

# 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.

### RESUMO

O exercício da prática médica em medicina de sono requer um amplo conhecimento farmacológico, especialmente quando se necessita tomar decisões quanto ao esquema farmacológico já adotado por um dado paciente. O atendimento a pacientes com múltiplas doenças e em uso de vários medicamentos tornou-se comum. O grande desafio enfrentado pelo médico é saber até que ponto um ou mais medicamentos podem estar contribuindo para a queixa de sonolência ou insônia. Qualquer droga com atividade no sistema nervoso central apresenta potencial para afetar o ciclo vigília-sono. O conhecimento sobre farmacocinética dos medicamentos será útil em determinar a probabilidade de efeitos adversos no funcionamento vigília-sono. Neste artigo, descrevemos o potencial sedativo ou em gerar insônia dos medicamentos utilizados nas principais doenças crônicas na população mundial.

**Descritores:** distúrbios do sono, drogas, hipersonia, sedação consciente, sono.

### 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<sup>(1)</sup>. 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<sup>(2)</sup>. 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<sup>(3)</sup>.

### 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<sup>(4)</sup>.

**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<sup>®</sup>), ABLOK<sup>®</sup>, and ANGIPRESS<sup>®</sup>)

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and metoprolol (LOPRESSOR<sup>®</sup> and SELOKEN<sup>®</sup>), and non-selective beta-blockers, such as propranolol (INDERAL<sup>®</sup>), cause sleep disorders, including insomnia and nightmares. However, the most recently launched drugs, carvedilol (CARDIOL<sup>®</sup>, CARVEDILAT<sup>®</sup>, BECARVE<sup>®</sup>, COREG<sup>®</sup>, ICTUS<sup>®</sup>, and KARVIL<sup>®</sup>) and labetalol (NORMODYNE<sup>®</sup> and TRANDATE<sup>®</sup>, not available in Brazil) have vasodilator activity by blocking the alpha-1 receptor and may cause sleepiness and fatigue<sup>(5,6,7)</sup>.

### 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 central receptors in the brainstem. These drugs have potential to cause sleepiness that is occasionally incapacitating, vivid dreams and nightmares<sup>(8)</sup>.

### Alpha-1 adrenergic blocking agents (Alpha-1 blockers)

- Doxazosin (CARDURAN<sup>®</sup>), prazosin (MINIPRESS<sup>®</sup>), and terazosin (HYTRIN<sup>®</sup>) - Associated with transient sleepiness. Prazosin can be used in the treatment of nightmares and in sleep disorders related to post-traumatic stress<sup>(9)</sup>.

**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<sup>(10)</sup>.

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

**Ischemic cardiopathy** (Coronary disease) - The major cause of morbidity and mortality in the Western world<sup>(11,12)</sup>. The manifestations of coronary diseases include stable angina, acute coronary syndromes, congestive heart failure, sudden death, and silent ischemia<sup>(13)</sup>. 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<sup>(14)</sup>.

**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)<sup>(15)</sup>.

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

The biguanides (metformin [GLIFAGE<sup>®</sup>, DIMEFOR<sup>®</sup>, METTA SR<sup>®</sup>, and GLUCOFORMIN<sup>®</sup>]) and meglitinides (repaglinide [NOVONORM<sup>®</sup>, PRANDIN<sup>®</sup>, and GLUCO-NORM<sup>®</sup>]) and nateglinide [STARFORM<sup>®</sup>]) are not known to cause hypoglycemia, sleepiness, or insomnia.

**Thiazolidinediones** (rosiglitazone [AVANDIA<sup>®</sup>] and pioglitazone [ACTOS<sup>®</sup>]) - 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<sup>(16)</sup>. The use of pioglitazone (ACTOS<sup>®</sup>) was not restricted by the same regulatory agency, and among its side effects there is no record of changes in the sleep-wake cycle<sup>(17)</sup>.

**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<sup>®</sup>) and liraglutide (VICTOZA<sup>®</sup>). Both act as hypoglycemic agents and decrease weight but do not affect sleep. Used as monotherapy, these drugs rarely lead to hypoglycemia<sup>(18,19)</sup>.

**DPP-4 inhibitors** - Studies suggest that sitagliptin (JANUVIA<sup>®</sup>) and its congeners do not cause sleep disturbances, sedation, or hypoglycemia and have a neutral action on the patient's weight<sup>(20)</sup>.

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

## DRUGS USED IN DYSLIPIDEMIAS

**Statins** - Atorvastatin (LIPITOR<sup>®</sup> and CITALOR<sup>®</sup>), lovastatin, rosuvastatin (CRESTOR<sup>®</sup>, ROSUCOR<sup>®</sup>, and VIVACOR<sup>®</sup>), 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<sup>(21)</sup>.

