Psychopharmacology of Hypnotics

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ABSTRACT:
PSYCHOPHARMACOLOGY OF HYPNOTICS

The following article identifies the appropriate strategies for the prescription of hypnotic drugs. Initially, a clinical evaluation of insomnia is provided which includes definitions of good and poor sleepers and the physiology of sleep. The paper then proceeds to discuss drugs commonly used in the treatment of sleep disorders, benzodiazepines and newer non-benzodiazepines compounds. The pharmacokinetic properties of these compounds are briefly described, as are effects of age. The review concludes with suggestions for the proper identification of patients requiring chemical treatment for sleep disorders and highlights methodologies for choosing the most beneficial pharmacological tools.

Key words: hypnotics, insomnia, benzodiazepines, hypnotics non-benzodiazepines

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ÖZET:
HİPNOTİKLERİN PSİKOFARMAKOLOJİSİ

Aşağıdaki makale hipnotik ilaçların reçetelendirilmesinde uygun stratejileri tanımlar. Başlangıçta uyku fizyolojisi ve iyi veya kötü uykucuların tanımlarını içeren insomniyanın klinik bir değerlendirilmesi yapılmıştır. Yazı, daha sonra uyku bozukluklarında yaygın olarak kullanılan ilaçları, benzodiyazepinleri ve benzodiyazepin olmayan daha yeni bileşikleri tartışarak sürmektedir. Yaş etkisi gibi farmakokinetik özellikler kısaca tanımlanmıştır. Bu gözden geçirme yazısı, uyku bozuklukları yönünden kimyasal tedavi gerektiren hastalara uygun tanı için öneriler ve en faydalı farmakolojik ölçülerin seçimine ışık tutucu metodolojilerle sonlanmıştır.

Anahtar sözcükler: hipnotikler, insomniya, benzodiyazepinler, benzodiyazepin olmayan hipnotikler

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INTRODUCTION

Insomnia is defined as a difficulty of initiating and maintaining sleep. These sleep disturbances are linked to a variety of medical or psychological problems. Sleep disruption is more prevalent in women, the elderly, individuals of a lower socio-economic status and patients with chronic medical or physical conditions (1,2). Insomnia may result in daytime functional impairment and symptoms such as fatigue, irritability, anxiety, decreased ability to concentrate and inability to perform complex tasks. Lack of restorative sleep may also affect major physiological systems such as cardiovascular, pulmonary, endocrine and thermoregulatory function (3). Insomnia is more often a symptom rather than an autonomous pathology and is often associated with depression in the majority of cases. The prescribing of a hypnotic drug requires a good understanding of the circumstances necessitating its utilisation. The major goal for the clinician is to make a correct evaluation of the pathology, which isn't always easy (4) and individual drug and patient considerations are important in matching the most appropriate agent to the individual patient (5).

1 - CLINICAL EVALUATION OF INSOMNIA

1.1 - THE GOOD SLEEPER

A good sleeper is one who rises wide-awake and alert, regardless of whether he slept for a short or long period of time. A good sleep occurs when the different stages of sleep, along with the five or six cycles during the night, occur in proper order.

1.1.1 - Sleep Duration

It is common for an adult to sleep for approximately 8 hours; this "classical" length need not be strictly adhered to as many inter-individual variations exist, which tend to vary with age.

Infants and children have longer sleep duration than adults and elderly people are reported to sleep less. However, in the elderly, the total duration of sleep, over a 24-hour period, tends to approximate

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the 8 hours per night sleep of an adult.

1.1.2 - The two phases of sleep

The EEG (electroencephalogram) has been used to characterise two main types of sleep pattern:

- Non Rapid-Eye-Movement sleep (NREM) is divided into 4 stages, from 1 to 4, with 4 being the deepest sleep. Stage 1 forms the transition between wakefulness and sleep. Muscle tone is relatively weak and while a certain amount of mental activity persists, concentration and imagination fluctuate. Stage 2 represents over 50% of total sleeping time. Muscle tone is weak and there is no eye movement. Stage 3 and 4 occupy approximately 20% of the sleep time. This stage of sleep is the recuperative phase, which is associated with growth hormone secretion and tissue repair. The EEG during NREM sleep becomes progressively slower in frequency and greater in amplitude. Blood pressure, heart rate, cardiac output, respiration rate, whole body and brain temperature, total body oxygen consumption and single neuronal brain activity decrease at sleep onset and remain reduced without much variation during NREM sleep.

