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Consensus on Drug Treatment, Definition and Diagnosis for Insomnia

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Abstract

Thirty-four experts and a literature supervisor got together in order to reach a 'consensus' regarding the definition, diagnosis and pharmacological treatment of insomnia. Insomnia is a subjective perception of dissatisfaction with the amount and/or quality of sleep. It includes difficulty in initiating or maintaining sleep or early awakening with inability to fall asleep again. It is associated with complaints of non-restorative sleep and dysfunction of diurnal alertness, energy, cognitive function, behaviour or emotional state, with a decrease in quality of life. The diagnosis is based on clinical and sleep history, physical examination and additional tests, although polysomnography is not routinely indicated. Therapy should include treatment of the underlying causes, cognitive and behavioural measures and drug treatment. Hypnotic therapy can be prescribed from the onset of insomnia and non-benzodiazepine selective agonists of the GABA-A receptor complex are the drugs of first choice. It is recommended that hypnotic treatment be maintained in cases where withdrawal impairs the patient's quality of life and when all other therapeutic measures have failed. Experience suggests that intermittent treatment is better than continuous therapy. The available data do not confirm safety of hypnotics in pregnancy, lactation and childhood insomnia. Benzodiazepines are not indicated in decompensated chronic pulmonary disease but no significant adverse effects on respiratory function have been reported with zolpidem and zopiclone in stable mild to moderate chronic obstructive pulmonary disease and in treated obstructive sleep apnoea syndrome. Data for zaleplon are inconclusive. If the patient recovers subjective control over the sleep process, gradual discontinuation of hypnotic treatment can be considered.

Insomnia is a highly prevalent condition. Chronic insomnia affects 10% of the general population,[1,2] and the figure increases to 34% when chronic and transient insomnia are combined.[3,4] The social and healthcare impact of these conditions is highly significant,[5-10] and has been well studied.[11-15] The importance of adequate treatment is therefore obvious. In this context, management of insomnia should only be addressed after an adequate diagnosis has been established, and should be aimed at aetiological treatment with pharmacological and, finally, non-pharmacological measures. This article presents a consensus on pharmacological measures.

Current adequate sleep medicine practice poses the need for making decisions when faced with problems that cannot be resolved quantitatively. This leads us to seek qualitative solutions, such as consensus recommendations or methods relating to specific problems. Consensus methods aim to establish agreements among experts over problems that can imply uncertainties in case of persisting discrepancies. The users of consensus recommendations subsequently decide if such recommendations are useful or sufficient for taking decisions.[16]

Because of their extensive use, consensus recommendations may also be subject to controversy about their validity, objectivity and value. This article therefore attempts to address the different limitations of a consensus so that they can be avoided, reduced or at least taken into account. We think that a precise and concise methodology will contribute to a higher credibility of the result and thus enhance its impact.

1. Methods

Achievement of consensus is a means to facilitate decision-making and to establish recommendations to guide medical practice. The responsibility of scientific promoters of a consensus is obvious, since it determines the credibility of the results.

As a working method to reach this consensus, a general coordinator was appointed (figure 1) and six

group coordinators, a reference literature supervisor and 27 scientists of acknowledged expertise in insomnia were chosen.

The steering group coordinator and the members of this group were responsible for scientific organisation. The work of the scientific supervisors comprised selection of the participating experts, preparation of the basic initial lines of work (three fields), processing of information, synthesis of the results to perform feedback, and preparation of the final results. Expert selection was based on general acknowledgement of their expertise in the field, representativeness within the profession, and the capacity to implement the final decisions of the consensus. Flexibility to openly explore different points of view was one of the qualities sought.

The scientific information taken from the selected articles was the basis for supporting expert opinion. If the subjectiveness of these experts had not been based on methodological rigour in the review and synthesis of the information available about insomnia, the resulting uncertainty could have deprived the consensus of value or, even worse, could have led to a consensus based on prejudice and lacking adequate data evaluation.

The mechanism used to reach consensus comprised a combination of the nominal group technique[16,17] and the Delphi method.[18,19] These are two formalised procedures with individual reflection techniques, promotion of creativity, structured discussions and the use of individual judgement to reach an overall group judgement. The participants were surveyed by the steering group, which analysed and synthesised the results and also provided feedback to the participating experts to help them define their positions and the overall group positions.

Consensus was obtained by the mathematical procedure of simple summing of individual judgements and removal of extreme positions, thus reaching a consensus common judgement. A 'consensus' was agreed when the expert group achieved at least 60% of favourable votes on each of the proposals after their discussion. The proposal was refused when it obtained less than 60% of votes.

The first part of the consensus was performed with the physical presence of the experts (nominal group technique), and the subsequent feedback was conducted using electronic mail (Delphi method).

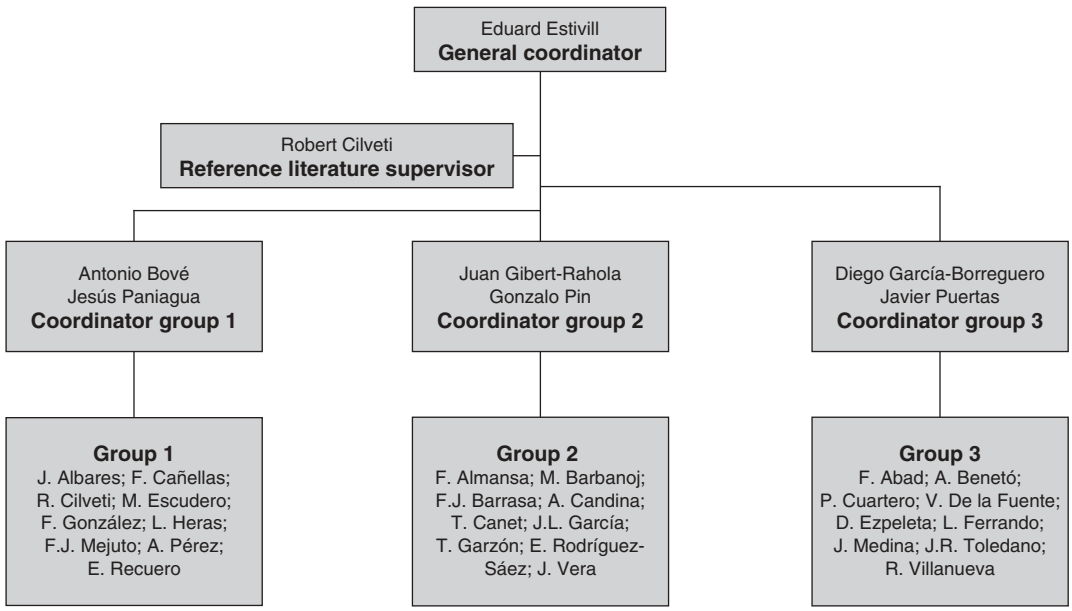

Fig. 1. Flow chart of consensus participants.

For adequate performance of the nominal group technique, three prior meetings were held between the general coordinator and the group coordinators. In a first meeting, the general coordinator provided the group coordinators with all the basic information published in the literature in the previous 5 years.