## 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.

**Beta-2** adrenergic agonists - Are currently commercially available as salmeterol (SEREVENT<sup>®</sup> and SERETIDE<sup>®</sup>) and formoterol (FLUIR<sup>®</sup>, FORASEQ<sup>®</sup>, FORMARE<sup>®</sup>, and FORMOCAPS<sup>®</sup>) and are often associated with budesonide (SYMBICORT<sup>®</sup> and ALENIA<sup>®</sup>) and arformoterol (FORADIL AEROLIZER<sup>®</sup> - not yet available in Brazil)<sup>(22)</sup>. Beta-2 adrenergic agonists have no effects on sleep per se, unless associated with inhaled corticosteroids, which can cause hyperactivity and insomnia<sup>(23)</sup>.

**Theophylline** - Theophylline and its derivatives act as respiratory stimulants and bronchodilators. The users can show initial or maintenance insomnia<sup>(24)</sup>.

**Anti-cholinergic agents** - This class of drugs, for example, ipratropium bromide (ATROVENT<sup>®</sup> and BROMOVENT<sup>®</sup>), are not described as causing sedation or insomnia.

**Corticosteroids** - Launched in 1950, the corticosteroids are the most successful drugs in treating diseases whose pathophysiological basis is rooted in the inflammatory process. Oral corticosteroids affect sleep even when used for a short period of time and more frequently cause insomnia than others. Even when used in inhalable form, which reduces their side effects, corticosteroids can cause hyperactivity, insomnia, and even psychosis<sup>(25,26)</sup>.

## DRUGS USED FOR ANALGESIA

The neurobiology of pain is quite complex, involving central and peripheral mechanisms. The activation of peripheral receptors (by tissue injury or inflammation) is modulated by central mechanisms. Pain contributes to the appearance of sleep disorders, and sleep deprivation increases sensitivity to 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<sup>®</sup>, GABANEURIN<sup>®</sup>) and pregabalin (LYRICA<sup>®</sup>, PREBICTAL<sup>®</sup>) 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<sup>®</sup>), 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<sup>(27,28)</sup>. 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 alkaloid 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<sup>(29)</sup>:

- Phenanthrenes - include codeine (CODATEN<sup>®</sup>, TYLEX<sup>®</sup>, and PACO<sup>®</sup>), morphine (DIMORF<sup>®</sup> inj.), oxycodone (OXYCONTIN<sup>®</sup>), and nalbuphine (NUBAIN<sup>®</sup> 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<sup>®</sup> A) and methadone (METYDON<sup>®</sup>);
- Tramadol (TRAMAL<sup>®</sup>, TRAMADOL<sup>®</sup>, SYLADOR<sup>®</sup>, TIMASEN<sup>®</sup> SR, SENSITRAM<sup>®</sup>, and ANANGOR<sup>®</sup>), 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<sup>(30)</sup>.

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<sup>®</sup>), zolmitriptan (ZOLMIG<sup>®</sup>), and rizatriptan (MAXALT<sup>®</sup>), and less sedation with sumatriptan (SUMAX<sup>®</sup> and IMIGRAN<sup>®</sup>) and naratriptan (NARAMIG<sup>®</sup>)<sup>(31,32)</sup>.

The nonsteroidal anti-inflammatory drugs, widely prescribed in daily medical practice, although recognized for their potential to reduce the synthesis of prostaglandin D<sub>2</sub> (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<sup>(33)</sup>.

## 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<sup>®</sup>), doxepin (SINEQUAN<sup>®</sup> and ADAPIN<sup>®</sup>; only obtained in compounding pharmacies in Brazil), and, to a lesser degree, imipramine (TOFRANIL<sup>®</sup>) and clomipramine (ANAFRANIL<sup>®</sup> and CLO<sup>®</sup>), are mainly explained by their histamine H<sub>1</sub> 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<sup>®</sup>] and moclobemide [AURORIX<sup>®</sup>]) 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<sup>(34)</sup>.

**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<sup>®</sup>, FLUXENE<sup>®</sup>, VEROTINA<sup>®</sup>, PSIQUIAL<sup>®</sup>, and EUFOR<sup>®</sup>), fluvoxamine (LUVOX<sup>®</sup>), paroxetine (AROPAX<sup>®</sup>, CEBRILIN<sup>®</sup>, DEPAXAN<sup>®</sup>, PAXIL<sup>®</sup>, and PONDERA<sup>®</sup>), sertraline (ASSERT<sup>®</sup>, ZOLOFT<sup>®</sup>, SEREDE<sup>®</sup>, TOLREST<sup>®</sup>, and SERENATA<sup>®</sup>), citalopram (CIPRAMIL<sup>®</sup>, PROCIMAX<sup>®</sup>, MAXAPRAN<sup>®</sup>, DENYL<sup>®</sup>, ALCYTAM<sup>®</sup>, and CITTÁ<sup>®</sup>), and escitalopram (LEXAPRO<sup>®</sup>, EXODUS<sup>®</sup>, ESPRAN<sup>®</sup>, and RECONTER<sup>®</sup>). 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<sup>(35)</sup>. Paroxetine most often causes sedation, although it may cause insomnia in some patients<sup>(36,37)</sup>.

