Drug-induced sleepiness and insomnia: an update

Sonolência e insônia causadas por drogas: artigo de atualização

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ABSTRACT

Medical practice of sleep medicine requires an extensive pharmacological knowledge, especially when you need to make decisions about the drug scheme already adopted by a given patient. The care of patients with multiple diseases and using of multiple drugs has become common. The great challenge facing the physician is to what extent one or more drugs may be contributing to the complaint of sleepiness or insomnia. Any drug with activity in the central nervous system has the potential to affect sleep-wake cycle. The pharmacokinetic drug knowledge's will be useful in determining the likelihood of adverse effects on sleep-wake functioning. In this article we describe the potential sedative or in generating insomnia by drugs used in the major chronic diseases in the population.

Keywords: conscious sedation, drugs, hypersomnia, sleep, sleep disorders.

INTRODUCTION

One of the major challenges faced by doctors practicing sleep medicine in private practices and public outpatient care is the recognition of the potential of certain drugs to cause sedation or, conversely, insomnia. Quite often, patients present more than one disease and therefore take various medications. The doctor's task is more complex as more comorbid conditions are found in these patients, which makes patient evaluation more difficult and intriguing.

In this update, we focus on the potential for sedation or insomnia of drugs used in the most common chronic diseases worldwide. Doctors often treat patients with multiple comorbidities. It is estimated that 25% of the population of North America presents more than one chronic disease(1). Among the more prevalent chronic diseases across the world are cardiovascular diseases (systemic hypertension, congestive heart failure, and coronary insufficiency), diabetes mellitus, chronic obstructive pulmonary diseases, arthritis, depression, and cerebrovascular accident(2). We will describe the drugs that are not intentionally used due to their effects on sleep, grouping them according to the diseases for which they are recommended, and we will describe their potential to induce sleepiness or insomnia in more detail. For drugs without such potential, we will only cite them as not possessing either property; at the end, we will describe some other drugs that have similar potential but are used for less prevalent chronic diseases.

The regulation of the sleep-wake cycle is complex and involves multiple neuronal sites and neurotransmitters. Any drug with activity in the central nervous system has the potential to affect this cycle. The knowledge of the pharmacokinetics of drugs will be useful in determining the likelihood of adverse effects on sleep or wakefulness(3).

DRUGS USED IN CARDIOVASCULAR DISEASES

Systemic hypertension - Systemic hypertension is one of the most frequent diseases and the most common among the cardiovascular diseases. Affecting 50% of people aged between 60 and 69 years, hypertension has an even higher prevalence after 70 years of age(6).

Adrenergic beta-blockers - A group of drugs widely used in the control of systemic hypertension, whose mechanism of action is not yet fully elucidated. Selective beta-blockers, such as atenolol (ATENOL®, ABLOK®, and ANGIPRESS®)
and metoprolol (LOPRESSOR® and SELOKEN®), and non-selective beta-blockers, such as propranolol (INDERAL®), cause sleep disorders, including insomnia and nightmares. However, the most recently launched drugs, carvedilol (CARDIOL®, CARVEDILAT®, BECARVE®, COREG®), ICTUS®, and KARVIL®) and labetalol (NORMODYNE® and TRANDATE®, not available in Brazil) have vasodilator activity by blocking the alpha-1 receptor and may cause sleepiness and fatigue.\(^{5,6,7}\)

**Central adrenergic agonists:**

**Methyldopa** - A safe antihypertensive drug, with central action, for use during pregnancy. The drug causes transient sedation. The patient may feel out of energy for a longer time and may develop depression.