The literature was selected from a MEDLINE search and through the PubMed service of the National Library of Medicine, using the key phrases 'Sleep initiation and maintenance disorders', 'therapy (drug therapy)' and 'adverse effects'. The type of publication was limited to 'review', 'meta-analysis', 'consensus (practice parameters)', 'guideline', 'controlled clinical trial' and 'randomised clinical trial'. This literature was subsequently completed by contributions considered relevant by the group coordinators and all other participants.

Three work groups were established with two coordinators in each group. The lines of work established for each group were: (i) insomnia; (ii) objectives of drug treatment for insomnia; and (iii) practical aspects of drug treatment. The two coordinators from each group prepared their own basic guidelines, which were subsequently presented to all the experts.

The nominal group technique was then carried out, randomly dividing the 28 participating experts into three groups. The coordinators presented the basic guidelines to their corresponding groups for subsequent discussion. After this, a vote was held to reach consensus or refuse the proposal. The general coordinator then presented the approved recommendations to all the experts.

The Delphi method was then applied. The coordinators analysed and synthesised the recommendations obtained, and feedback was applied with the rest of the group. Finally, once the responses were known, the final recommendations were prepared.

2. Insomnia

2.1 Definition of Insomnia

The subjective parameters of the patient to be considered for defining insomnia are:

- Sleep latency (time to onset).
- Sleep maintenance (nocturnal awakenings, early awakening).
- Quality of sleep.
- Frequency and duration of sleep disturbance.
- Diurnal residual effects.
- Impact on family and on social and occupational life.
- Quality of life.[20,21]

The term 'insomnia' originates from the Latin 'in' (no) and 'somnus' (sleep), which in strict terms implies inability to sleep or a total lack of sleep. In clinical terms, insomnia represents a subjective perception of dissatisfaction with the amount and/or quality of sleep. This includes difficulty in initiating or maintaining sleep, or early awakening with the inability to fall asleep again. Insomnia is associated with complaints of non-restorative sleep and dysfunction of diurnal alertness, energy, cognitive function, behaviour or emotional state, with a secondary decrease in quality of life.

2.2 Classification of Insomnia

There are multiple classifications and definitions of insomnia,[21,22] the most representative of which include (Appendix 1):

- Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).
- International Classification of Diseases, 10th edition (ICD-10).
- International Classification of Sleep Disorders (ICSD).

Insomnia can be classified based on different concepts: co-morbidity, duration, severity and form of presentation.

2.2.1 According to Co-Morbidity

Acceptance of the types of insomnia included in the ICSD is proposed (Appendix 1).[23]

2.2.2 According to Duration

- Transient or acute: less than 4 weeks.
- Short-term or subacute: longer than 4 weeks but less than 3–6 months.
- Long-term or chronic: longer than 3–6 months.

2.2.3 According to Severity

- Mild or slight: occurring almost every night. Associated with a minimum impairment of quality of life.
- Moderate: occurring every night. Associated with moderate impairment of quality of life, with associated symptoms (irritability, anxiety, fatigue, etc.).
- Severe: occurring every night. Associated with moderate impairment of quality of life, with more severe associated symptoms (irritability, anxiety, fatigue, etc.).[24]

2.2.4 According to Form of Presentation

- Sleep onset or insomnia.
- Sleep maintenance insomnia.
- End of sleep insomnia.[25]

2.3 Diagnosis of Insomnia

Insomnia is a medical disorder that can become significant in itself or as a secondary manifestation of some other disease.[22] It is also a common problem that is nevertheless under-diagnosed. Increased awareness, diagnosis and treatment is required;[22] only 5% of patients with insomnia specifically consult their physician, while 70% never inform their doctor of their disorder.[26] Moreover, it should be taken into account that insomnia is often the only symptom of a psychiatric or neurological disease that has not yet been diagnosed.[26,27]

For an accurate diagnosis of the types of insomnia according to co-morbidity, see Appendix 2.[23] In general terms, a number of basic and additional optional requirements may be defined for diagnosing insomnia.

2.3.1 Basic Requirements

- Clinical history.
- Sleep history (patient and couple).
- Physical examination and supplemental tests.

2.3.2 Optional Requirements

- Sleep diaries, sleep questionnaires, visual analogue scales (VAS), etc.
- Polysomnography.
- Multiple sleep latency test (MSLT).
- Actigraphy.
- Referral to a physician expert in sleep medicine.
- Others.

2.3.3 Clinical History

In diagnosing insomnia, the following should be considered:

- The clinical history should include one or two of the following: difficulty falling asleep; and difficulty maintaining sleep (or early awakening with inability to fall asleep again).
- The disorder must also cause a significant functional impairment during waking hours or marked distress.

It will always be appropriate to look for:

- Concomitant diseases (medical, psychiatric).
- Drug treatments.
- History of substance abuse (coffee, cola beverages, alcohol, tobacco, etc.).[23,28-30]

2.3.4 Sleep History

The sleep history of the patient should comprise:

- Sleep parameters (latency, awakenings during sleep, early awakening, perceived quality of sleep, etc.).
- Frequency and evolution time since the condition started.
- Triggering factors.
- Residual effects.
- Sleep hygiene (naps, sleep rituals and habits, time of going to bed and getting up on both work days and weekends, holidays, etc.).
- Response to previous treatments.[23,28-30]

2.3.5 Polysomnography

Polysomnography (PSG) is not indicated for the routine diagnosis of insomnia. It should be performed when, after the sleep history and physical examination have been performed, the following are suspected:

- Respiratory disorders related to sleep.
- Neuromuscular disorders.
- Narcolepsy.
- Some parasomnias.
- Sleep-related epilepsy.
- Suspected periodic limb movements with restless leg syndrome or other conditions.

- Other diseases that can be diagnosed by PSG.[4,29]

3. Objectives of Drug Treatment of Insomnia

This chapter develops the efficacy and safety criteria of the currently available benzodiazepine and non-benzodiazepine hypnotics, as well as the characteristics that an ideal hypnotic should have.

3.1 Insomnia Treatment Methods

Following an evaluation of the medical and/or psychiatric problems, the aim of the physician is to abolish or mitigate the underlying problems in order to improve the patient's quality of life, and prevent the progression of acute insomnia to chronic insomnia. Elimination of the complaints without improving current sleep may have a negative effect on patient health, safety and productivity.

The possibilities for dealing with insomnia revolve around two types of measures that are most often complementary: biological measures (psychopharmacological and chronobiological) and psychological measures (cognitive and behavioural), with use being made of different resources:

- **Aetiological treatment**: overall treatment implies as the first step the differential diagnosis of the causes of insomnia, since the knowledge of its aetiology will define the appropriate therapy.[31,32]
- **Psychological and educational interventions**: application of measures to ensure healthy habits in terms of sleep hygiene, techniques for the control of stimuli, relaxation techniques, sleep restriction and cognitive therapy.[33]
- **Pharmacology**: hypnotics and/or non-hypnotic drugs (antidepressants, antipsychotics, etc.).
- **Surgery**.
- **Chronotherapy and phototherapy**.

Drug treatment is particularly indicated for patients with clear evidence of sleep disorders. This occurs more often in patients with a recent clinical history of insomnia. Therefore, hypnotics are often used in patients with no other concomitant disease and who continue with their usual daily life activities.