**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 Venlafaxine (VENLIFT<sup>®</sup>, VENLAXIN<sup>®</sup>, EFEXOR<sup>®</sup> and ALENTHUS<sup>®</sup>), desvenlafaxine (PRISTIQ<sup>®</sup>), duloxetine, and milnacipran (IXEL<sup>®</sup>). These drugs can cause insomnia or sleepiness<sup>(38)</sup>. Among users of duloxetine and venlafaxine, insomnia is among the most cited adverse effects (10% to 50% of cases)<sup>(39)</sup>.

**Serotonin antagonists and reuptake inhibitors** - Trazodone (DONAREN<sup>®</sup>) is an antidepressant that blocks serotonin reuptake and inhibits serotonin receptors, mostly the 5-HT<sub>2</sub>, and is a histamine H<sub>1</sub> 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)<sup>(40)</sup>.

**Norepinephrine-dopamine reuptake inhibitors** - Bupropion (WELBUTRIN<sup>®</sup>, ZYBAN<sup>®</sup>, BUPIUM<sup>®</sup>, ZETRON<sup>®</sup>, and BUP<sup>®</sup>) 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<sup>(41)</sup>.

**Noradrenergic and specific serotonergic antidepressant** - Mirtazapine (MENELAT<sup>®</sup>, RAZAPINA<sup>®</sup>, and REMERON<sup>®</sup>), 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 H<sub>1</sub> and serotonin 5-HT<sub>2</sub> receptors, which accounts for its great sedative potential<sup>(42)</sup>.

**Norepinephrine reuptake inhibitors** - Reboxetine (PROLIFT<sup>®</sup>) 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<sup>(43)</sup>; it may cause insomnia<sup>(44)</sup>.

**Miscellaneous antidepressants** - Maprotiline (LUDIOMIL<sup>®</sup>): 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 H<sub>1</sub> receptor (antihistaminic effect). Agomelatine (VALDOXAN<sup>®</sup>) is a new antidepressant, approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) 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 MT<sub>1</sub> and MT<sub>2</sub> and assists in restoring circadian rhythm. Both insomnia and sleepiness are common and transient symptoms in the first two weeks of agomelatine use<sup>(45,46)</sup>.

**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<sup>(47)</sup>.

## 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<sup>(48)</sup>.

The anticonvulsants are arbitrarily classified<sup>(49)</sup> into standard (or old): carbamazepine (TEGRETOL<sup>®</sup>); phenobarbital (GARDENAL<sup>®</sup>), which is the most sedative of the group<sup>(50,51)</sup>; phenytoin (HIDANTAL<sup>®</sup>); valproic acid (DEPAKENE<sup>®</sup>); and primidone (PRIMID<sup>®</sup>); and the so-called "new" class, including gabapentin, lamotrigine (LAMITOR<sup>®</sup> and LAMICTAL<sup>®</sup>), vigabatrin (SABRIL<sup>®</sup>), topiramate (AMATO<sup>®</sup>, ÉGIDE<sup>®</sup>, and TOPAMAX<sup>®</sup>), levetiracetam (KEPPRA<sup>®</sup>), and zonisamide (ZONEGRAN<sup>®</sup>) (the last two are not yet available in Brazil). According to controlled placebo studies, they cause mainly sedation at the beginning of treatment<sup>(52,53)</sup>. Lamotrigine, in addition to its sedative effect, can also cause insomnia<sup>(54)</sup>. Felbamate (FELBATOL<sup>®</sup>), 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<sup>(55)</sup>.

## OTHER DRUG GROUPS

### Type 1 histamine receptor antagonists

**First-generation antihistamines** - Diphenhydramine (NOTUSS<sup>®</sup>, ENDCOFF<sup>®</sup>, and BENALET<sup>®</sup>) and hydroxyzine (HIDROALERG<sup>®</sup>,

HIXIZINE<sup>®</sup>, and HIXILERG<sup>®</sup>) are lipophilic and easily cross the blood-brain barrier, with important antagonist action on histamine H1 receptors<sup>(56,57)</sup>. Moreover, they show muscarinic anticholinergic effects, central alpha-adrenergic action, and serotonergic effects. They cause sedative effects significant enough that they are indicated as hypnotics by some professionals (off-label).

