Sleep promoters and insomnia

Hipnoindutores e insônia

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Abstract

The purpose of this update article is to briefly describe the profile, clinical application and indication for use of some of the most popular sedative and hypnotic compounds. Approximately two-thirds of all prescriptions for hypnotics are written for chronic users. Benzodiazepines are among the most commonly prescribed drugs worldwide. Women, the elderly, psychiatric patients and patients suffering from medical conditions are among chronic users of hypnotics. Zolpidem is currently the most widely prescribed hypnotic in most countries. It appears to be safer than benzodazepines and might be an option for long-term and controlled ("as needed") use. For insomnia patients in the USA and UK, antidepressants with sedative effects are also among the most frequently prescribed drugs for sedation. In this study, the use and sedative effects of trazodone, mirtazapine, doxepin and amitriptyline are described. The authors also examine the use and sleep-inducing properties of melatonin, as well as the rational use of sedative antipsychotics for chronic insomnia, particularly in psychiatric patients. Finally, some phytotherapeutic compounds are discussed.

Keywords: *Sleep initiation and maintenance disorders; Benzodiazepines; Melatonin; Antipsychotic agents; Hypnotics and sedatives; Pyridines*

Resumo

O objetivo deste artigo de atualização é o de descrever brevemente o perfil, a utilização clínica e a indicação de alguns dos sedativos e compostos hipnóticos mais utilizados. Cerca de 2/3 de todas as prescrições hipnóticas vão para o uso crônico. Os benzodiazepínicos estão entre as drogas mais prescritas mundialmente. As mulheres, os idosos e os pacientes psiquiátricos e clínicos estão entre os usuários crônicos de hipnóticos. O Zolpidem é, atualmente, o hipnótico mais prescrito na maioria dos países. Parece ser mais seguro em comparação aos benzodiazepínicos e poderiam ser uma opção para o uso de longo prazo e controlado ("quando necessário"). Os antidepressivos sedativos encontram-se também entre as medicações mais prescritas para sedação em pacientes com insônia nos EUA e no Reino Unido. São descritos efeito sedativo e uso de trazodona, mirtazapina, doxepina e amitriptilina. Os autores também discutem o uso de melatonina e suas propriedades sedativas e o uso racional de antipsicóticos sedativos para insônia crônica, em especial em pacientes psiquiátricos. Finalmente, alguns compostos fitoterápicos são mencionados.

Descritores: *Distúrbios do ínicio e da manutenção do sono; Benzodiazepinas; Melatonina; Agentes antipsicóticos; Hipnóticos e sedativos; Piridinas*

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Introduction

An ideal hypnotic should present, among others, the following characteristics: 1) no effect on memory or cognition; 2) rapid absorption; 3) specific binding to the receptor; 4) maintenance of physiological sleep; 5) no residual effects; 6) optimal half-life; 7) no potential for abuse, tolerance or dependence; 8) no active metabolites; 9) no respiratory depression effect; 10) no interaction with alcohol or other central nervous system depressants.[1]

Benzodiazepines: chronic use and effects on sleep

Benzodiazepines are among the most commonly consumed drugs worldwide.[2-3] In 2001, 6.96 billion daily doses of benzodiazepines prescribed as hypnotics were consumed worldwide; an impressive number if we consider that the world population in that year was 6.135 billion people.[4]

The estimated rate of consumption of sleep-promoting drugs among insomniacs in the city of São Paulo is approximately 20%, benzodiazepines being the most commonly consumed.[5] Another study showed that, in the city of São Paulo, the highest consumption of tranquilizers was registered among women and among older individuals with some psychiatric morbidity.[6] Of 4148 individuals evaluated in a study carried out in Great Britain,[7] 7.7% were found to have used benzodiazepines within the preceding year, the highest consumption being registered among women.[8] A total of 80% of patients started using benzodiazepines daily after the first prescription, and 34% of these patients were taking high doses (> 30 mg of diazepam). Among in-patients, 70% present a history of alcohol abuse or abuse of other drugs, and 30% had some organic brain disease. The following were the main reasons for prescription: insomnia, depression, anxiety, somatic complaints, pain symptoms[9-10] and stress symptoms. Other authors have reported that some known risk factors for insomnia, such as being female, aging, working split shifts, mental disorders or physical illness,[11-12] are superimposed on those for the use of benzodiazepines. It is notable that, among the elderly, retirees or inactive individuals, as well as widowers, are more predisposed to insomnia and the chronic use of benzodiazepines. Finally, routine prescription of benzodiazepines for minor psychiatric disorders has been reported.[13]

However, some factors associated with dependence on benzodiazepines and the withdrawal syndrome are observed: in the over-45 age bracket; consumption for more than a year; drug pharmacology; factors intrinsic to the patient; personality disorder; chronic dysphoria; chronic insomnia; chronic physical illness; and previous history of substance dependence.