- Rapid-eye-movement sleep (REM or paradoxical sleep) roughly corresponds to the onirical period, the dreams being long, emotional and animated. In this phase, cerebral activity is similar to stage 1 of NREM sleep. Within REM sleep there are two major physiologic phenomena: tonic events and phasic events. Tonic events include a continuous EEG pattern of low amplitude fast-frequency waves; lowered electro-myographic activity in certain muscles and pelvic congestion in females and penile tumescence in the male. Tonic increases include those in respiration rate, body and brain temperature and oxygen consumption. Furthermore, cerebral blood flow increases across all regions of the brain. Phasic events are of brief duration are discontinuous and occur sporadically, they include conjugated REMS, cardiorespiratory changes and sporadic muscle twitches of the face and extremities.

1.1.3 - Normal Sleep Architecture

Sleep is characterised by a remarkably stable architecture and is composed of 5-6 cycles of non-REM sleep alternating with REM sleep at approx. 90 min. intervals. Each cycle comprises a NREM sleep and a REM sleep period.

During the night, NREM sleep periods decrease in terms of duration and depth, while the REM sleep period increases in duration. The sleep pattern becomes more fragile with advancing age, so that in the elderly the number of nocturnal awakenings increases and REM sleep becomes more evenly distributed throughout the night. The sleep architecture may be modified by disease and certain drugs.

1.1.4 - Physiological variations

Whether the subject is a "long sleeper" or a "short sleeper", the quantity of deep sleep remains constant; short sleepers have generally reduced amount of REM-sleep, which often results in early awakenings.

Bedtime exerts an influence upon nocturnal sleep duration. An earlier bedtime often corresponds with a longer duration of sleep. "Normal" bedtime, typically at around 11 p.m., generally involves 8 hours of sleep per night, while an early morning bedtime, even under excellent conditions (absence of noise and lights), entails a shorter quantity of sleep. This latter condition is observed with patients having a nocturnal professional occupation.

In contrast with the effects on REM sleep, NREM sleep quantity is not affected by bedtime.

1.2 - THE POOR SLEEPER

A poor sleeper is one who awakens, reporting that the quality of sleep was poor and of short duration and generally has a poor disposition in the morning. Identification of true insomniacs can be aided by questioning the family whenever possible. Indeed, most patients tend to overestimate their sleep disorders, often involuntarily, and thus are wrongfully categorised as insomniacs. Conversely, one may be an insomniac even with an appropriate amount of sleep. In fact, the actual cause for sleep disorders is not a lack of sleep, but the disorganisation of sleep architecture, as proved by EEG recordings.

Four major categories of sleep disorders may be identified:

- Excessive sleep duration
- Increased number and duration of nocturnal awakenings

- Early morning awakening
- Subjective feeling of poor sleep

The EEG may reveal:

- A shortened REM-sleep
- A NREM sleep with an increase of stages 1, 2, 3 and a scattered stage 4 throughout the night.

1.2.1 - Difficulties in initiating sleep

Difficulties in initiating sleep occur in anxious individuals who require more than 1 hour to fall asleep, even in optimal conditions. Most often, these patients are not sufficiently relaxed prior to or at bedtime.

The prescription of an anxiolytic may be requested during the day or, possibly, at night. In this case, the concomitant prescription of an anxiolytic and a hypnotic must be avoided as they may complete at a common receptor site, and result in decreased efficacy (6,7).

Difficulties in falling asleep may result from an excessive intake of stimulating substances: such as coffee, tea or soft drinks containing caffeine, although each individual may react in a unique manner to these substances.

Caffeine is a weak antagonist of benzodiazepines with a site of action at the BZD-ionophore-chloride channel complex (8). The net effect of caffeine is to diminish the efficacy of benzodiazepines. Other causes of difficulties in initiating sleep include, chronic work overload; intense physical efforts, especially in the evening; jet lag linked to transmeridian travels and shift work.