**Second-generation antihistamines** - Loratadine (LORALERG<sup>®</sup>), levocetirizine (ZINA<sup>®</sup> and ZYXEM<sup>®</sup>), desloratadine (SIGMALIV<sup>®</sup>, DESTADIN<sup>®</sup>, and DESALEX<sup>®</sup>), and cetirizine (ZYRTEC<sup>®</sup> and CETIRTEC<sup>®</sup>) 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<sup>(58)</sup> 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<sup>®</sup>], ranitidine [ZYLIMUM<sup>®</sup>, ANTAK<sup>®</sup>, and LABEL<sup>®</sup>], famotidine [FAMOX<sup>®</sup>], and nizatidine [AXID<sup>®</sup>]) 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<sup>®</sup> D, LORALERG<sup>®</sup> D, and TYLENOL<sup>®</sup> 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<sup>(59)</sup>.

**Stimulants** - Methylphenidate (RITALIN<sup>®</sup> and CONCERTA<sup>®</sup>), dextroamphetamine/levoamphetamine (ADDERALL<sup>®</sup>), lisdexamfetamine (VENVANSE<sup>®</sup>), and modafinil (STAVIGILE<sup>®</sup>) 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<sup>(60)</sup>.

**Antipsychotics** - The antipsychotics classically act by antagonizing dopamine D2 receptors in the mesolimbic system<sup>(61)</sup>. 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<sup>®</sup>, CLOPSINA<sup>®</sup>, and CLORPROMAZ<sup>®</sup>), haloperidol (HALDOL<sup>®</sup>), and thioridazine (MELLARIL<sup>®</sup>). The new antipsychotics, termed atypical, are risperidone (RISS<sup>®</sup>, RESPIDON<sup>®</sup>, RISPERDAL<sup>®</sup>, and ZARGUS<sup>®</sup>), clozapine (LEPONEX<sup>®</sup>), olanzapine (ZYPREXA<sup>®</sup>), aripiprazole

(ABILIFY<sup>®</sup>), and quetiapine (SEROQUEL<sup>®</sup>, QUETTROS<sup>®</sup>, and QUEROPAX<sup>®</sup>). In addition to blocking dopamine D2 receptors, they antagonize the serotonin receptors (especially 5-HT<sub>2A</sub>)<sup>(62)</sup>. Antipsychotics, formerly called neuroleptics or major tranquilizers<sup>(63)</sup>, 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<sup>(64)</sup>.

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<sup>(65)</sup>. 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-HT<sub>1A</sub> receptor or to the restless legs syndrome caused by dopamine blockade, even with the use of atypical antipsychotics<sup>(66)</sup>.

**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-HT<sub>1A</sub> receptor agonist) are considered drugs of first choice in the treatment of anxiety disorders<sup>(67)</sup>. Antiepileptic drugs and atypical antipsychotics can also be indicated for use in anxiety. Among the benzodiazepines approved for use in anxiety disorders, alprazolam (APRAZ<sup>®</sup>, FRONTAL<sup>®</sup>, and ALTROX<sup>®</sup>), clonazepam (RIVOTRIL<sup>®</sup> and CLONOTRIL<sup>®</sup>), diazepam (VALIUM<sup>®</sup>), and lorazepam (LORAX<sup>®</sup>) act by increasing GABA neurotransmission through the GABA<sub>A</sub> receptor, and the greatest effect on sleep is sedation. Buspirone (BUSPAR<sup>®</sup> and ANSITEC<sup>®</sup>) 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<sup>(68,69)</sup>.

**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<sup>(70)</sup>. 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<sup>®</sup>), cabergoline (DOSTINEX<sup>®</sup>), priribedil (TRIVASTAL<sup>®</sup>), and pergolide

(PERMAX<sup>®</sup>) and the non-ergot derivatives pramipexole (SIFROL<sup>®</sup> and LIVIPARK<sup>®</sup>), ropinirole (REQUIP<sup>®</sup>), and rotigotine (NEUPRO PATCH<sup>®</sup>). A complementary treatment includes inhibitors of catechol-*O*-methyltransferase, entacapone (CONTAM<sup>®</sup>), and tolcapone (TASMAR<sup>®</sup>), 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<sup>®</sup>, JUMEXIL<sup>®</sup>, and DEPRILAN<sup>®</sup>); this effect is mainly attributed to its amphetamine derivatives<sup>(71)</sup>. Amantadine (MANTIDAN<sup>®</sup>), 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<sup>(72)</sup>.