According to a different theoretical model, insomnia is the result of an interaction between sleep-interfering processes (e.g. kinds of arousal and processes whereby various stimuli, behaviours and cognitive activities lead to arousal) and sleep-interpreting processes (sleep-related beliefs, attitudes, experiences, etc.). Hypnotics tend to suppress any kinds of hyperarousal. The treatment model focuses both on a reduction of sleep-interfering arousal processes (e.g. hypnotics) and on a modification of sleep-interpreting processes (by means of behavioural and psychoeducational interventions, i.e. sleep hygiene).

3.2 Evolution of Drug Treatment

Since its introduction in modern pharmacopoeias, hypnotic treatment has experienced significant improvements in efficacy and safety. Three generations of hypnotics can be defined:

Barbiturates[34,35] were introduced at the beginning of the 20th century. Their main characteristics are:

- They are effective hypnotics, but they do not induce physiological sleep.
- They induce tolerance and dependence.
- An overdose can have serious and even fatal consequences, particularly when combined with alcohol consumption.
- They are currently contraindicated as hypnotics.

Benzodiazepines[34,36-38] were introduced in the 1960s. Their main characteristics are:

- They are nonselective agonists of the GABA-A receptor complex, which also confers them with anxiolytic, muscle relaxant and anticonvulsant properties.
- They are effective for reducing sleep latency and for increasing total sleep time, but they alter sleep architecture.
- They can cause untoward effects and complications: diurnal sedation, cognitive and psychomotor impairment, rebound insomnia and withdrawal syndrome.
- They can induce tolerance and dependence at high doses and with long-term treatment.

Non-benzodiazepine hypnotics appeared in the 1980s, and include drugs such as imidazopyridines (zolpidem), cyclopyrrolones (zopiclone) and pyrazolopyrimidines (zaleplon).[21,34,36,39,40] Their main characteristics are:

- They are selective agonists of the GABA-A receptor complex, which confers them with hypnotic actions without anxiolytic, muscle relaxant or anticonvulsant actions.
- They respect architecture of physiological sleep in healthy persons and even improve it in patients with insomnia (data for zolpidem and zopiclone only).
- Zaleplon and zolpidem do not cause rebound insomnia or a withdrawal syndrome when administered at therapeutic doses.

3.3 Pharmacokinetic Parameters of Benzodiazepines and Hypnotics

Table I shows the pharmacokinetic characteristics of benzodiazepines, and non-benzodiazepine hypnotics.[41-45] In order to understand the action and efficacy of these agents, it is necessary to review a number of pharmacological concepts (see Appendix 4 for a detailed explanation):

- **Absorption**: determines the rapidity of action of the drug.
- **Distribution volume**: determines redistribution and the duration of effects, as well as the half-life.
- **Half-life**: responsible for the residual effects of the drug.

3.4 Efficacy Criteria for Hypnotic Treatment

A series of parameters should be considered for defining the efficacy of hypnotic treatment:[46]

- **Sleep latency**: this is the time taken by the patient to fall asleep, and depends on the absorption rate of the hypnotic, which largely determines its rapidity of action.
- **Sleep maintenance**: the capacity of the hypnotic to maintain sleep stability during sleep. It is largely dependent upon the distribution volume and hypnotic half-life, which determine the duration of action, and upon the persistence or otherwise of active metabolites.
- **Sleep architecture**: the hypnotic should tend to maintain the physiological macro- and microstructure of sleep, as well as its efficacy; this depends on the drug's specific mechanism of action.
- **Quality of life**: this includes influence upon physical, psychological and social aspects of the patient.

Table I. Pharmacokinetics of benzodiazepines and non-benzodiazepine hypnotics

Generic name	Onset of action	Half-life (h)	Active metabolites
Benzodiazepine anxiolytics			
Alprazolam	Fast to intermediate	12–15	No
Chlordiazepoxide	Intermediate	8–28	Yes
Clonazepam	Slow	18–50	No
Dipotassium clorazepate	Fast	48	Yes
Diazepam	Fast	20–50	Yes
Estazolam	Fast	10–24	No
Lorazepam	Intermediate	10–20	No
Oxazepam	Intermediate to slow	5–20	No
Prazepam	Slow	70	Yes
Temazepam	Intermediate to slow	9.5–12	No
Benzodiazepine hypnotics			
Triazolam	Fast	1.7–5	No
Midazolam	Fast	1–4	No
Brotizolam	Fast	5	Yes
Loprazolam	Fast	5–8	Yes
Lormetazepam	Fast	12–20	No
Flunitrazepam	Fast	19–22	Yes
Flurazepam	Fast	40–114	Yes
Nitrazepam	Fast	24	Yes
Quazepam	Fast	25–41	Yes
Non-benzodiazepine hypnotics			
Zolpidem	Fast	1.5–4.5	No
Zopiclone	Fast	3–6	Yes
Zaleplon	Fast	1	No

3.5 Overall Management of Insomnia

Combining these efficacy criteria, overall treatment of insomnia should by definition be aimed at:[47]

- Resolution of: Initiation insomnia (by shortening sleep latency); maintenance insomnia – the presence of nocturnal awakenings and/or early awakening (by increasing total sleep time).
- Preservation of sleep architecture.
- Improving the quality of life of the patient.

3.6 Effects of Hypnotics on Sleep Architecture

The hypnotics exert a series of effects on sleep architecture that have been studied by PSG, and which are summarised in table II.[31,35,40,46,48-51]

3.7 Safety Criteria for Hypnotics

When the safety of a hypnotic is assessed, a number of parameters should be considered, including particularly:

- The patient's age.
- Prior duration of insomnia.
- Untoward effects and complications, alertness during waking hours.
- Rebound insomnia.
- Effects on memory and psychomotor performance.
- Possible occurrence of withdrawal effects.
- Effects on breathing.
- Specific adverse effects.

3.7.1 Untoward Effects and Complications, Alertness during Waking Hours

When a hypnotic is selected, an estimate should be made of its possible untoward effects and complications, and its impact on alertness during waking hours.

Insomnia is not only a sleep problem, but also affects the activities of the patient during the waking hours.[46] Patients usually experience:

- Drowsiness, fatigue, decreased alertness, etc.
- Difficulty performing daily life activities.
- Difficulty maintaining productivity at work.

Attention deficits are common in patients with insomnia, both when medicated and otherwise.[52] Treatment with some hypnotics can exacerbate these conditions, depending on the duration of action of the drug.[46] Insomnia is a 24-hour problem.

When the untoward effects and complications of hypnotics are assessed, a series of parameters dependent upon both the drug and patient should be taken into account[50,51,53-57] (for a detailed explanation, see Appendix 4):

- Drug-dependent:
  Pharmacokinetic characteristics
  Potency: intrinsic affinity and activity at receptor level.
- Patient-dependent:
  Age and underlying disease
  Drowsiness, fatigue and alertness
  Daily family, social and work activity.

The untoward effects and complications of hypnotic treatment at therapeutic doses are summarised in table III.[35,40,50-52,58-61]

3.7.2 Rebound Insomnia

Rebound insomnia[60] is defined as a worsening of at least one of the following three subjective parameters related to the situation that led to treatment:

- sleep latency;
- nocturnal awakenings;
- total sleep time;

and the presence of at least one of the following three parameters:

- sensation of non-restorative sleep;
- diurnal fatigue;
- anxiety.