Dependence on some benzodiazepines may develop within days or weeks. The main withdrawal symptoms are generally opposite to the expected therapeutic effects of the drug or cause an intensified recurrence of the original symptoms. The term "rebound" is used to describe the (transitory but more intense) return of an original symptom, whereas "recurrence" (or "relapse") presents the same pattern of symptom intensity and presentation previously seen and is more persistent. "Addition", which is rarer among individuals with primary insomnia, implies recreational use, ingestion of high doses, long-term use, etc. The withdrawal syndrome secondary to the discontinuation of the substance consists, therefore, in the onset of new signs and symptoms, as well as the worsening of pre-existing ones.

Rebound, recurrence and withdrawal syndrome may be seen in combination. All of the symptoms mentioned improved within one to four weeks, except those of recurrence. Among the symptoms related to the abrupt discontinuation of chronic use are rebound anxiety, insomnia, rapid heart rate, increased arterial pressure, sweats, nausea, vomiting, tremors, agitation, diarrhea, convulsions, as well as psychiatric or neurological symptoms. Some related mechanisms involve the severe loss of GABAergic inhibition and sharp increase in the excitation of the central nervous system. However, there are clear differences among benzodiazepines in their capacity to produce abstinence symptoms that may be independent of the elimination half-life.[14] In a recent study, lorazepam offered more resistance to the relatively gradual discontinuation (15 days), in therapeutic doses equivalent to 10 mg of diazepam, with an increase in the occurrence of symptoms.[15]

Studies with different benzodiazepines in therapeutic doses show that long-term use (> 6 months) leads to a loss of efficacy in the treatment of insomnia and a reduction in the quantity of slow-wave sleep, as well as other alterations in the electroencephalography (EEG) during sleep.[15-16]

In elderly patients, benzodiazepines must be prescribed with caution since there have been reports of increased risk for mortality due to chronic use.[17] Other data show that more than 50% of elderly patients would like to discontinue their benzodiazepines.[18] Therefore, we can conclude that benzodiazepines should be prescribed for short-term use for the treatment of insomnia, and that it is necessary to develop protocols to assist patients to stop using benzodiazepines. However, a better understanding of use patterns and reasons for use, the effects of chronic use and the cessation strategies adopted by physicians and users is also necessary.

It is also known that benzodiazepines alter the sleep architecture.[15,19-20] The following are their main effects on sleep: 1) sedative-hypnotic, being involved in the decrease in sleep latency, the increase in total sleep time and the decrease in the number of awakenings; 2) alterations in the sleep architecture, such as an increase in stage 2 non-rapid eye movement (NREM) sleep, a decrease in slow-wave sleep, an increase in latency for REM sleep, a decrease in the density of rapid eye movements in REM sleep, and minor or no alterations in the percentage of REM sleep. In addition, benzodiazepines also alter the EEG during sleep, with a decrease in delta activity, an increase in higher frequencies (above 12 Hz) and an increase in sigma activity or benzodiazepine spindles (Table 1).

Table 1 – Benzodiazepine effects on sleep architecture and on the electroencephalogram

Effects on sleep architecture	Effects on EEG during sleep
↓ Sleep latency	↓ Delta power (delta activity)
↑ Total sleep time	↑ High frequencies (above 12 Hz) on the EEG
↓ Time awake after sleep onset	↑ Sigma power ("BZD spindles")
↑ Latency for REM sleep	
↑ Stage 2 NREM sleep	
↓ Slow-wave sleep	
May not change the total percentage of REM sleep	
↓ REM density	

EEG: electroencephalogram
Adapted from Poyares et al, 2005, Bases da Medicina e Biologia do Sono, Editora Manole, in press