**Clonidine and analogues** - They are agonists of the alpha-2 receptor in the brainstem. These drugs have potential to cause sleepiness that is occasionally incapacitating, vivid dreams and nightmares.\(^{8}\)

**Alpha-1 adrenergic blocking agents (Alpha-1 blockers)** - Doxazosin (CARDURAN®), prazosin (MINIPRESS®), and terazosin (HYTRIN®) - Associated with transient sleepiness. Prazosin can be used in the treatment of nightmares and in sleep disorders related to post-traumatic stress.\(^{9}\)

**Calcium channel blockers** - These drugs prevent the transport of calcium into the cell, thus decreasing the contraction of smooth muscles of blood vessels, thereby reducing vascular resistance. In general, calcium channel blockers do not cause sleep disturbances, but sleepiness may occur early in treatment when using higher doses and disappear with use or with dose adjustment.\(^{10}\)

**Other drugs** - Several studies suggest that there is no effect of sleepiness or insomnia from angiotensin-converting enzyme inhibitors (Losartan [CORUS® and LOSARTEC®], captopril, enalapril [EUPRESSIN® and RENITEC®], ramipril [NAPRIX®], ECATOR®, TRIATEC®, and others), diuretics, or vasodilators (hydralazine [APRESOLINA®]).

**Ischemic cardiopathy** (Coronary disease) - The major cause of morbidity and mortality in the Western world.\(^{11,12}\) The manifestations of coronary diseases include stable angina, acute coronary syndromes, congestive heart failure, sudden death, and silent ischemia.\(^{13}\) The organic nitrates (isosorbide) and the antiplatelet agents (acetylsalicylic acid, clopidogrel) are among the most prescribed drugs in cardiology and are not cited as causing insomnia or sleepiness.

**DRUGS USED IN DIABETES MELLITUS**

**Diabetes mellitus** - Refers to a hyperglycemic syndrome resulting from various causes. Its prevalence is approximately 10% in the U.S. population. It is classified, according to the disease state and other characteristics, as type 1, insulin-dependent diabetes, or type 2, non-insulin-dependent diabetes.\(^{14}\)

**Insulin** - The use of insulin by itself does not cause sleepiness or sedation, except when facing hypoglycemia; the signs and symptoms attributed to hypoglycemia are divided into two groups: (1) adrenergic and cholinergic neurogenic manifestations (tachycardia, tremor, anxiety, hunger, and sweating); and (2) neuroglycopenic symptoms (dizziness, headache, confusion, blurred vision, unusual behavior, incoordination, seizures, sleepiness, lethargy, and even coma).\(^{15}\)

**Sulfonylureas** - Sulfonylureas of the first generation (chlorpropamide [DIABINESE®], tolbutamide [ORINASE®], tolazamide [TOLINASE®]) or the second generation (Glimipiride [AMARYL®], glibenclamide [DAOINIL® and LISAGLUCON®], glipizide [MINIDIA®], gliclazide [DIAMICRON®]) do not have the potential to cause insomnia or sedation, except when they cause hypoglycemia (see insulin).

The biguanides (metformin [GLIFAGE®, DIMEFOR®, METTA SR®, and GLUCOFORMIN®]) and meglitinides (repaglinide [NOVONORM®, PRANDIN®, and GLUCONORM®] and nateglinide [STARFORM®]) are not known to cause hypoglycemia, sleepiness, or insomnia.

**Thiazolidinediones** (rosiglitazone [AVANDIA®] and pioglitazone [ACTOS®]) - the sale of rosiglitazone was recently forbidden in Brazil by the Brazilian Health Surveillance Agency (ANVISA, September 2010) due to the high probability of myocardial infarction, heart failure, pericardial effusion, and other cardiac disorders associated with its use.\(^{16}\) The use of pioglitazone (ACTOS®) was not restricted by the same regulatory agency, and among its side effects there is no record of changes in the sleep-wake cycle.\(^{17}\)

**GLP-1 receptor agonists** - Glucagon-like peptide 1 (GLP-1) is an endogenous peptide whose release into the bloodstream is stimulated after a meal; in turn, GLP-1 stimulates the release of insulin and reduces circulating glucose level. In recent years, the pharmaceutical industry has produced two GLP-1 receptor agonists. Brazil already has these two drugs: exenatide (BYETTA®) and liraglutide (VICTOZA®). Both act as hypoglycemic agents and decrease weight but do not affect sleep. Used as monotherapy, these drugs rarely lead to hypoglycemia.\(^{18,19}\)

**DPP-4 inhibitors** - Studies suggest that sitagliptin (JANUVIA®) and its congeners do not cause sleep disturbances, sedation, or hypoglycemia and have a neutral action on the patient’s weight.\(^{20}\)

**Alpha glycosidase inhibitors** - In Brazil, the representative alpha-glycosidase inhibitor is acarbose (GLUCOBAY®), which has no effect on sleep. When used as single therapy, acarbose does not cause hypoglycemia.