When assessing rebound insomnia, the following parameters (explained in detail in Appendix 4) should be taken into account:[60-62]

- Pharmacological characteristics of the hypnotic.
- Impairment of sleep parameters: sleep latency, nocturnal awakenings, total sleep time, reparatory sleep sensation, diurnal fatigue and anxiety.
- The time of occurrence of rebound insomnia.
- Rebound insomnia and anxiety in response to the latter.

Table II. Effects of hypnotics on sleep architecture (↓ = decrease, ↑ = increase, ←→ = no significant effects)

Drug	Half-life	PSG in healthy individuals	ACP effects[a]	Rebound and residual effects[b]	Latency	Total sleep time	Delta sleep	REM	Sleep quality	Comments
Benzodiazepine hypnotics										
Triazolam	Short	[c]	<pathol. ACP rate	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Midazolam	Short	[c]	[c]	Rebound insomnia	↓	↑	↓	↓	↑	↑stage 2
Brotizolam	Short	[c]	[c]	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Loprazolam	Intermediate	[c]	[c]	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Lormetazepam	Intermediate	[c]	[c]	Rebound insomnia	↓	↑	↓	↓	↑	↑stage 2
Flunitrazepam	Intermediate	↓ slow waves	[c]	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑stage 2
Flurazepam	Long	↓ slow waves	[c]	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
Nitrazepam	Long	[c]	[c]	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑stage 2
Quazepam	Long	[c]	[c]	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
Non-benzodiazepine hypnotics										
Zolpidem	Short	No or few changes	<pathol. ACP rate	No rebound or residual effects	↓	↑	↑	←→	↑↑	↓ waking
Zopiclone	Short	No or few changes	<pathol. ACP rate	No rebound	↓	↑	↑	←→	↑↑	↓ waking
Zaleplon	Short	No changes	[c]	No rebound or adverse effects	↓	↑	↑	↓	[c]	[c]

a Alternating cyclic pattern: pseudo-periodic activation phenomenon of slow sleep characterised in the EEG by limited duration waves that can appear spontaneously or after waking stimuli. <ACP means that these compounds decrease the ACP index.

b Confirmed by the multiple sleep latency test (MSLT). < = decreases.

c No conclusive data.

Table III. Undesired effects and complications of treatment with hypnotics at therapeutic doses[a]

Drug/chemical class (half-life)	'Hangover' effect	Rebound insomnia	Tolerance	Dependence/ abuse	Comment
Benzodiazepine hypnotics					
Triazolam/Benzodiazepine (short: <6h)	0	+++	+++	++	Triazolam may have fewer respiratory depressive effects than other benzodiazepines. No more than 0.25mg should be administered to avoid increasing adverse CNS effects
Midazolam	0	+++	+++	++	
Brotizolam	0	+++	+++	++	
Loprazolam/Benzodiazepine (medium: 6–24h)	+/++	++/+++	++/+++	++	More marked hangover effect at higher doses
Lormetazepam	+/++	++/+++	++/+++	++	
Flunitrazepam	+/++	++/+++	++/+++	++	
Flurazepam/Benzodiazepine (long: >24h)	+++	0[b]	+	++	Avoid in elderly, since increased risk of falls and fractures
Nitrazepam	+++	0[b]	+	++	
Quazepam	+++	0[b]	+	++	
Non-benzodiazepine hypnotics					
Zolpidem/Imidazopyridine (short)	0	+	0	0	Hangover effect and tolerance can occur with supratherapeutic doses and/or very long-term treatment
Zopiclone/Cyclopyrrolone (short)	++	++	++	+	Doses >7.5mg increase adverse effects without improving efficacy
Zaleplon/Pyrazolopyrimidine (short)	[c]	0	± after 5 wks	[c]	No sedation seen on following day, 5–6.5h after 10mg taken at midnight, with no significant psychomotor changes

a Refer also to table IV and section 4.6.

b With long half-life benzodiazepines, rebound insomnia is uncommon and appears late.

c No conclusive data are available in the consulted literature.

0 = no effect; + = mild effect; ± = no tolerance observed until that time; ++ = moderate effect; **+++** = severe effect.

- Diurnal wellbeing (see table III).

3.7.3 Possibility of Withdrawal Effects

The parameters to be considered when assessing the possibility of withdrawal effects include (see Appendix 4 for a detailed discussion):

- The type of hypnotic.
- The dose.
- Long-term or continuous treatment.
- Risk population (history of addictive behaviour).
- Tolerance.
- The possibility of abuse.

The risk factors for physical and/or psychological benzodiazepine addiction are:

- High doses for long periods of time (>6 months).
- Drug abusers.
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

The possibility of the occurrence of dependence/abuse is specified for each drug in table III.[20,50,51,54,63-69]

3.7.4 Effects on Memory and Psychomotor Performance

The parameters to be considered for assessing the effects of hypnotics upon memory and psychomotor performance are (see Appendix 4 for more detail):

- Pharmacological characteristics of the drug.
- Objective and subjective measures.

Table IV. Effects of hypnotics on memory and psychomotor performance

Drug	Memory		Psychomotor performance
	night of administration	following day	
Short-acting benzodiazepine hypnotics[76]	↓	←→	↓
Intermediate-acting benzodiazepine hypnotics[76]	↓	↓ or ←→	↓
Long-acting benzodiazepine hypnotics[76]	↓	↓	↓
Zolpidem[51]	←→ or ↓	←→	←→
Zopiclone[50,51,66]	↓	←→	←→ or ↓
Zaleplon[40]	←→	←→	←→

↓ = worsening; ←→ = no significant effects.

- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.
- Psychomotor performance (sedation).
- Memory impairment.

A desirable characteristic of hypnotics is that they have a minimum effect on memory and psychomotor performance. The effects of hypnotics on memory and psychomotor performance are shown in table IV.[50,51,53,70-75]

3.7.5 Insomnia and Respiratory Function

Insomnia is common in patients with chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), restrictive pulmonary diseases, obstructive sleep apnoea syndrome, either as a result of the disease itself or because of the medication used (β-agonists, theophylline, etc.).

In these patients, special monitoring is required when hypnotics are administered, because of the possibility of respiratory depression (see table V).[76-80]

3.7.6 Insomnia and Cardiac Function

Subjective complaints of insomnia increase the risk of future coronary events.[27,81]

3.8 Characteristics of the Ideal Hypnotic

Based on the concepts addressed here, the characteristics of the ideal hypnotic may be summarised as follows:

- Fast sleep induction.
- Optimum duration of effect.
- Specific mechanism of action.
- Production of physiological sleep.
- No psychomotor effects.
- No effects on memory.
- No rebound insomnia.
- No development of tolerance.
- No physical dependence.
- No respiratory depression.
- Increased quality of life.
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

4. Practical Aspects of the Treatment of Insomnia

4.1 Premises

According to the above data, the selective agonists of the GABA-A receptor complex are the drugs of first choice in the drug treatment of insomnia.[22]

Once treatment has started, monitoring and evaluation of response are required. It is recommended that hypnotic medication be maintained in cases where treatment discontinuation would impair the patient's quality of life, and when all other therapeutic measures (pharmacological and non-pharmacological) have failed to yield the desired results.