Other hypnotics and zolpidem

In the 1980s and 1990s, new hypnotics such as cyclopyrrolones (zopiclone), imidazopyridines (zolpidem), pyrazolopyrimidine (zaleplon) and imidazobenzodiazepines were synthesized. Zolpidem and zaleplon have a similar mechanism. Since they are more selective in the binding with the ϖ1 receptor, they are well tolerated and are hardly ever associated with the appearance of tolerance and dependence caused by long-term use. They differ, however, in the elimination half-life, ultra-short (0.9 h) for zaleplon and short (2.4 h) for zolpidem. Therefore, these drugs have been the treatment of choice for insomnia in many countries. There are more studies on zolpidem because this is a drug that has been used the longest.[21-22] Zolpidem and zaleplon are effective in decreasing sleep onset latency, although zolpidem leads to an additional increase in total sleep time. Neither compound presents residual effects during the day. However, zolpidem may increase slow-wave sleep, which is generally decreased in insomnia patients,[23] without altering REM sleep or stage 2 NREM sleep. There have been very few studies and zolpidem seems to be contraindicated for children. Its elimination half-life may be shortened in children, but there is a paucity of data on use in this age bracket. However, there have been few studies showing that it is safe for young adults,[24] revealing preservation of the normal curve of nocturnal growth hormone secretion.

Treating insomnia - which is generally chronic - is a significant clinical problem. There is an apparent paradox created by prescribing hypnotics for short-term use for a chronic disorder. In fact, studies show that approximately two-thirds (53 to 83%) of patients with chronic insomnia may require long-term treatment.[25-27] Treatment with benzodiazepines for a period longer than four weeks may increase the risk of dependence.[28] However, insomnia symptoms vary in approximately two-thirds (49 to 83%) of patients,[29] and may occur on nonconsecutive nights in 72% of cases. Studies of more than 6500 patients treated with a 10 mg/day dose of zolpidem for three to five nights per week showed that insomnia was significantly reduced and that the pattern of inappropriate nocturnal use was limited, without the appearance of habituation, rebound insomnia, or any significant residual daytime symptoms.[30-33]

Sedative antidepressants

Some antidepressants present a significant sedative effect that has been explored in the treatment of insomnia, especially in insomnia concomitant with depression disorder. Trazodone, mirtapazine, doxepin and amitriptyline have a stronger sedative effect. Other antidepressants may also present some sedative effect. However, some, rather than having a sedative effect, may even cause insomnia as a side effect. Some epidemiological data have shown that the use of antidepressants in the treatment of insomnia has become more widespread due to this potential for inducing sedation and alleviating anxiety (as is the case for some compounds).[34-35] The increased use of sedative antidepressants in the treatment of chronic insomnia may also be explained in part by their long-term use profile and in part by the high incidence of depressive symptoms among insomniacs.

Some mechanisms, such as antagonism of type 1 histaminergic receptors, anticholinergic activity or a possible influence on α-adrenoreceptors, have been proposed in order to explain the sedative effect of these compounds. For some antidepressants, tolerance to the sedative effect may develop due to continued use.[36] It is notable that the sedative effect may occasionally occur with the use of much smaller doses than those needed to produce an optimal antidepressant effect, such as with more than 10 mg of amitriptyline, 15 mg of mirtazapine or 25 mg of trazodone. There have been few studies, and there is still a need for guidelines on appropriate therapeutic doses for the treatment of insomnia. In general, antidepressants may cause either a slight or a marked decrease in REM sleep, although their effects on sleep vary. The higher the antidepressant potency in increasing noradrenaline levels, the more REM may be suppressed. In addition, sedative antidepressants may increase total sleep time and decrease sleep onset latency. A potential, although infrequent, side effect is increased periodic movement of the limbs during sleep, especially among tricyclic antidepressants.

Antipsychotics

Antipsychotics are used in the treatment of almost all forms of psychosis, including schizophrenia, schizoaffective disorders, affective profiles concomitant with psychotic symptoms and psychosis associated with organic mental diseases. They have also been prescribed as anxiolytics or sedatives for patients at high risk for developing benzodiazepine dependence, although it is also necessary to take into account the risk of tardive dyskinesia for some compounds.[37] However, there is little evidence, even empirical, that chronic insomnia should be treated with antipsychotics.[38]

Despite being ever more frequently used, antipsychotics show serious limitations: they are not efficacious for all patients, they have significant side effects and even those patients who initially responded well to treatment may continue to present signs and symptoms of the disease.