**DRUGS USED IN DYSLIPIDEMIAS**

**Statins** - Atorvastatin (LIPITOR® and CITALOR®), lovastatin, rosuvastatin (CRESTOR®, ROSUCOR®, and VIVACOR®), and simvastatin are indicated for elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol with or without hypercholesterolemia, or moderate levels of triglycerides with low HDL cholesterol, which contribute for the emergence of atherosclerotic vascular disease. Statins are reported to cause insomnia.\(^{21}\)

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

**Bronchodilators** - Three classes of drugs act as bronchodilators and protect the airway: (a) the beta-2 adrenergic agonists, (b) theophylline, and (c) the anticholinergic agents.
Launched in 1950, the corticosteroids and adrenergic agonists are chemically different groups. Among the most important are the endogenous alkaloid receptors, which are produced by the human body and act, among other functions, as potent endogenous analgesics. Opioids, antidepressants, and anticonvulsants are some of the substances effective in relieving or eliminating pain. A range of neurotransmitters modulate the mechanisms of pain, including substance P, endorphins, norepinephrine, and serotonin. Analgesic nonsteroidal anti-inflammatory drugs and opioids, antidepressants, and anticonvulsants are some of the many substances effective in relieving or eliminating pain.

Gabapentin (NEURONTIN®), GABANEURIN® and pregabalin (LYRICA®, PREBITAL®) are anticonvulsants approved by the U.S. Food and Drug Administration (FDA) for use in postherpetic neuralgia and peripheral neuropathies. The proposed mechanism of action of duloxetine (CYMBALTA®), an antidepressant approved for use in peripheral neuropathies, is the inhibition of serotonin and norepinephrine reuptake in the central nervous system, which would increase the activity of these neurotransmitters and thus the subsequent reduction of pain perception by modulating its signal. All these substances cause sedation to a greater or lesser degree, depending on the dose, duration of use, and individual sensitivity.

Opioids - alkaloids derived from opium-have been known since ancient Mesopotamia (3,400 BC), and their hallucinogenic and analgesic properties have been used throughout recorded history. The discovery of endogenous opioid receptors occurred in the 1970s. Soon, substances were found that were chemically similar to opioids, called endogenous morphine or endorphins, which are produced by the human body and act, among other functions, as potent endogenous analgesics. Opioids are divided into chemically different groups. Among the most important are:

- Phenanthrenes - include codeine (CODATEN®, TYLEX®, and PACO®), morphine (DIMORF® inj.), oxycodone (OXYCONTIN®), and nalbuphine (NUBAIN® inj.);
- Phenylpiperidines - include fentanyl, a drug widely used in intensive care units and 80 times more potent than morphine; and meperidine. Both are exclusively used in hospitals;
- Diphenylheptanes - include propoxyphene (DOLOXENE® A) and methadone (METHYDON®);
- Tramadol (TRAMAL®, TRAMADOL®, SYLADOR®, TIMASEN® SR, SENSITRAN®, and ANANGOR®), a unique opioid drug, atypical, not included in the previous groups; an analog of codeine.

Sleepiness is the main side effect of opioids. The sedation level may depend on the drug, dosage, and duration of use, as well as the severity of the underlying disease. Chronic use for cancer or chronic pain is associated with both insomnia and daytime sleepiness and fatigue, but these may be secondary to the disease or psychological factors. The most serious adverse effect of opioids is respiratory depression during sleep or after surgery.

Triptans are selective agonists of the serotonin 1B/1D receptors, prescribed for the acute treatment of migraine attacks. Sleepiness is a common adverse effect, and its incidence varies according to the drug used. Greater somnolence occurs after using, for example, eletriptan (RELPAX®), zolmitriptan (ZOLMIG®), and rizatriptan (MAXALT®), and less sedation with sumatriptan (SUMAX® and IMIGRAN®) and naratriptan (NARAMIG®).