Overall management of insomnia should be based on three types of measures (see figure 2):

- Treatment of the underlying causes.
- Sleep hygiene and cognitive-behavioural measures.

Table V. Effects of hypnotics on respiratory and cardiac function

Drug	COPD and compensated restrictive pulmonary diseases	Treated OSAS	Cardiac function
Short-acting benzodiazepine hypnotics[a]	↓	↓	?
Intermediate-acting benzodiazepine hypnotics	↓	↓	?
Long-acting benzodiazepine hypnotics	↓	↓	?
Zolpidem	←→	←→	←→
Zopliclone	←→	→←	?
Zaleplon	?←→	?→←	?

a In mild to moderate stable diseases, triazolam does not impair oxygen saturation

COPD = chronic obstructive pulmonary disease; **OSAS** = obstructive sleep apnoea syndrome; ↓ = Worsening; ? = inconclusive or missing data; ←→ = no changes.

- Drug treatment.[22]
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

Drug treatment should never be an isolated measure. Active involvement of the patient in his/her treatment at all times is very important.

4.2 When to Administer Hypnotic Drugs

When insomnia occurs with an associated disease, the underlying or aggravating cause must always be treated. As a general rule, whenever hypnotic therapy is started, this should be associated with sleep hygiene measures.[22,30,82,83]

The type of treatment will depend on the type of insomnia:

- **Transient insomnia**: hypnotic therapy can be indicated from the onset of symptoms.[84]
- **Subacute insomnia**: hypnotic therapy can also be indicated from the onset of symptoms, and cognitive-behavioural therapy should be recommended.[84]
- **Chronic insomnia**: consider consultation with an expert in sleep medicine. If hypnotic therapy is administered, this should be temporary and intermittent, in order to ensure rapid symptom relief. Cognitive-behavioural therapy must always be performed, and will be the cornerstone of treatment.[22,85] This consensus group recommends that prescription should never exceed 8 weeks without re-evaluation.
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

4.3 Duration of Treatment: Reality vs Fiction

Few data are available on long-term treatment efficacy, since only a few studies addressing this subject have been published:

- Controlled studies for periods of up to 8 weeks.
- Open-label studies for periods of up to 1 year.
- Observational studies lasting several years.[86,87]
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

However, there is an even greater lack of references in the literature concerning the risks of long-term treatment, and the benefits of short- versus long-term therapy.[88] Depending on the country, Health Authorities recommend a maximum initial duration of hypnotic therapy of 2–8 weeks; however, in clinical practice hypnotics are usually prescribed for much longer periods than those studied in clinical trials.[89]

Clinical experience in the drug treatment of insomnia shows some issues that should be taken into account as regards the duration of treatment with benzodiazepine and non-benzodiazepine hypnotics.

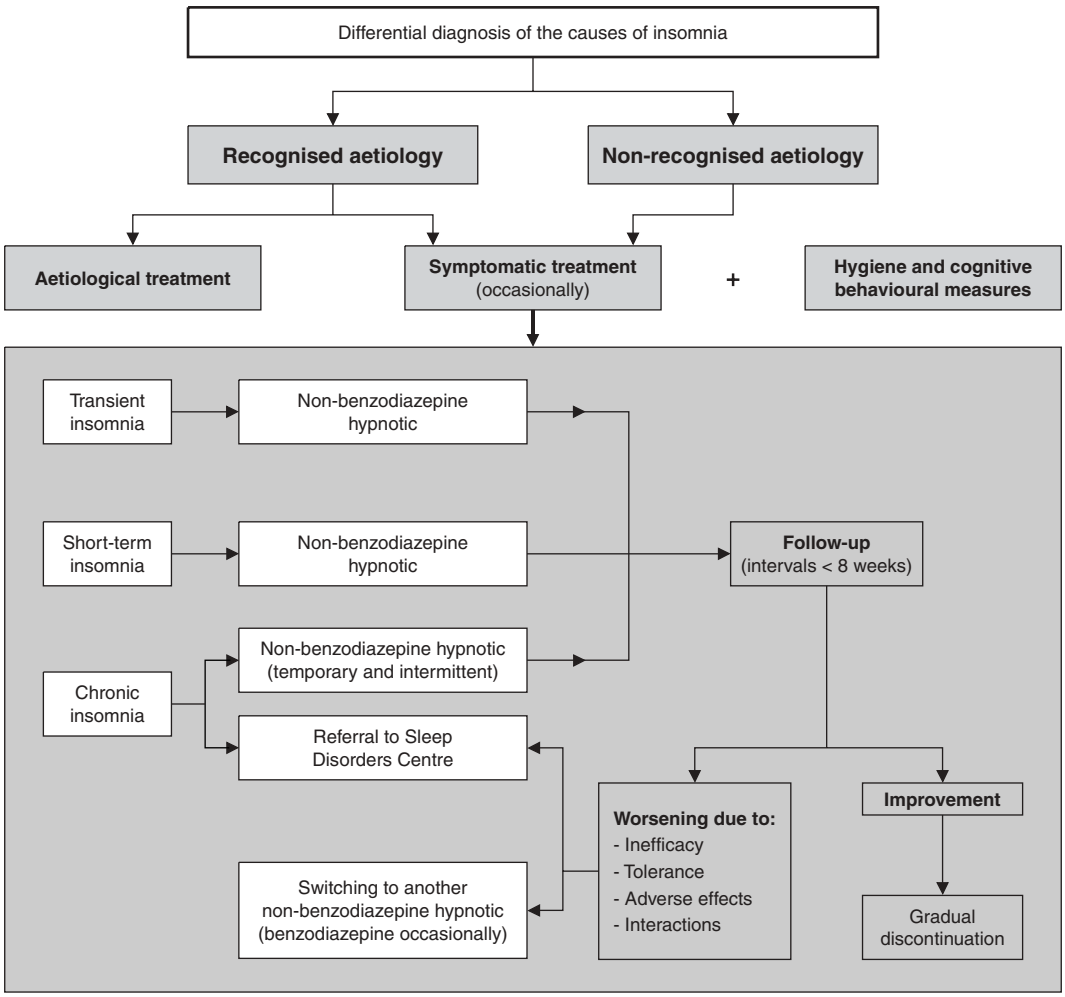

Fig. 2. Flow chart of drug treatment for insomnia

4.3.1 Clinical Experience with Benzodiazepine Hypnotics

Ten percent of patients with chronic insomnia take benzodiazepine hypnotics on a continuous basis for over 1 year.[90] The effectiveness of benzodiazepine hypnotics is only documented (by PSG) during the first 4 weeks of treatment. Their long-term therapeutic efficacy has not been established; there are no objective data for periods longer than 4 weeks.[91]

However, various retrospective studies suggest the persistence of subjective efficacy in most patients for months or even several years.[92] Short and intermediate half-life benzodiazepine hypnotics lead to pharmacological tolerance (as measured by PSG) within 1–2 weeks.[35]

4.3.2 Clinical Experience with Non-Benzodiazepine Hypnotics

There are insufficient data in the literature about the risk of dose escalation. Zolpidem has been shown to be effective in continued treatment for periods of up to 1 year in observational studies.[93,94] For zopiclone, efficacy data are only available for periods of up to 4 weeks.[51] In European countries where zaleplon is approved, 2-week treatments are

authorised. In the US, the figure is 4 weeks;[40] there are controlled studies that support its therapeutic efficacy for up to 28 days.[90]

4.4 Continuous versus Intermittent Administration

The widespread long-term administration of hypnotics has led to the appearance of alternative dosage regimens, such as intermittent therapy.[95] The available studies are few, and the dosage regimens differ (pre-established intermittent scheme, 'as required', etc.). Some of these regimens initially define the periods in which medication will be administered, while in others the number of units of medication to be taken in a given time interval is specified, allowing the patient to choose the days of medication.