Higher doses of dopaminergic drugs are more likely to be associated with the sedative effect<sup>(73)</sup>. 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<sup>(74)</sup>.

#### 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<sup>®</sup> capsule, oral solution and Patch), galantamine (REMINYL<sup>®</sup> ER capsule), donepezil (ERANZ<sup>®</sup>, EPEZ<sup>®</sup>, and ZILEDON<sup>®</sup> tablets), and the NMDA receptor antagonist memantine (ALOIS<sup>®</sup>, ZIDER<sup>®</sup>, HEIMER<sup>®</sup>, and EBIX<sup>®</sup>; controlled-release memantine: NAMENDA<sup>®</sup> 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<sup>(75)</sup>.

#### 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

- Anderson G, Hovath J. The Growing Burden of Chronic Disease in America [Internet]. 2004 [cited 2012 Dec 22]; 119(3): 263-270. Available from: <http://ncbi.nlm.nih.gov/PMC/articles/PMC1497638>.
- Barros MBA, César CLG, Carandina L, Torre GD. Desigualdades sociais na prevalência de doenças crônicas no Brasil, PNAD-2003. *Ciênc. saúde coletiva* [Internet]. 2006 [cited 2012 Dez 12]; 11(4): 911-926. Available from: [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S1413-81232006000400014&lng=en](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1413-81232006000400014&lng=en).
- Schweitzer PK. Drugs that Disturb Sleep and Wakefulness. In: Kryger MH, Roth T, Dement WC (editors). *Principles and Practices of Sleep Medicine*. St. Louis, MO: Elsevier Saunders. 2011. p. 555. <http://dx.doi.org/10.1016/B978-1-4160-6645-3.00046-3>
- Chobanian AV, Barkis GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42: 1206-1252. <http://dx.doi.org/10.1161/01.HYP.0000107251.49515.c2> PMID:14656957
- Pearce CJ, Wallin JD. Labetalol and Other Agents that block both alpha and beta-adrenergic receptors. *Cleverland Clin J Med*. 1994; 61: 59-69. PMID:8124849
- Tufik S. Medicamentos e Sono. In: Tufik S. *Medicina e biologia do sono*. São Paulo: Manole. 2008. p. 181-205.
- Bortolotto Luiz Aparecido, Fernanda M Consolim-Colombo. Beta bloqueadores Adrenérgicos (Adrenérgicos Betabloqueadores). *Rev Bras Hipertens*. 2009; 16 (4): 215-220.
- Brunton LL, Chabner BA, Knollmann BC. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGrawHill. 2011. p.314.
- Taylor HR, Freeman MK, Cates ME. Prazosin for treatment of nightmares related to posttraumatic stress disorder. *Am J Health Syst Pharm*. 2008; 65(8):716-22. <http://dx.doi.org/10.2146/ajhp070124> PMID:18387899
- Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's. As Bases Farmacológicas da Terapêutica*. 9. ed. Rio de Janeiro: McGraw Hill. 1996. p.565.
- Boden W. Angina pectoris and stable ischemic heart disease. In: Goldman L, Schafer AI. *Goldman's Cecil medicine: ebook*. Philadelphia: ELSEVIER-ER. 2012. p. 412-424.
- R W Elford, M Yed. The Impact of Preventive Cardiology on Coronary Artery Disease. *CMAJ*. 1988; 139(8): 719-724. PMID:3139276 PMID:1268289
- Brown A L et al. Preventative Cardiology and Ischemic Heart Disease. In: Foster Corey et al. *The Washington Manual Medical Therapeutics: e-book*. Philadelphia: Lippincott Williams & Wilkins. 2010. p. 65-154.
- Maraschin et al. Diabetes Mellitus Classification. *Arq Bras Cardiol*. 2010; 95(2): e40-6. <http://dx.doi.org/10.1590/S0066-782X2010001200025>
- Burge M R et al. Hypoglycemia and Self-Care in Elderly Patients with Diabetes Mellitus. In: Monshi M N, Lipsitz L A. *Geriatric Diabetes: e-book*. New York: INFORMA HEALTHCARE. 2007. p. 332. <http://dx.doi.org/10.3109/9781420019810-26>
- ANVISA cancela registro do medicamento avandia. [internet]. 2010 [cited 2013 Jan 29]. Available from: <http://s.anvisa.gov.br/wps/s/r/beckK>
- Cloridrato de pioglitazona [internet]. [cited 2013 Jan 29]. Available from: [http://www4.anvisa.gov.br/bularioeletronico/default.asp\\_bula\\_PDF](http://www4.anvisa.gov.br/bularioeletronico/default.asp_bula_PDF)
- Chia CW, Egan JM. Incretin-Based Therapies in Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab*. 2008; 93(10): 3703-3716. <http://dx.doi.org/10.1210/jc.2007-2109> PMID:18628530 PMID:2579648
- Amori RE, Lau J, Pittas AG. Efficacy and Safety of Incretin Therapy in Type 2 Diabetes: Systematic Review and Meta-analysis. *JAMA*. 2007; 298(2):194-206 <http://dx.doi.org/10.1001/jama.298.2.194> PMID:17622601
- Blonde L. Current antihyperglycemic treatment strategies for patients with type 2 diabetes mellitus. *Clev Clin J Med*. 2009; 76 Suppl 5: S4-S11. <http://dx.doi.org/10.3949/ccjm.76.s5.02> PMID:19952303
- Tuccori M, Lapi F, Testi A, Coli D, Moretti U, Vannacci A, Motola D, Salvo F, Rivolta AL, Blandizzi C, Mugelli A, Del Tacca M. Statin-associated psychiatric adverse events: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. *Drug Saf*. 2008; 31(12):1115-23. PMID:19026028