The nonsteroidal anti-inflammatory drugs, widely prescribed in daily medical practice, although recognized for their potential to reduce the synthesis of prostaglandin D₂ (one of the substances involved in the production and release of melatonin and nocturnal body temperature regulation), do not adversely affect the sleep–wake cycle and may even improve the quality of sleep due to analgesic effects, as was concluded by a placebo-controlled study of tenoxicam.

DRUGS USED IN DEPRESSIVE DISORDERS

First-generation antidepressants - Tricyclic antidepressants and monoamine oxidase inhibitors. This class of drugs can improve alertness during the day, but they are often associated with reports of daytime sleepiness. Insomnia is also described. It is always difficult to analyze the effects of antidepressants on the sleep–wake cycle because the disease itself leads to sleep disturbance (specifically, sleepiness or insomnia) and other symptoms that overlap with the sleep disturbance: lassitude, fatigue, and decreased cognitive performance. The sedative effects of the tricyclic antidepressants amitriptyline (TRYPTANOL®), doxepin (SINEQUAN® and ADAPIN®; only obtained in compounding pharmacies in Brazil), and, to a lesser degree, imipramine (TOFRANIL®) and clomipramine (ANAFRANIL® and CLO®), are mainly explained by their histamine H1 receptor antagonism, but alpha-adrenergic
receptor antagonism and muscarinic cholinergic receptor antagonism are also involved. The insomnia caused by monoamine oxidase inhibitors (MAOIs) (tranylcypromine [PARNATE®] and moclobemide [AURORIX®]) is attributed to the inhibition of norepinephrine, dopamine and serotonin metabolism within the synaptic cleft, thereby increasing the concentration and availability of these neurotransmitters. Sedative effects are also reported with the use of MAOIs[34].

Selective serotonin reuptake inhibitors (SSRIs) - Although they show selectivity in inhibiting serotonin uptake, they act weakly in inhibiting the reuptake of norepinephrine and dopamine and antagonize muscarinic cholinergic receptors. The currently available SSRIs are fluoxetine (PROZAC®, FLUXENE®), sertraline (SERETId®, SEREDE®, and ALENTHUS®), paroxetine (AOPAX®, CEBRILIN®, DEPAXAN®, PAXIL®, and PONDERA®), and venlafaxine (VENLAFAXINE®, EFFEXOR® and ALENTHUS®), desvenlafaxine (PRISTIQ®), duloxetine, and milnacipran (IXEL®). These drugs have different actions on several subtypes of serotonin receptors and may cause sleepiness (sedation) or insomnia as adverse effects. Fluoxetine, the most studied SSRI antidepressant to date, most often causes insomnia[55]. Paroxetine most often causes sedation, although it may cause insomnia in some patients[36,37].

Serotonin-norepinephrine reuptake inhibitors - These so-called dual inhibitors have an important role in the inhibition of reuptake of both the neurotransmitters serotonin and norepinephrine and include Venlaflaxine (VENLIFT®, VENLAXIN®, EFFEXOR® and ALENTHUS®), desvenlafaxine (PRISTIQ®), duloxetine, and milnacipran (IXEL®). These drugs may cause insomnia or sleepiness[38]. Among users of duloxetine and venlafaxine, insomnia is among the most cited adverse effects (10% to 50% of cases)[39].

Serotonin antagonists and reuptake inhibitors - Trazodone (DONAREN®) is an antidepressant that blocks serotonin reuptake and inhibits serotonin receptors, mostly the 5-HT2, and is a histamine H1 receptor antagonist, as well as an alpha-1 and alpha-2 adrenergic receptor antagonist. The most important effect of trazodone is sedation; due to this effect, it is indicated as a hypnotic in low doses (50-100 mg)[39].

Norepinephrine-dopamine reuptake inhibitors - Bupropion (WELBUTRIN®, ZYBAN®, BUPIM®, ZETRON®, and BUP®) acts on dopaminergic and serotonergic pathways at the same time, both pathways related to wakefulness; it can cause insomnia in approximately 10% of its users[40].