Thus, Cluydts et al.[96] predefined the administration of zolpidem for 5 days a week, with treatment discontinuation for two days, and reported results similar to those obtained when continuous treatment was given for two consecutive weeks. On the other hand, Walsh et al.[97] used a flexible regimen for 8 weeks, allowing patients to take zolpidem 3–5 times a week, with discontinuation for at least 2 days a week. In this study, no rebound effects were seen after discontinuing medication. Recently, Allain et al. have conducted a 4-week study with 245 patients with primary insomnia from 58 primary-care centres in France. Patients were given four tablets of zolpidem 10mg or placebo, two to be taken on the first two nights and the two remaining when required throughout the week. This 'as needed' pattern was feasible and well tolerated.[98] In summary, further studies are required with larger patient samples to determine the most adequate dosage regimens and their efficacy.[96]

The experience of the Consensus Group suggests that intermittent treatment should be preferred to continuous therapy. However, the lack of data supporting this impression is recognised.

4.5 Elderly Patients

Although insomnia can be a problem at any stage of life, it is particularly common after the age of 65 years. A number of changes in sleep physiology are associated with age, such as loss of total sleep time, reduction in slow-wave sleep, increased number of arousals and in sleep latency, and changes in circadian distribution (increased daytime sleep propensity, with loss of circadian amplitude).[99] Furthermore, insomnia is facilitated by the concomitant presence of psychosocial influences with an increased risk for psychiatric disorder, medical illness and the use of medications and alcohol.[100]

Evaluation of insomnia in the older patient requires a careful history and physical examination, supplemented by a sleep diary.[101,102] Treatment of underlying conditions and nonpharmacological improvements in sleep hygiene are first-line therapy, but pharmacological agents may be needed.[103] However, treatment of the elderly with benzodiazepines carries a higher risk of ataxia, confusion, paradoxical activation, hallucinations, respiratory depression, as well as muscle weakness and, subsequently, trauma and other accidents.[104,105]

In elderly patients, the dose should be adequately adjusted to the lowest effective possible.[106] Pharmacokinetic parameters such as rate of absorption, distribution and elimination of drugs change in the elderly. This is of special relevance for drugs whose metabolites are active compounds, thus showing an increase in daytime sedation and other residual adverse effects. The dose should be the lowest clinically indicated dose, and it should be used for a short period of time (3–5 nights) before the clinician and patient jointly indicate its effectiveness. Patients should not be allowed to initiate a dose escalation.[101,102,107]

Non-benzodiazepines with rapid elimination may offer a lower adverse effect profile than other hypnotic agents when used for insomnia in the elderly. The hypnotic efficacy, untoward effects and tolerability of hypnotics in these patients are shown in table VI.[50,52,108,109]

4.6 Pregnancy and Lactation

Overall, the available data do not allow us to confirm the safety of hypnotics in pregnant and nursing women. The drug manufacturers therefore

Table VI. Hypnotic efficacy, untoward effects and tolerability of hypnotics in elderly patients

Drug	Efficacy	Untoward effects or complications	Tolerability
Benzodiazepine hypnotics	Good	↓	Good
Zolpidem	Good	←→	Good
Zopiclone	Good	←→ **or** ↑	Good
Zaleplon	Good	←→	Good

↑ = increased; ←→ = no significant effects.

do not recommend treatment in such patients.[26,40,50,51] Nevertheless, some distinctions can be made:[110]

- Zolpidem is included in category B of the US FDA classification as regards the risk of drug use in pregnant women (its use is allowed in low-risk situations).
- Zopiclone is included in category C of the US FDA classification (its use may be justified under strict therapeutic control).
- Most benzodiazepines belong to category D (data exist of fetal risk; strict medical control), except for dipotassium clorazepate and bromazepam (category C) and flurazepam and triazolam (category X: have caused fetal malformations and irreversible lesions. Teratogenic risk clearly exceeds the therapeutic benefit).
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

4.7 Children

The efficacy and safety of hypnotics in the treatment of childhood insomnia has not been established. In specific and well-evaluated cases, the use of hypnotics for limited periods of time may be considered.[111] When drug treatment is considered, the patient should be referred to an expert in sleep disorders.

4.8 Menopause

In the case of insomnia among peri- or postmenopausal women, it is necessary to first evaluate the possible existence of disorders commonly seen in this age group, such as depression, anxiety or apnoea, which can interfere with sleep. If such disorders exist, priority should be given to treatment of the underlying pathology.

Sleep maintenance difficulties are often caused by nocturnal vasomotor symptoms (sweating, hot flushes, etc.).[112] These symptoms usually improve with hormone replacement therapy,[113,114] although other associated non-pharmacological measures are often required. In some cases, such vasomotor symptoms exist, but are not perceived by the patient.

4.9 Patients with Respiratory Disease

The use of hypnotics should be individualised in patients with stable, chronic respiratory disease or mild to moderate sleep apnoea syndrome.

Benzodiazepine hypnotics are not indicated in patients with decompensated COPD or in those with hypercapnia,[77,115] or in patients with decompensated restrictive pulmonary disease. No clinically significant adverse effects upon respiratory function have been reported in patients with stable mild to moderate COPD during treatment with zolpidem and zopiclone.[77,78]

In treated obstructive sleep apnoea syndrome, zolpidem[77,115] and zopiclone[76] cause no impairment. The existing data on zaleplon in patients with respiratory disease are inconclusive.

4.10 Patients with Psychiatric Disease

4.10.1 Depression

When insomnia is secondary to documented depression, priority should be given to antidepressant therapy.[116] The addition of a non-benzodiazepine hypnotic may be indicated.[117]

4.10.2 Anxiety

In insomnia caused by an anxiety disorder, the addition of an anxiolytic on awakening to the hypnotic is useful.[20]

4.10.3 Schizophrenia

In patients with schizophrenia and insomnia, maximum priority should be given to antipsychotic treatment.

4.10.4 Dementia and Acute Confusional Syndromes

In these patients, an evaluation should be made of the administration of sedative antidepressants, light therapy and sleep hygiene measures (adapting the hours in bed to the age of the patient, etc.). Benzodiazepines are contraindicated because of their cognitive effects. They can sometimes induce paradoxical effects.