22. Campos LEM.  $\beta$ 2-agonista de longa duração na doença pulmonar obstrutiva crônica (DPOC). *J. Pneumologia* [Internet]. 2000 [cited 2013 Jan 27]; 26(3): 129-136. Available from: [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S0102-3586200000300005&lng=en](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-3586200000300005&lng=en).
23. Saricoban HE, Ozen A, Harmanci K, Razi C, Zahmacioglu O, Cengizler MR. Common behavioral problems among children with asthma: is there a role of asthma treatment? *Ann Allergy Asthma Immunol*. 2011;106(3):200-4. <http://dx.doi.org/10.1016/j.anaai.2010.11.016> PMID:21354021
24. Bailey WC, Richards JM Jr, Manzella BA, Brooks CM, Windsor RA, Soong SJ. Characteristics and correlates of asthma in a university clinic population. *Chest*. 1990; 98:821-828 <http://dx.doi.org/10.1378/chest.98.4.821> PMID:2209137
25. Bailey WC, Richards JM, Manzella BA, et al. Characteristics and correlates of asthma in a university clinic population. *Chest*. 1990; 98:821-828. <http://dx.doi.org/10.1378/chest.98.4.821> PMID:2209137
26. Lozada F, Silverman S, Migliorati C. Adverse side effects associated with prednisone in the treatment of patients with oral inflammatory ulcerative diseases. *J Am Dent Assoc*. 1984; 109:269-270. PMID:6590608
27. Wong DT, Bymaster FP, Mayle DA, Reid LR, Krushinski JH, Robertson DW. LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology*. 1993; 8(1):23-33. <http://dx.doi.org/10.1038/npp.1993.4> PMID:8424846
28. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001; 25(6):871-880. [http://dx.doi.org/10.1016/S0893-133X\(01\)00298-6](http://dx.doi.org/10.1016/S0893-133X(01)00298-6)
29. Trescott AM, Datta S, Lee M, Hansen H. Opioid Pharmacology. *Pain Physician*. 2008; 11: S133-S153. PMID:18443637
30. Schug SA, Zech D, Grond S. Adverse effects of systemic opioid analgesics. *Drug Saf*. 1992; 7(3):200-13. <http://dx.doi.org/10.2165/00002018-199207030-00005> PMID:1354445
31. Dodick D, Martin V. Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. *Cephalalgia*. 2004; 24: 417-424. <http://dx.doi.org/10.1111/j.1468-2982.2004.00694.x> PMID:15154851
32. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT<sub>1B/1D</sub>) agonists in acute migraine treatment: a meta-analysis of 53 trials. *Lancet*. 2001; 358(9294):1668-75. [http://dx.doi.org/10.1016/S0140-6736\(01\)06711-3](http://dx.doi.org/10.1016/S0140-6736(01)06711-3)
33. Lavie P, Hahir M, Lorder M, Scharf Y. Nonsteroidal anti-inflammatory drug therapy in rheumatoid arthritis. Lack of association between clinical improvement and effect on sleep. *Arthritis Rheum*. 1991; 34: 655-659. <http://dx.doi.org/10.1002/art.1780340605> PMID:2053912
34. Remick RA, Froese C, Keller FD. Common side effects associated with monoamine oxidase inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry*. 1989; 13:497-504. [http://dx.doi.org/10.1016/0278-5846\(89\)90137-1](http://dx.doi.org/10.1016/0278-5846(89)90137-1)
35. Cordioli AV, editor. *Psicofármacos: consulta rápida*. Porto Alegre: Artmed. 2011. p. 310.
36. Wagstaff A J et al. Paroxetine: An Update of its use in Psychiatric Disorders in Adults. *Drugs*. 2002; 62(4): 655-703. <http://dx.doi.org/10.2165/00003495-200262040-00010> PMID:11893234
37. Pae Cu, Patkar A A. Paroxetine: Current status in Psychiatric. *Expert Rev Neurother*. 2007; 7(3): 313-4.
38. Häuser W, Urrütia G, Turt S, Uçe Yler N, Walitt B. Serotin and Noradrenaline reuptake inhibitors (SNRI) for fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2013, Issue 1. Art. No.: CD 010292. doi: 10.1002/14651858.CD010292. <http://dx.doi.org/10.1002/14651858.CD010292>
39. Drummond EH. *The complete guide to psychiatric drugs: straight talk for best results*: e-book. New Jersey: John Wiley & Sons. 2006. p. 197, 283.
40. Stahl S M. Mechanism of Action of Trazodone: a Multifunction Drug. *CNS Spectr*. 2009; 14(10) 536-46. PMID:20095366
41. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Prim Care Companion J Clin Psychiatry*. 2004; 6(4): 159-166. <http://dx.doi.org/10.4088/PCC.v06n0403> PMID:15361919 PMID:154842
42. Winokur A, DeMartino NA 3rd, McNally DP, et al. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. *J Clin Psychiatry*. 2003; 64:1224-1229. <http://dx.doi.org/10.4088/JCP.v64n1013> PMID:14658972
43. Massana J, Möller HJ, Burrows GD, Montenegro RM. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int Clin Psychopharmacol*. 1999; 14(2):73-80. <http://dx.doi.org/10.1097/00004850-199903000-00003> PMID:10220121