Noradrenergic and specific serotonergic antidepressant - Mirtazapine (MENELAT®, RAZAPINA®, and REMERON®), also indicated as a hypnotic, promotes antagonism of presynaptic noradrenergic alpha-2 receptors (which control the release of norepinephrine in the synaptic cleft, thus increasing the availability of the neurotransmitter) and exerts a potent antagonistic effect on histamine H1 and serotonin 5-HT2 receptors, which accounts for its great sedative potential[40].

Norepinephrine reuptake inhibitors - Reboxetine (PROLIFT®) is a derivative of viloxazine, which acts almost exclusively on the inhibition of norepinephrine uptake. Its efficacy as an antidepressant in severe depression is greater than fluoxetine[41]; it may cause insomnia[42].

Miscellaneous antidepressants - Maprotiline (LUDIOMIL®): classified as a tetracyclic antidepressant with an action profile and side effects similar to tricyclic antidepressants. It produces sedation most likely by its high antagonistic affinity to histamine H1 receptor (antihistaminic effect). Agomelatine (VALDOXAN®) is a new antidepressant, approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) in 2008 for use in major depression. With an unusual mechanism of action for this drug group, it acts as an agonist of melatonin receptors MT1 and MT2 and assists in restoring circadian rhythm. Both insomnia and sleepiness are common and transient symptoms in the first two weeks of agomelatine use[40,46].

Lithium - A drug of first choice for all stages of bipolar disorder. At the onset of treatment, it is subjectively associated with improvement of nighttime sleep and increased daytime sleepiness[47].

DRUGS USED IN EPILEPSY SYNDROME

Epilepsy affects over 50 million people worldwide, with over 40 clinical syndromes already described. Currently, strategies for treatment of this disease are only symptomatic, not curative, aiding in the suppression of clinically manifested seizures with either mono- or poly-drug therapy. Since the 1990s, 10 new anticonvulsants have been approved for additional treatment of partial seizures. The mechanisms of action of anticonvulsants include sodium channel blockade on the neuronal cytoplasmic membrane level, effects on gamma-aminobutyric acid (GABA) action (agonism of receptors and reuptake and transaminase inhibition), blockade of glutamate receptors, and other mechanisms, several of which are unknown[40].

The anticonvulsants are arbitrarily classified[39] into standard (or old): carbamazepine (TEGRETOL®); phenobarbital (GARDENAL®), which is the most sedative of the group[40,41]; phenytoin (HIDANTAL®); valproic acid (DEPAM®); and primidone (PRIMID®); and the so-called “new” class, including gabapentin, lamotrigine (LAMITOR® and LAMICTAL®), vigabatrin (SABLIR®, topiramate (AMATO®, EGIDE®, and TOPAMAX®), levetiracetam (KEPPRA®), and zonisamide (ZONEGRAN®) (the last two are not yet available in Brazil). According to controlled placebo studies, they cause mainly sedation at the beginning of treatment[52,53]. Lamotrigine, in addition to its sedative effect, can also cause insomnia[42]. Felbamate (FELBATOL®), a broad-spectrum anticonvulsant that is not available in Brazil, currently has its use restricted in the U.S. due to reported cases of liver failure and bone marrow aplasia one year after its release; it can also cause insomnia in users[55].

OTHER DRUG GROUPS

Type 1 histamine receptor antagonists

First-generation antihistamines - Diphenhydramine (NOTUSS®, ENDCOFF®, and BENALET®) and hydroxyzine (HIDOALERG®,
HIXIZINE® and HIXILERG® are lipophilic and easily cross the blood-brain barrier, with important antagonist action on histamine H1 receptors. Moreover, they show muscarinic anticholinergic effects, central alpha-adrenergic action, and serotoninetic effects. They cause sedative effects significant enough that they are indicated as hypnotics by some professionals (off-label).

**Second-generation antihistamines** - Loratadine (LORALERG®), levocetirizine (ZINA® and ZYXEM®), desloratadine (SIGMALIV®), and cetirizine (ZYRTEC®) are fat-soluble molecules that do not easily cross the blood-brain barrier. Therefore, they exert little effect on the central nervous system. A meta-analysis of 18 studies concluded that second-generation antihistamines cause much less sedative effects than the first-generation antihistamines, although mild sedation has been detected. Among the second-generation drugs, cetirizine is cited as showing a greater subjective sedative effect.