4.11 Other Drug and Non-Drug Treatments

4.11.1 Antihistamines

Doxylamine and diphenhydramine are antihistamines commonly used as sleep inducers, despite the fact that they cause diurnal sedation, psychomotor impairment and anticholinergic adverse effects.[35] There is a lack of controlled studies with subjective measurement of sleep.

4.11.2 Valerian

Few and non-conclusive studies have been conducted of valerian as a hypnotic.[35,118,119] When used during the day it can be useful to improve night sleep, because of its anxiolytic effect.

4.11.3 Melatonin

Melatonin has been shown to be involved in the regulation of the sleep-waking cycle, and in improving jet-lag symptoms and the delayed sleep-phase syndrome. The studies concerning its hypnotic efficacy are inconclusive, and there are no data on the optimum dose, time of administration, indications, contraindications and toxicity.[20,120] Its prescription is not authorised in Spain, but it has been introduced on the market in the US and in other western countries.

4.11.4 Antidepressants

Antidepressants are indicated for the treatment of insomnia secondary to depression, but there are few data to support their use in other forms of insomnia.[37,121] Adverse effects may occur (orthostatic hypotension, arrhythmias, overdose-related mortality, etc.).

Antidepressants are used for the treatment of insomnia secondary to depression and other disorders such as post-traumatic shock,[122] but their effect is related to overall clinical improvement. However, some of them, such as selective serotonin reuptake inhibitors (SSRIs), can alter sleep structure, possibly because of activation of serotonin 5-HT_2 receptors, whereas others, such as nefazodone or bupropion, do not alter it or improve it.[86,123,124] No differences have been shown in their effects on sleep between fluoxetine, sertraline and paroxetine, which supports their effect being independent of their sedative or stimulant properties and only related to their antidepressant efficacy.[87]

Administration of SSRIs can increase subjective dream intensity, but there are studies that indicate that they reduce dreams during their administration, but increase them when treatment is discontinued. This could be a result of serotoninergic suppression of the REM sleep phase during administration and to cholinergic rebound produced during their withdrawal.[125]

No data are available on the efficacy of antidepressants in other types of insomnia.[121] Moreover, their undesirable effects, especially with administration of the tricyclic antidepressants (anticholinergic and cardiovascular adverse effects),[35] must also be taken into account.

4.11.5 Alcohol (Ethanol)

Alcohol is contraindicated for the treatment of insomnia.

4.11.6 Homeopathy

Although widely used, there are no data to either support or question the therapeutic efficacy of homeopathy.

4.12 Follow-Up Measures

Periodic and individualised follow-up is recommended at intervals not exceeding 8 weeks.[4,82,126] The physician should encourage the patient to make use of a sleep diary.

4.13 When to Switch an Ineffective Hypnotic

4.13.1 General Criteria for Switching Hypnotics

A change in hypnotic should always be considered in the case of:

- Therapeutic inefficacy at the recommended doses.
- Development of tolerance.
- Occurrence of adverse effects.
- The possibility of pharmacological interactions with other treatments.
- High doses for long periods of time (>6 months).
- Elderly patients.
- The presence of psychiatric disease.
- Risk population (history of addictive behaviour).
- Tolerance.

4.13.2 Benzodiazepine Treatment in the Elderly

Some studies have questioned the efficacy of benzodiazepines in the elderly, based on the observation that patients treated with benzodiazepine hypnotics continue to experience sleep disorders similar to those of non-medicated patients. Considering the known morbidity associated with the long-term use of benzodiazepine hypnotics (falls, traffic accidents, etc.), controlled withdrawal of these drugs is recommended in some patients. There is no general rule to switch to non-benzodiazepine hypnotics in this group. If symptoms persist a trial with non-benzodiazepine hypnotics can be made. If the feeling of control over sleep has been recovered, gradual but full discontinuation must be tried.[52]

4.13.3 Switching from Benzodiazepine Hypnotics to Non-Benzodiazepine Hypnotics

There are various studies on the replacement of benzodiazepine hypnotics given long term to patients with chronic insomnia by non-benzodiazepine hypnotics such as zolpidem[127,128] and zopiclone.[51] Benzodiazepine hypnotics should be gradually discontinued, as shown in figure 3. Non-benzodiazepine hypnotics must be introduced during benzodiazepine hypnotic dose reduction.[127]

4.14 Criteria for Discontinuation of Hypnotic Therapy

Once the patient has recovered the sensation of control over the sleep process, gradual treatment discontinuation should be considered. When insomnia is associated with a disease (e.g. depression) or a given life event, treatment discontinuation should be considered when these factors change.

Treatment discontinuation must never be sudden. Once the drug is discontinued, rebound insomnia may occur, but this is transient and does not necessarily require treatment resumption. Relapses may also occur if the causes of insomnia persist.

Therapy discontinuation may be planned, withdrawing the drug over a period of several weeks to several months. If serious or prolonged psychiatric symptoms occur on treatment discontinuation, the patient should be re-evaluated.

A possibility is to divide the doses (if tablets are administered) or eliminate some nighttime doses (in the case of capsules). It is a good idea to begin with Friday or Saturday nights. One dose a week or one

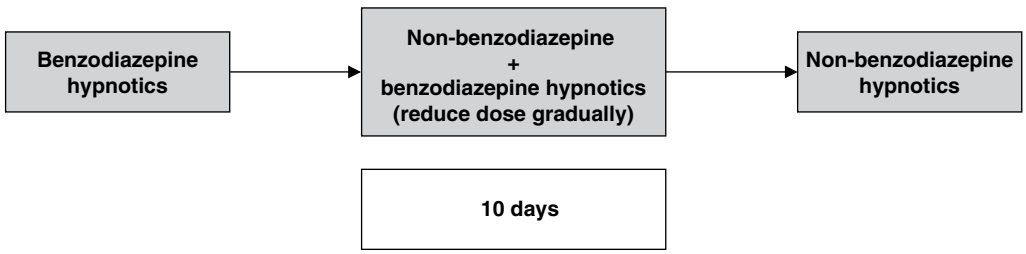

Fig. 3. Gradual system for switching from benzodiazepine hypnotics to non-benzodiazepine hypnotics.

Table VII. Types of insomnia according to different classifications: International Classification of Sleep Disorders (ICSD), International Classification of Diseases, 9th and 10th editions (ICD-9 and ICD-10, respectively), and Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)

ICSD		ICD-9		ICD-10		DSM-IV	
name	code	name	code	name	code	name	code
1a. Adjustment sleep disorder	307.41-0	Transient disorder of initiating or maintaining sleep	307.41	Non-organic insomnia	F51.0		
1b. Psychophysiological insomnia	307.42-0	Persistent disorder of initiating or maintaining sleep	307.42	Non-organic insomnia	F51.0	Primary insomnia	307.4
		Other insomnia	780.52	Disorder of initiating or maintaining sleep	G47.0		
5b. Central sleep apnoea syndrome	780.51-0	Insomnia with sleep apnoea	780.53	Sleep apnoea	G47.3	Breathing-related sleep disorder	780.5
5c. Central alveolar hypoventilation syndrome	780.51-1						
5f. Altitude insomnia	289	Altitude insomnia	289	Other altitude effects	T20.2		
7a. Short sleeper	307.49.0						
8e. Fatal familial insomnia	337.9	Fatal familial insomnia	337.9	Other degenerative diseases	G31	Insomnia due to *...indicate medical pathology*	780.X
11. Idiopathic insomnia	780.52.7	Other insomnia	780.52	Disorder of initiating or maintaining sleep	G47.0	Primary insomnia	307.4

dose every 2 weeks may be eliminated. Before final discontinuation of continuous therapy, an intermittent treatment regimen should be prescribed.