1.2.2 - Repeated and prolonged nocturnal awakenings

It is common to awaken during the night for very short moments, a few seconds or a few minutes. Some life events may cause longer and more frequent nocturnal awakenings, which are distressing to the patient. Generally the awakenings are accounted for by anxiety phenomena, linked to private and professional life, and may lead to somatisations such as feelings of imminent death, asphyxia, or tachycardia.

1.2.3 - Premature awakening

This category includes early morning awakenings where the patient awakes at 3, 4 or 5 a.m. and is unable to return to sleep. In this case affective disorders must be considered, particularly if symptoms such as anxiety, moral pain or feelings of guilt appear. Early morning awakenings may also signal the onset of depression.

Pain disorders such as rheumatism, arthritic diseases, gastrointestinal tract pains of terminal care patients, also lead to premature awakenings due to a decrease in effective analgesia at night. Psychotic patients may also suffer from early awakenings, even when undergoing neuroleptic therapy.

1.2.4 - Subjective feeling of poor sleep

Feelings of poor sleep are problematic as they are not based on clear clinical facts and thus are difficult to evaluate. Typically, the patient awakes with the feeling of having had a superficial sleep, not necessarily accompanied with nocturnal awakenings. The individual may also awaken with the unpleasant sensation of a poor recovery from the previous day's fatigue. Nightmares and anxiety may also be present.

The clinician must endeavour to collect the most objective facts before prescribing an hypnotic drug. Administration of an hypnotic drug should be of a short duration, just a few days, until the quantity and quality of sleep is normalised (9).

2 - HYPNOTICS

A hypnotic drug is one that produces drowsiness and facilitates the onset and maintenance of sleep from which the individual may be easily aroused. For the purposes of considering the prescribing of hypnotics, insomnia may be classified into 3 major types based on the duration of symptoms (10,2):

- Transient insomnia is generally present for 2 to 3 days and is associated with an acute stress or disruption of circadian patterns (e.g. jet lag, shift work)
- Short-term insomnia persists for ≤ 3 weeks and is usually associated with situational stress caused, for example, by bereavement or a conflict which may be related at work or in the family.
- Long-term (chronic) insomnia has usually been present for > 3 weeks and in up to 50% of patients in this category, is related to an underlying psychiatric illness. Chronic drug or alcohol abuse, primary sleep disorders (e.g. sleep

apnoea), psychophysiological insomnia may be the cause of sleep disruption in the remainder of patients in this category.

All hypnotics in current clinical use alter the sleep architecture by reducing the quantity and quality of REM sleep phase in particular. Drugs used as hypnotics are all sedatives, belonging to various chemical and pharmacological classes. Two main categories are used:

- Benzodiazepines
- Non-benzodiazepine hypnotics.

2.1 - BENZODIAZEPINES

Due to their considerable safety, the benzodiazepines have now largely replaced the barbiturates and alcohols as the drugs of choice in the treatment of insomnia. Benzodiazepines marketed as hypnotics have a common pharmacokinetic characteristic: they are readily absorbed. However relatively little attention has focused on their elimination half-life.

Tablo 1. Pharmacokinetics of several benzodiazepines marketed as hypnotic or for pre-anaesthetic medications (11)

Generic name	Absorption time p.o.	$t_{1/2\alpha}$
Triazolam	0,5 to 1h	3 to 4 h
Loprazolam	2 to 4 h	8 to 10 h
Midazolam	0,3 to 0,5 h	1 to 4 h
Nitrazepam	1,5 to 2 h	18 to 25 h
Lormetazepam	1 to 1,5 h	10 to 12 h
Temazepam	0,3 to 0,7 h	5 to 15 h
Estazolam	1 to 1,5 h	18 to 24 h
Flunitrazepam	1 to 1,5 h	20 to 30 h
Diazepam	0,5 to 1,5 h	20 to 100 h

Benzodiazepines are usually divided into short-acting and long-acting drugs, depending on their elimination half-life (inferior or superior to 10 hours for a hypnotic). However, this classification is not completely satisfactory as the elimination half-life is not necessarily the major determinant for the cessation of the hypnotic activity. The disappearance of most benzodiazepines from plasma occurs in 2 phases.