**Type 2 histamine receptor antagonists** - The H2 antagonists (cimetidine [TAGAMET®], ranitidine [ZYLIUM-®], famotidine [FAMOX®], and nizatidine [AXID-®]) have difficulty crossing the blood-brain barrier, which make them unlikely to affect the central nervous system. However, these drugs can interact with other classes of drugs that have sedative effects (carbamazepine and benzodiazepines) or insomnia effects (theophylline and beta-blockers), increasing their levels and adverse effects.

**Pseudoephedrine** (CLARITIN® D, LORALERG® D, and TYLENOL® SINUS) and Phenylpropanolamine - Compounds that despite sharing pharmacological properties with epinephrine (ephedrine) have less pronounced stimulatory effects on the central nervous system. Pseudoephedrine is often used in association with analgesics or antihistamines, indicated as nasal decongestants in rhinitis, and over-the-counter in cold medication. The major sleep disorder reported with the use of pseudoephedrine is insomnia.

**Stimulants** - Methylphenidate (RITALIN® and CONCERTA®), dextroamphetamine/levoamphetamine (ADDERALL®), lisdexamfetamine (VENVANSE®), and modafinil (STAVIGILE®) are indicated primarily for the treatment of narcolepsy and attention deficit-hyperactivity disorder. Several studies and subjective reports describe an increased incidence of insomnia with the use of these stimulants; cognitive functions may improve as an effect of these drugs.

**Antipsychotics** - The antipsychotics classically act by antagonizing dopamine D2 receptors in the mesolimbic system. However, they often affect other brain regions, causing undesirable prolactinemia symptoms, extrapyramidal signs, and anhedonia, alterations most commonly reported with the use of classical or typical antipsychotics: chlorpromazine (AMPLICTIL®), Clopsina® and CLORPROMAZ®, haloperidol (HALDOL®), and thioridazine (MELLARIL®). The new antipsychotics, termed atypical, are risperidone (RISS®, RESPIDON®, RISPERDAL®, and ZARGUS®), clozapine (LEPONEX®), olanzapine (ZYPREXA®), and aripiprazole (ABELIFY®), and quetiapine (SEROQUEL®, QUETTROS®, and QUEROPAX®). In addition to blocking dopamine D2 receptors, they antagonize the serotonin receptors (especially 5-HT2A) and 5-HT3A. Antipsychotics, formerly called neuroleptics or major tranquilizers, effect some blockade of alpha-adrenergic, muscarinic cholinergic, and histamine receptors, which gives them a sedative property to a greater or lesser degree, depending on the action at these sites.

Among the classical drugs, chlorpromazine and thioridazine are more sedative than haloperidol. Among the newer antipsychotics, clozapine causes more sleep, and this symptom accounts for 24% of cases of treatment discontinuation. Aripiprazole is the one that shows the least sedation. Insomnia may be caused by typical and atypical antipsychotics. This symptom is attributed to their ability to act as agonists of serotonergic 5-HT1A receptor or to the restless legs syndrome caused by dopamine blockade, even with the use of atypical antipsychotics.

**Anxiolytic drugs** - Several medications are currently used to treat anxiety disorders. Antidepressants that inhibit serotonin and norepinephrine (duloxetine, venlafaxine, and desvenlafaxine), the SSRIs, the benzodiazepines, and buspirone (partial 5-HT1A receptor agonist) are considered drugs of first choice in the treatment of anxiety disorders. Antiepileptic drugs and atypical antipsychotics can also be indicated for use in anxiety. Among the benzodiazepines approved for use in anxiety disorders, alprazolam (APRAZ®, FRONTAL®, and ALTROX®), clonazepam (RIVOTRIL® and CLONOTRIL®), diazepam (VALIUM®), and lorazepam (LORAX®) act by increasing GABA neurotransmission through the GABA_A receptor, and the greatest effect on sleep is sedation. Buspirone (BUSPAR® and ANSITEC®) has an anxiolytic efficacy similar to that of benzodiazepines, but its actual onset may take 4-6 weeks, unlike that of benzodiazepines. However, buspirone has the great advantage of not causing addiction or sedation; however, it can cause insomnia as an undesirable symptom.