Conventional or first-generation antipsychotics had significant extrapyramidal side effects and, for this reason, they were known as "neuroleptics". The discovery of new drugs (atypical or second generation antipsychotics) that have fewer motor side effects has led to the use of the term "antipsychotic" rather than the term "neuroleptics".[39] Among the older antipsychotics, chlorpromazine and thioridazine have stronger sedative effects than that of haloperidol. Clozapine may produce deep and frequently prolonged sedation.[40]

Although antipsychotics have inconsistent effects on sleep patterns, they tend to normalize the sleep alterations characteristic of many psychoses. The capacity to prolong and increase the effects of hypnotic and opioid drugs seems to be related to the sedative potency of the antipsychotic agent and is partially independent of the potency of its antipsychotic effect. Therefore, more potent antipsychotic agents, which do not cause sleepiness, also do not increase the sedation produced by other drugs.[41]

Low tolerance to the side effects of antipsychotics limits the dosage to be given to elderly individuals. Physicians should use caution when prescribing agents of moderate and high potency and should start with low, fractionated doses, in the expectation that elderly patients will need lower doses than those used for younger patients. Wiegand[42] suggests using antipsychotics in elderly patients when long-term treatment is needed, especially when patients present abnormal nighttime behavior. Wortelboer et al[43] state that antipsychotics should be used in elderly insomnia patients only when specifically indicated, and that further studies are necessary in order to endorse their use.

Estivill at al[44] used olanzapine in nine patients (6 females and 3 males) with chronic insomnia. Single doses ranged from 2.5 to 10 mg. Outcomes were described as positive in eight patients, of whom five were given only the antipsychotic and three were in polytherapy. The authors concluded that, although the study sample was too small to demonstrate the effectiveness of the drug in the treatment of chronic insomnia, the clearly favorable outcomes in eight patients should encourage research into the effects of these drugs.

Adler[45] emphasized that antipsychotics, as well as antidepressants, are essential for the treatment of sleep disorders accompanying some well-defined psychiatric disorders. However, the author also stated that these drugs, especially antidepressants, could be used as a second-line medication in the treatment of primary insomnia. Other situations in which antipsychotics are indicated could include cases of severe or chronic insomnia, or both, that present unsatisfactory responses to the treatments performed, when there is risk of dependence on benzodiazepines or analogs. Antipsychotics could also be prescribed during benzodiazepine withdrawal. Nevertheless, due to the high incidence of side effects, it is recommended that the risks and benefits of the use of antipsychotics in the treatment of insomnia be carefully evaluated. In summary, antipsychotics are not the medication of choice in the treatment of primary chronic insomnia.[1]

Other substances

Phytotherapeutic agents may be included in this group. There are few data in the literature that quantify and prove the efficacy of such substances in the treatment of insomnia. The majority of the studies involve the use of *Valeriana officinalis*. The valerenic acid and the valepotriates are the most commonly described active principles, and the valerenic acid and the chamomile extract may present, *in vitro*, an increase in the GABAergic transmission.[46-47] Valepotriates are principles whose absorption is less stable. Valerenic acid decreases sleep latency, as well as the amount of stage 1 NREM sleep, and increases the amount of slow-wave sleep in insomniacs and in patients suffering from sleep fragmentation.[48-50]

Side effects that may affect the gastrointestinal tract are rare, and cardiovascular effects are even rarer. Further studies of the use of passiflora, kava-kava and chamomile are necessary. *Valeriana officinalis* active extracts may be prescribed for mild insomnia.

Melatonin

Melatonin is the principal output of the pineal gland, identified 2000 years ago. Although pineal calcification begins early in life, there is no evidence that this process leads to pinealocyte degeneration or a decrease in metabolic activity. The main pineal hormone is melatonin, whose production decreases with age.

The main route for melatonin synthesis is the retina, which receives the light-dark impulses. Retinal afferents carry these impulses to the suprachiasmatic tract, from which they continue to the hypothalamic suprachiasmatic nucleus, which is the clock that regulates circadian rhythms. Subsequently, the stimuli reach the hypothalamus paraventricular nucleus, the spinal cord and the superior cervical ganglion. The induction of melatonin synthesis occurs after stimulation of β and α-noradrenergic receptors located in the pinealocytes of the pineal gland. A total of 85% of the melatonin synthesis results from the interaction between noradrenaline and β-receptors, whereas only 15% results from the interaction of α-adrenoreceptors.[51] Immediately after its synthesis, melatonin, or N-acetyl-5-methoxytryptamine, is released into circulation and distributed to all of the organs due to its liposolubility.[52]