The alpha-rapid phase is a redistribution of the drug from well-perfused tissues, (mostly from the brain), to fats and other low-perfused tissues (peripheral compartment).

The beta-low phase represents the elimination from the body.

Tablo 2. Residual fraction (r 12.1) and half-life ($t_{1/2\alpha}$) of benzodiazepines (12)

	r12.1*	$t_{1/2\alpha}$
Midazolam	< 0.01	2
Triazolam	0.16	2
Flunitrazepam	0.25	22
Oxazepam	0.40	8
Desmethyldiazepam	0.71	84

*Residual Fraction= The parcentage after 12 Hrs.

The relative contributions of the alpha and beta phases to plasma elimination are not clear. What is clear is that repeated administration of benzodiazepines can lead to an accumulation in depot tissues and plasma.

For example, a patient may awaken without a problem after bedtime administration of flunitrazepam or nitrazepam. But a real risk of accumulation and thus carry-over effects exists with repeated administration of this category (longer half-lives) of drugs. In contrast, patients treated with triazolam (3 to 4 hours of half-life) may wake up in the middle of the night.

Benzodiazepines with anxiolytic properties may also be used for anxious patients by increasing the evening dose, keeping in mind that their rate of absorption is often slower (11).

2.1.1 - Advantages of benzodiazepines

Benzodiazepines possess a large therapeutic index and thus the risk of suicide is very low.

REM-sleep is for the most part unaffected quantitatively, but is seemingly qualitatively affected in that it is distributed in a different manner throughout the night, with the greatest amount occurring at the end of the night.

Additionally, benzodiazepine drug interactions are rare (13). However, the actions of these drugs seem to be potentiated and/or prolonged with local or general anaesthetic agents, opioid analgesics, antidepressants, neuroleptics, lithium, isoniazide and alcohol.

2.1.2 - Disadvantages of benzodiazepines

The major disadvantage of benzodiazepine use is linked to habituation to the drug over time. It is not dependence perse, as pharmacological tolerance is

not observed.

Rebound insomnia and anxiety may be observed upon termination of treatment, the latter of which is often present the day following interruption of treatment (14).

Slow reduction in the dose of the hypnotic over several days may reduce the risk of such rebound. With benzodiazepines having a half-life in excess of 24 hours, it is beneficial to avoid everyday intake, which may lead to cumulative phenomena of sedation. Amnesic problems, specifically anterograde amnesia, have been described following benzodiazepine treatment. This memory impairment occurs in patients of all ages but particularly in the elderly, when high doses are used.

Many benzodiazepines such as flunitrazepam (15); nitrazepam (16); oxazepam (17); desmethyldiazepam (18); and triazolam (19,20) exhibit amnesic properties. Diazepam seems to be responsible for a rapid onset of amnesia that is of a shorter duration than that seen with lorazepam (21,22).

Patients should be advised that quickly absorbed compounds such as diazepam, flunitrazepam or triazolam should only be taken at bedtime. Amnesia may occur upon either morning or nocturnal awakening. Memory loss is not linked to the pharmacokinetics of the drug.

There is evidence that with long-term hypnotic use sleep latency shows more tolerance than sleep time. It is generally accepted that each hypnotic has a minimal effective dose and that increasing this does a little to improve the duration of sleep is more likely to increase the side effects (23).

2.2 NON-BENZODIAZEPINE HYPNOTIC DRUGS

Over the last few years, a search has been undertaken for compounds chemically unrelated to benzodiazepines that may produce fewer unwanted effects (tolerance, muscle relaxation, rebound insomnia and amnesia), but retain hypnotic properties. Indeed the use of benzodiazepines for insomnia has been superseded in part by the newer short-acting nonbenzodiazepine hypnotics (24). The use of antidepressants in the management of insomnia has also increased in recent years, but while this group of drugs may improve sleep in patients with depression, evidence from controlled clinical trials in patients without mood disorders is limited (1) and they are also associated with anticholinergic adverse events (2). The newer non-benzodiazepine hypnotics include zopiclone, zolpidem and most recently, zaleplon.