44. Aronson J K, editor. *Meyler's side effects of Psychiatric Drugs: e-book*. Oxford. United Kingdom: ELSEVIER. 2009. P. 109.
45. European Medicines Agency. [Internet]. London: EMA; c1995-2011 [cited 2012 Dec 30]. Available from: [www.ema.europa.eu](http://www.ema.europa.eu).
46. Sansone RA, Sansone L. Agomelatine: a novel antidepressant. *Innov Clin Neurosci*. 2011; 8(11):10-14
47. Obermeyer WH, Bencra RM. Effects of drugs on sleep. *Neurol Clin*. 1996; 14:827-840. [http://dx.doi.org/10.1016/S0733-8619\(05\)70287-5](http://dx.doi.org/10.1016/S0733-8619(05)70287-5)
48. Walker M C, Sures R, Fisher A. Mechanism of Antiepileptic Drug Action. In: Shorvon S et al, editors. *The Treatment of Epilepsy: e-book*. Hong-Kong: WILEY-BLACKWELL. 2009. P 91-108. <http://dx.doi.org/10.1002/9781444316667.ch7>
49. Kennedy GM, Lhatoo SD. CNS adverse events associated with antiepileptic drugs. *CNS Drugs*. 2008; 22:739-760. <http://dx.doi.org/10.2165/00023210-200822090-00003>
50. Bazil CW. Effects of antiepileptic drugs on sleep structure. Are all drugs equal? *CNS Drugs*. 2003; 17:719-728. <http://dx.doi.org/10.2165/00023210-200317100-00003>
51. Malow BA, Bowes RJ, Lix X. Predictors of sleepiness in epilepsy patients. *Sleep*. 1997; 20:1105-1110. PMID:9493919
52. Salinsky MC, Oken BS, Binder LM. Assessment of drowsiness in epilepsy patients receiving chronic antiepileptic drug therapy. *Epilepsia*. 1996; 37:181-187. <http://dx.doi.org/10.1111/j.1528-1157.1996.tb00010.x> PMID:8635429
53. Leppik IE. Antiepileptic drugs in development: prospects for the near future. *Epilepsia*. 1994; 35(Suppl. 4):S29-S40. <http://dx.doi.org/10.1111/j.1528-1157.1994.tb05953.x> PMID:8174517
54. Berry R. Insomnia. In: Berry R, Editor. *Fundamentals of Sleep Medicine*. Philadelphia: ELSEVIER. 2012. p. 481-512 <http://dx.doi.org/10.1016/B978-1-4377-0326-9.00025-7> PMID:23140314
55. Tatum IV WO, Kaplan P, Jallon P, Editors. *Epilepsy A to Z: a concise encyclopedia*: e-book. New York: DemosMedical. 2009.p 130-1.
56. Okamura N, Yanai K, Higuchi M, et al. Functional neuroimaging of cognition impaired by a classical antihistamine, d-chlorpheniramine. *Br J Pharmacol*. 2000; 129:115-123. <http://dx.doi.org/10.1038/sj.bjp.0702994> PMID:10694210 PMID:1621119
57. Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci*. 2002; 72: 409-414. [http://dx.doi.org/10.1016/S0024-3205\(02\)02276-2](http://dx.doi.org/10.1016/S0024-3205(02)02276-2)
58. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation anti-histamines: meta-analysis. *J Allergy Clin Immunol*. 2003; 111: 770-776, cited by Schweitzer PK. *Drugs That Disturb Sleep and Wakefulness*. In: Kryger MH, Roth T, Dement WC, Editors. *Principles and Practices of Sleep Medicine*. St. Louis: ELSEVIER SAUNDERS. 2011. p. 414-418
59. Bertrand B, Jamart J, Arendt C. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: a double-blind multicentre study. *Rhinology* 1996;34:91-96. PMID:8876070
60. Penny Corkum et al. A Framework for the Assessment and Treatment of Sleep Problems in Children with Attention-Deficit/Hyperactivity Disorder. *Pediatr Clin N Am*. 2011; 58: 667-683. <http://dx.doi.org/10.1016/j.pcl.2011.03.004> PMID:21600348
61. Krystal A, Goforth H, Roth T. Effects of antipsychotic medications on sleep in schizophrenia. *Int Clin Psychopharmacol*. 2008; 23:150-160. <http://dx.doi.org/10.1097/YIC.0b013e3282f39703> PMID:18408529
62. Shader, Richard I, Editor. *Manual of Psychiatric Therapeutics: e-book*. Massachusetts: Lippincott Williams & Wilkins. 2003. p. 293.
63. Lucien Steru et al. The Automated Tail Suspension Test : A Computerized Device Which Differentiates Psychotropic Drugs. *Prog Neuropsychopharmacol Biol Psychiatry*. 1987; 11(6): 659-671. [http://dx.doi.org/10.1016/0278-5846\(87\)90002-9](http://dx.doi.org/10.1016/0278-5846(87)90002-9)
64. Krystal D A. Antidepressant and Antipsychotic Drugs. *Sleep Med Clin*. 2010; 5(4): 571-589. <http://dx.doi.org/10.1016/j.jsmc.2010.08.010> PMID:21499530 PMID:3076958
65. Fitton A, Heel RC. Clozapine: a review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs*. 1990; 40:722-747. <http://dx.doi.org/10.2165/00003495-199040050-00007>
66. Cohrs S. Sleep disturbance in patients with schizophrenia: impact and effect of antipsychotics. *CNS Drugs*. 2008; 22:939-962. <http://dx.doi.org/10.2165/00023210-200822110-00004> PMID:18840034