Serum melatonin levels are low during the day and high at night, reaching their peak between 2:00 and 4:00 am and dropping before dawn. The physiological significance of this rise in melatonin levels during the night is probably related to several effects such as a decrease in body temperature, changes in cerebral monoamine levels and induction of sleepiness.[53-55]

Melatonin is linked to the light-dark cycle and, consequently, to the wake-sleep cycle.[52] Its therapeutic effect may be observed in some sleep initiation and maintenance disorders, particularly in the phase delay syndrome, a condition in which individuals tend to go to sleep late and wake up late.[56] In such cases, it is important to set the time to wake up in the morning and subtract approximately eight hours in order to determine the time to go to bed. Melatonin may be administered up to three hours before bedtime. The objective is to hasten sleep onset. Patients are also encouraged to spend time in the sun or undergo therapeutic phototherapy in the morning, and to do physical exercises designed to inhibit melatonin production in the morning and hasten its secretion at night. In contrasting conditions, i.e. in patients with phase advancement, melatonin should be administered in the morning. Melatonin may be useful for treating other circadian rhythm disorders, such as that occurring in split-shift workers and in individuals experiencing jet lag.[57]

The mechanism by which melatonin exerts its hypnotic influence has yet to be well elucidated. Some authors believe that this effect results from the rise in indoleamine levels at sleep onset, suggesting that endogenous melatonin participates in the regulation of the wake-sleep cycle and leads to a cascade of events that activate somnogenic structures, or even that melatonin metabolites may have a hypnotic effect.[58]

Although some studies have also shown that melatonin has beneficial effects on the treatment of insomnia, the results are controversial since the melatonin effect depends on its dosage and the time of day at which it is administered.[59-64] Nave et al[64] showed that 3 and 6 mg of melatonin administered 30 or 120 min prior to the beginning of the polysomnography has the effect of reducing sleep onset latency. However, Attenburrow et al[65] found no differences in sleep latency when lower doses of melatonin (0.3 and 1 mg) were used or when melatonin was administered two hours before bedtime.

In a recent study, it was demonstrated that melatonin induces sleep that is more consolidated. The authors compared the results obtained from normal individuals taking 10 mg of melatonin an hour before going to bed to those obtained from those taking a placebo.[66] Ten minutes of uninterrupted sleep following the beginning of the exam was used as a criterion for considering the onset of more consolidated sleep. In the volunteers treated with melatonin, the onset of consolidated sleep (10 consecutive minutes of sleep) was hastened. Melatonin may be used to treat insomnia in elderly patients and in patients who present, in addition to insomnia, irregularities in the wake-sleep cycle.[67-69] The identification of melatonin metabolism and its effect on sleep has fostered research into the synthesis of new pharmaceuticals, such as ML-1 receptor agonists, e.g. ramelteon, for treating insomnia.[70]

Studies have demonstrated that melatonin also shows oncostatic[71] and antioxidant[72] action as well as activating action

on the immune system.[73] To Michaud et al,[74] melatonin would have an inhibiting effect on dopamine production. They suggest that this substance could be related to the worsening of the restless legs syndrome. According to Cohen et al,[75] melatonin is involved in the genesis of histamine cephalgia as well as in hypnic headache. The authors suggest that these types of headaches could constitute a circadian rhythm disorder related to REM sleep. According to some authors, acupuncture, yoga and meditation increase melatonin secretion, thereby reducing insomnia and anxiety.[76-77]

Agents with the potential for inducing sleep under study for clinical use

Indiplon, a novel pyrazolopyrimidine agent, has the *in vivo* profile of an efficacious sedative-hypnotic, as well as presenting high pharmacological specificity and *in vitro* allosteric potentiation of GABA(A) receptors, with selectivity for alpha 1 subunit[78] similar to that of zolpidem.

Studies suggest that ramelteon is a potent selective MT-1/ MT-2 receptor agonist and that it was more effective in promoting and maintaining sleep than melatonin. However, its potential for use in the treatment of sleep disorders has yet to be investigated.[79] Eszopiclone is an isomer and a cyclopyrrolone (like zopiclone) that presents, in studies, potential for use in the symptomatic treatment of insomnia at a dose of 3 mg.[80]

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