2.2.1 - Zopiclone, a cyclopyrrolone, is a non-benzodiazepine derivative that binds at the BZD-ionophore: chloride channel complex (25). Its absorption time is approximately 2 hours and the elimination half-life is 5 hours. Metabolites of zopiclone have similar elimination half-lives to that of the parent compound (26). Renal excretion occurs after enterohepatic cycling.

Trials in sleep laboratories have shown that zopiclone leads to an increase in total sleep duration, a decrease of sleep latency, a decrease of stage 1 sleep and increases of stages 2, 3 and 4 sleep. Few side effects with this drug have been reported, however, some patients have complained of a modification of taste with buccal bitterness. As with other hypnotics, side effects such as headache, asthenia and drowsiness have also been reported with zopiclone.

2.2.2 - Zolpidem is an imidazopyridine compound that binds to benzodiazepine receptors and is indicated for the short-term treatment of insomnia. Some studies have shown that this derivative exhibits a higher affinity for the BZ_1 receptor subtype than for the BZ_2 or peripheral BZ_3 subtypes. When administered orally, zolpidem has a bioavailability of 70%, and reaches Tmax between 0.5 and 3.0 hours. Plasma protein binding is approximately 92%, and the mean elimination half live is between 2 and 3 hours. Zolpidem is eliminated via renal excretion. Metabolites of zolpidem are all inactive, with 56% being excreted in urine and 37% in faeces. There is no induction of enzymatic processes produced with this drug.

Trials in sleep laboratories have shown that zolpidem treatment leads to an increase in total sleep duration, a decrease in sleep latency, an increase in stage 2 and in deep stages 3 and 4 sleep (27).

Zolpidem generally has similar efficacy to other hypnotics (including benzodiazepines). It appears to have minimal next-day effects on cognition and psychomotor performance when administered at bedtime. In addition, there is little evidence of tolerance to the hypnotic effects of zolpidem (with some reported cases described in patients taking zolpidem at high doses for up to several years), or rebound insomnia or withdrawal symptoms after continua-

tion of the drug when it is given as recommended or over longer periods (28). The side effects of this drug are linked to dosage and include drowsiness, day somnolence, asthenia, general nausea and dizziness.

2.2.3 - Zaleplon is a pyrazolopyrimidine that is indicated for the short term management of insomnia for use in patients who have difficulties in initiating sleep. It is a selective agonist of the benzodiazepine w1 (type 1) receptor subtype. The maximum plasma concentration (Cmax) is about 1 hour after administration and the bioavailability of zaleplon is 30.6% (29). The rate, but not the extent, of absorption is increased if zaleplon is administered with or immediately after a high fat-meal. Zaleplon undergoes first pass metabolism. It is metabolised to inactive metabolites, primarily by oxidative metabolism, and then predominantly renally eliminated. The elimination half-life is about 1 hour. Zaleplon is absorbed and eliminated more rapidly than zolpidem and the volume of distribution of zaleplon is higher. Absorption and elimination parameters of zaleplon are not influenced by age or gender, although a dosage reduction is recommended in elderly patients (30). Drugs that strongly inhibit or induce CYP3A4 have the potential to alter plasma concentrations of zaleplon.

The relative hypnotic efficacy of zaleplon in comparison with other non-benzodiazepine hypnotics is not yet clearly established. The most commonly observed adverse effect is a headache. Zaleplon was not found to impair psychomotor function or memory even immediately after dose administration (10). Rebound insomnia was not observed after sudden discontinuation of up to 12 months treatment. The potential for withdrawal syndrome with zaleplon appears to be low (10).

The pharmacokinetic profile of zaleplon (short t1/2b and lack of active metabolites) makes this drug particularly well suited for patients with sleep onset insomnia. Its short duration of action and its rapid absorption enables zaleplon to be used on an "as needed basis" (31).

Appropriate use of hypnotics

In patients, it is necessary to identify the nature and type of sleep disorder to avoid any unnecessary and uncontrolled prescriptions. All hypnotics may cause drug dependency when they are used over weeks or months. Some compounds are more suitable than others for inducing sleep due to their quick absorption properties, however residual effects the next morning may be a problem for some patients. The physician should therefore evaluate the risks and avoid prescribing long-action benzodiazepines (> 15 hours).