**Anti-Parkinson drugs** - Complaints related to sleep disorders are common in patients with Parkinson’s disease; approximately 60% of these patients report insomnia, 30% report excessive daily sleepiness, 59% present with REM sleep behavior disorder, and up to 21% of cases report restless legs syndrome. These complaints tend to worsen with progression of the disease and may result from abnormalities in the sleep-wake cycle, nocturnal motor symptoms, other drugs in use, or even other disorders: sleep apnea, periodic limb movements, or comorbid or psychiatric diseases. Dopamine replacement is a priority in this disease. Because sleep is greatly affected in Parkinson’s disease, it is always difficult to attribute a specific change in the sleep-wake cycle to the administration of a prescription drug or determine whether such changes are part of the disease manifestation itself. The most commonly used drugs for Parkinson’s disease are levodopa and dopamine agonists. Dopamine agonists include the ergot derivatives bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), pinbedil (TRIVASTAL®), and pergolide...
(PERMAX®) and the non-ergot derivatives pramipexole (SIFROL® and LIVIPARK®, ropinirole (REQUIP®), and rotigotine (NEUROPA PATCH®). A complementary treatment includes inhibitors of catechol-O-methyltransferase, entacapone (CONTAM®), and tolcapone (TASMAR®), which prolong the effect of levodopa, improving its bioavailability. Anticholinergics and selegiline (MAO-B) also have their place in the treatment of Parkinson’s disease. The antiparkinson medication with the greatest tendency to cause insomnia is selegiline (NIAR®), JUMEXIL®, and DEPRILAN®; this effect is mainly attributed to its amphetamine derivatives(76). Amantadine (MANTIDAN®), an N-methyl-D-aspartate (NMDA) receptor antagonist, is used in the initial stages of Parkinson’s disease, but it is associated with a higher incidence of insomnia. Interestingly, this compound has been listed as a better therapeutic option in the treatment of attention deficit-hyperactivity disorder, with similar results and lower rates of side effects than stimulants commonly used in this condition(76).

Higher doses of dopaminergic drugs are more likely to be associated with the sedative effect(77). However, higher doses are prescribed in more advanced cases of Parkinson’s disease. Sudden sleep attacks, which can cause traffic accidents, are also described. Such attacks, which may occur without previous symptoms, are observed with the use of any dopaminergic agent, but less frequently with levodopa alone(78).

**Drugs for the treatment of Alzheimer’s disease** - According to neuropathological studies, the degeneration of cholinergic neurons is the main causative problem of Alzheimer’s disease. In recent years, drugs inhibiting the enzyme that degrades acetylcholine in the synaptic cleft (acetylcholinesterase) have been developed, enabling a more effective treatment of these patients. Currently there are four drugs approved by the FDA for the treatment of Alzheimer’s disease, rivastigmine (EXELON® capsule, oral solution and Patch), galantamine (REMINYL® ER capsule), donepezil (ERANZ®, EPEZ®, and ZILEDON® tablets), and the NMDA receptor antagonist memantine (ALOIS®, ZIDER®, HEIMER®, and EBIX®); controlled-release memantine: NAMENDA® XR 28 mg, not available in Brazil. Of these drugs, the only ones approved for use in moderate/advanced stages of the disease are donepezil and memantine. The others are indicated for use only in the mild to moderate stages. Donepezil is the only one with the potential to alter sleep and can be administered in the morning or evening. Donepezil is recommended for use only in the morning in case of insomnia or nightmare(79).

**CONCLUSION**

Many drugs used in the treatment of chronic diseases have the ability to cause sedation or insomnia as adverse effects. Drugs with higher fat-solubility more easily traverse the blood-brain barrier. Any drug with activity in the central nervous system has the potential to affect the sleep-wake cycle; preserving the quality and operation of this cycle can be important for successful treatment of the underlying disease.

**REFERENCES**