67. Damstein, Bernard Lerer, Sthefen Stahl, Editors. *Evidency Based Psychopharmacology*: e-book. Ney York: Cambridge University Press. 2005, 91-97.
68. Marangell L B, Martinez J M, Editors. *Concise Guide to Psychopharmacology*: e-book. London, England: American Psychiatric Publishing Inc. 2006. p. 75-6.
69. Schweitzer P. Excessive Sleepiness due to Medications and Drugs. In: Thorpy MJ, Billiard M, editors. *Sleepiness, Causes, Consequences and Treatment*: e-book. New York: Cambridge University Press. 2011. p. 384-400 <http://dx.doi.org/10.1017/CBO9780511762697.036>
70. Raphaelson M, Inati S. K. Treating Sleep Disorders in Neurology Practice. *Neurol Clin.* 2012; 30:1007-1025. <http://dx.doi.org/10.1016/j.ncl.2012.08.015> PMID:23099127
71. Neider L, Chaudhuri K R. Sleep Disfunction. In: Pahwa R, Lyons K E, Editors. *Handbook of Parkinson's Disease*: e-book. New York: INFORMA HEALTHCARE. 2007. p. 91-107
72. Sheik Hosenbocus, Raj Chahal. Amantadine: A Review of use in Child and Adolescent Psychiatry. *J Can Acad Child Adolesc Psychiatry.* 2013; 22(1): 55-60. PMID:23390434 PMCid:3565716
73. T. Simuni. Somnolence and other sleep disorders in Parkinson's disease: the challenge for the practicing neurologist. *Neurol Clin.* 2004; 22:S107-S126. <http://dx.doi.org/10.1016/j.ncl.2004.06.006> PMID:15501360
74. Paus S, Brecht H M, Koster J et al. Sleep Attacks, Daytime Sleepness, and Dopamine Agonist in Parkinson's Disease. *Mov Disord.* 2003; 18: 659-67. <http://dx.doi.org/10.1002/mds.10417> PMID:12784269
75. Marder K, editor. Dementia and memory loss. In: Brust JCM, Editor. *Current Diagnosis & Treatment in Neurology*. New York: McGraw Hill. 2012. p. 78-99.