Elderly patients are particularly sensitive to benzodiazepines (21). When prescribing benzodiazepines to an elderly patient, the "trap" of sedation must be avoided; that is, the patient's life style may be altered due to increased fatigue and sedation. The risk associated with elderly patients' use of hypnotic drugs are attributable to concomitant comorbid conditions, use of multiple medications, altered pharmacokinetics and increased central nervous system sensitivity to these drugs (32).

Among the elderly, recent studies have shown that benzodiazepines metabolised by oxidation in the liver, have reduced clearance. This finding is more often observed in elderly men than women. Diazepam is one benzodiazepine that is metabolised through enzymatic oxidation, while oxazepam and lorazepam do not undergo oxidation and are simply conjugated prior to elimination. A patient's oxidation capacity may be assessed by a test employing antipyrine, however from a prophylactic point of view, it is simpler to just decrease the dose administered.

Both hepatic and renal clearance are important considerations. Measuring creatinine clearance must assess the slowing of the renal elimination of benzodiazepines. Additionally, the volume of distribution is increased in the elderly, more significantly among elderly men than women. This may be accounted for by a decrease in oxidative power, which results in the accumulation of liposoluble derivatives. It is important to note that in the elderly, there is an increase in lipid mass relative to the muscular (aqueous) mass. The increased volume of distribution and decreased total clearance lead to an increased half-life.

Another consideration is that elderly patients are often polymedicated (33). Although drug interactions with benzodiazepines are rare, the possibility of two benzodiazepines competing at the same receptor site exists (6,7). The combination of benzodiazepines with alcohol is to be avoided due to a potentiation of effect.

The longer-acting hypnotics have been shown to

result in a higher risk of falls and hip fractures in the elderly. This relationship is not apparent with short-acting hypnotics.

Taken together, these data suggest that it is pragmatic to decrease the dose of benzodiazepines for the elderly.

Conclusion

Prescribing a hypnotic must not become systematic. A dependence syndrome rapidly develops making the medication of primary importance to the patient. A kind of "dissociation" is then observed. Continuous treatment must be avoided and the patient should be advised to take the drug only two or three times a week, when a bad night is anticipated. Sleep patterns may be adversely affected by inactivity and boredom. Elderly patients may develop a feeling of uselessness, leading them to neglecting their daily routine and feeling depressed and withdrawn.

Finally, it is necessary to identify patients whose sleep will benefit simply from a change in their environment or lifestyle. If the problem is of a more severe nature, then the type of disorder should be assessed according to the following criteria: difficulties in falling asleep, nocturnal awakenings or early morning awakenings. The particular hypnotic employed to alleviate the symptoms should then be chosen based on the relevant pharmacokinetic profile, the desired rate of onset and duration of effect, the medical status of the patient, presence of other medications, types of side effects that might be most easily tolerated and likelihood of overdose.

References:

