotigotine* can be used as a transdermal patch. PLMS should be treated when it is associated with RLS, insomnia or EDS. An unusual but interesting adverse effect of dopamine agonist is the pathological gambling (60).

There are some other drug categories that can be efficient in PLMS: AEDs (Gabapentin, Pregabalin, Valproate), opioids, iron supplementation and benzodiazepines (Clonazepam) (1,4).

Analgesics

The most used analgesics are the *nonsteroidal anti-inflammatory drugs (NSAIDs)*, the *antipyretics* (Acetaminophen) and the *opioids* (Codeine, Morphine).

Acetaminophen doesn't change sleep quality and architecture at therapeutic doses (61).

There are some studies who say that NSAIDs can modify sleep by inhibiting prostaglandin synthesis which is believed to promote sleep (61).

Opioids decrease N3 and REM at high dosages and among addicted persons increase WASO and decrease total sleep time (62,63). Central sleep apnea can arise from chronic use of long-acting opioids (Methadone, Hydrocodone, Morphine). They may also produce ataxic breathing during sleep (Biot's breathing). On the other hand, they may improve sleep significantly in patients with chronic severe pain (64).

Orexin antagonists

A new class of hypnotics is in phase of development. Orexin receptors are distributed widely in the brain and their activation promotes wakefulness. Two neuropeptide orexins have been identified, OX1, mainly present in locus coeruleus, and OX2, expressed mainly in hypothalamic histaminic areas (3). Insertion of an antagonist (Suvorexant) suppresses the arousal and these drugs are now used in trials with patients with primary insomnia (25).

Prazosin

It is a selective alpha-1-adrenergic antagonist and it is now considered a first-line drug for the treatment of nightmares of posttraumatic stress disorder (68).

Menopausal hormone replacement therapy

Sleep problems are frequent in menopausal and perimenopausal women. Aging, weight gain, depression, vasomotor instability, sleep apnea, fibromyalgia can represent one or multiple causes of poor sleep at these patients. Menopausal hormone replacement therapy (HRT) may improve sleep structure and quality (1-3).

Progesterone is a GABA agonist with anxiolytic and sedative effects. It has a stimulating effect on breathing with some efficiency in mild obstructive sleep apnea in menopausal women (69,71,72).

Estrogen promotes sleep by decreasing sleep latency, reducing the number of arousals and awakenings and increasing the amount of slow-wave sleep and REM. It is a serotonin and GABA agonist (70,72).

CONCLUSION

From sleep medicine point of view, when we manage patients with neurological diseases and sleep problems, we bear in mind not only inducing

and promoting sleep, but dosing the sleep side-effects of our medication: antidepressants, antihistaminergic drugs and neuroleptics may aggravate the RLS; SSRI antidepressants may induce insomnia complaints; benzodiazepines, barbiturates, muscle relaxants and opiates are able to lead to sleep breathing disorders; antidepressants, Z-drugs, neuroleptics, antihistamines may induce parasomnia behaviors, AED usually modify sleep macrostructure at the beginning of treatment.

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