1. Wagner J, Wagner ML, Hening WA. Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. Ann Pharmacother 1998; 32:680-91.
2. Kupfer DJ, Reynolds III CF. Management of insomnia. N Engl J Med 1997; 336:341-6.
3. Roth T. Overview of insomnia for the primary care physician. In: Roberts WO, editor. Insomnia: treatment options for the 21st century. Minneapolis (MN):McGraw-Hill Healthcare Information Group. 2000:5-13.
4. Dement W. Sleep disorders and their substrates. Nouv Presse Med 1982; 11:2967-2980.
5. Mitler MM. Nonseletive and selective benzodiazepine receptor agonists—where are we today? Sleep 2000; 23 (Suppl 1):S39-47.
6. Richard P, Mark D, Deligne P. Competition pharmacologie entre les benzodiazépines, mise en evidence chez l'homme entre le diazepam et le flunitrazepam. Ann Anesthesiol Fr. 1981; 22:191-203.
7. Evans JL, Lewis SA. Drug withdrawal state. An EEG sleep study. Arch Gen Psychiat 1968; 19:631-634.
8. Boulenger JP, Patel J., Marangos P.J. Effects of caffeine and theophylline on adenosine and benzodiazepine receptors in human brain. Neurosci Lett 1982; 30:161-166.
9. Doghramji K. The need for flexibility in dosing of hypnotic agents. Sleep 2000 23 (Suppl 1):S16-20;discussioon S21-2.
10. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. Drugs 2000; 60:413-45
11. Bourin M, Bradwejn J. The importance of pharmacokinetic in prescribing benzodiazepines. In Pharmacocinétique : de la recherche à la clinique. Ed. J. Brès, G. Panis, John Libbey Eurotext 1992:99-112.
12. Amrein R., Eckert M., Hafeli H., Leisham. Pharmacokinetic and clinical consideration in the choice of a hypnotic. Br J Clin Pharmacol 1983; 16:55-105.
13. Bourin M, Couëtoux du Tertre A, Payeur R. Evaluation of safety and side effects in the process of anti-anxiety drug development. Eur Psychiatry 1993; 8:285-291.
14. Morgan K, Tomeny M. Benzodiazepine withdrawal and rebound insomnia. Acta Psychiatr Scand 1989; 80:297-298.
15. Bixler EO, Scharf MB, Soldatos CR. Effects of hypnotic drugs on memory. Life Sci 1979; 25:1379-1388.
16. Liljequist R, Mattila MJ. Acute effects of temazepam and nitrazepam on psychomotor skills and memory. Acta Pharmacol Toxicol 1979; 44:364-369.
17. Liljequist R, Palva E, Linnoila M. Effects on learning and memory of 2-week treatments with chlordiazepoxide lactam-N-demethyldiazepam, oxazepam and methylloxazepam alone or in combination with alcohol. Int Pharmacopsychiat 1979; 14:190.
18. Poitras R. A propos d'épisodes d'amnésies antérogrades associées à l'utilisation du triazolam. Union Med Can 1980; 109:427-429.

19. Roth T, Hartse KM, Saab PG, Piccione PM, Kramer M. The effects of flurazepam, lorazepam and triazolam on sleep memory. Psychopharmacology 1980; 70:231-237.

20. Dundee IW, Mc Gowan Waw, Lilburn AC, Hegarty JE. Comparison of the actions of diazepam and lorazepam. Br J Anaesth 1979; 51:439-446.

21. Gallon S, Gale GD, Lancee WJ. Comparison of lorazepam and diazepam as premedicaments. Br J Anaesth 1977; 49:1265-1268.

22. Goa KL, Heel RC. Zopiclone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. Drugs 1986; 32:48-65.

23. Leonard BE. Drug treatment of insomnia. In: Fundamentals of psychopharmacology.2nd edition. John Wiley & Sons Ltd. 1997:173-184.

24. Lader MH. Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? Eur Neuropsychopharmacol 1999; 9(Suppl 6):S399-405.

25. Gaillot J, Heusse D, Houghton G, Aurele JM, Dreyfus J. Pharmacokinetics and metabolism of zopiclone. Pharmacology 1983; 27 (suppl 2):76-91.

26. Morgan K. Hypnotics in the elderly. What cause for concern ? Drugs 1990; 40:688-696.

27. Nicholson AN, Pascoe PA. Hypnotic activity of an imidazopyridine (zolpidem). Br J Clin Pharmac 1986; 21:205-211.

28. Holm KJ, Goa KL. Zolipdem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs 2000; 59:865-89.

29. Rosen AS, Fournié P, Darwish M, Danjou P, Troy SM. Zaleplon pharmacokinetics and absolute bioavailability. Biopharm Drug Dispos 1999; 20:171-5.

30. Darwish M. The effects of age and gender on the pharmacokinetics of zaleplon.(abstract) Eur Neuropsychopharmacol 1999; 9(Suppl 5):S360.

31. Wagner ML. Zaleplon CNS Drugs 1999; 2é(Suppl 2):S354-8.

32. Ancoli-Israel S. Insomnia in the elderly: a review for the primary care practitioner. Sleep 2000 2" (Suppl 1) S23-30; discussion S36-8.

33. Weedle PB, Poston JW, Parish PA. Use of hypnotic medicines by elderly people in residential homes. J R Coll Gen Pract 1988; 38:156-158.