5. Conclusion

The duration of hypnotic pharmacological treatment in chronic insomnia is a very controversial issue. The Health Authorities of each country give recommendations limiting its duration to a few weeks. However, in the opinion of most of the physicians dealing with sleep disorders, there are no clear guidelines on treatment duration, and it is known that in daily practice physicians need to follow different schedules and dosages for each patient.

Thus, continuous administration is usually scheduled for the first treatment weeks, followed by the introduction of intermittent administration at a time depending on the evolution of insomnia, evaluated during patient follow-up visits.

Pharmacological treatment should be supplemented with behavioural and sleep hygiene measures from the outset. As with any chronic ailment, treatment will possibly go on for the patient's lifetime. We know that two-thirds of hypnotic prescriptions are for chronic insomniacs, who have improved and worsened periods, and short repeated treatment schedules would avoid pharmacological tolerance and the development of dependence.

It is known that, in the morning after hypnotic intake, cognitive functions are affected, especially with those hypnotics with a long half-life, and this fact also supports the use of shorter treatment periods.

Attempting to reach a consensus on scientific concepts is always an arduous task, particularly when it involves the use of drugs. The need to reach agreements limits certain aspects, but allows basic statements to be made that can be highly useful for daily clinical practice. We are aware of the limitations that a document of this type can have, but we are also satisfied with the work done and the practical aspects that we will be able to share with our colleagues who treat patients with insomnia. We understand that this is a pharmacological consensus and that other consensuses are needed on nonpharmacological measures, which are as basic as the former. Our work is a first step that should be improved on and completed in the future. We hope that interaction with colleagues who use it will provide information that will allow this scientific document to be expanded and re-published in the near future.

6. Appendix 1 (see Table VII)

7. Appendix 2. Types of Insomnia (International Classification of Sleep Disorders (ICSD))

1. Associated with behavioural/psychophysiological disorders

a) Adjustment sleep disorder
b) Psychophysiological insomnia
c) Inadequate sleep hygiene
d) Limit-setting sleep disorder
e) Sleep-onset association disorder
f) Nocturnal eating/drinking syndrome
g) Others

2. Associated with psychiatric disorders

a) Psychoses
b) Mood disorders
c) Anxiety disorders
d) Panic disorders
e) Alcoholism
f) Others

3. Associated with environmental factors

a) Environmental sleep disorder
b) Food allergy insomnia
c) Toxin-induced sleep disorder
d) Others

4. Associated with drug dependencies

a) Hypnotic-dependent sleep disorder
b) Stimulant-dependent sleep disorder
c) Alcohol-dependent sleep disorder
d) Others

5. Associated with sleep-induced respiratory impairment

a) Obstructive sleep apnoea syndrome
b) Central sleep apnoea syndrome

c) Central alveolar hypoventilation syndrome
d) Chronic obstructive pulmonary disease
e) Sleep-related asthma
f) Altitude insomnia
g) Others

6. Associated with movement disorders

a) Sleep starts (hypnic jerks)
b) Restless leg syndrome
c) Periodic limb movement disorder
d) Nocturnal leg cramps (nocturnal myoclonus)
e) Rhythmic movement disorder
f) REM sleep behaviour disorder
g) Nocturnal paroxysmal dystonia
h) Others

7. Associated with alterations of the sleep-waking cycle temporal model

a) Short sleeper
b) Time-zone change (jet-lag) syndrome
c) Shift-work sleep disorder
d) Delayed sleep-phase syndrome
e) Advanced sleep-phase syndrome
f) Non-24-hour sleep/wake disorder
g) Irregular sleep/wake pattern

8. Associated with parasomnias

a) Confusional awakenings (sleep drunkenness)
b) Night terrors (pavor nocturnus, incubus attacks)
c) Nightmares
d) Sleep hyperhidrosis
e) Others

9. Associated with disorders of the central nervous system

a) Parkinsonism
b) Dementia
c) Degenerative brain disease
d) Sleep-related epilepsy
e) Fatal familial insomnia
f) Others

10. Associated with indeterminate sleep disorders

a) Sleep state misperception
b) Abnormal deglution
c) Others

11. Idiopathic insomnia

12. Other causes of insomnia

a) Sleep-related gastro-oesophageal reflux
b) Fibrositis
c) Menstrual-associated sleep disorder
d) Pregnancy-associated sleep disorder
e) Terrifying hypnagogic hallucinations
f) Sleep choking syndrome
g) Sleep-related laryngospasm
h) Others.

8. Appendix 3. Minimum Criteria for Diagnosing the Type of Insomnia (International Classification of Sleep Disorders (ICSD))

1. Associated with behavioural/psychophysiological disorders

a) *Adjustment sleep disorder*

- Complaint of insomnia or excessive sleepiness
- Complaint is a reaction temporarily associated with an identifiable stressing event
- The disorder is expected to remit if the stress is reduced or the level of adaptation is increased

b) *Psychophysiological insomnia*

- Complaint of insomnia combined with a complaint of diminished performance during waking hours
- Learned associations that prevent sleep are identified:

1. Forcing sleep, which suggests inability to sleep at the desired time, though with the ability to sleep in the course of other relatively monotonous activities, such as watching television or reading

2. Awakenings conditioned by the room or sleep-related activities, indicated by poor sleeping at home but improved sleeping away from home or when no room routines are performed

c) *Inadequate sleep hygiene*

- Complaint of insomnia or excessive sleepiness
- Presence of at least one of the following:

1. Daytime naps at least twice a week

2. Variable bedtime or awakening hours

3. Frequent episodes (2–3 times a week) of extended time in bed

4. Routine use of products containing alcohol, tobacco or caffeine in the period preceding bedtime

5. Performance of exercise near bedtime

6. Plans to become implicated in exciting or emotionally bothersome activities near bedtime

7. Frequent use of the bed for unrelated activities (e.g. to watch television, read, study, eat, etc.)

8. Sleeps in an uncomfortable bed (mattress in poor condition, inadequate bedlinen, etc.)

9. Allows the room to be too bright, poorly ventilated, untidy, too warm, too cold or otherwise conditioned to preclude sleep induction

10. Carries out activities requiring high levels of concentration shortly before bedtime

11. Allows mental activities in bed, such as thinking, planning, remembering, etc.

d) *Limit-setting sleep disorder*

- Evasive or refuses to go to bed at appropriate time
- Once sleep period has started, sleeping is of normal quality and duration

e) *Sleep-onset association disorder*

- Complaint of insomnia
- Complaint is temporarily associated with the absence of certain conditions (e.g. being picked up in arms, moved or breastfed, listening to radio or watching television, etc.)
- With the particular association present, sleep is normal in terms of onset, duration and quality
- No evidence of significant underlying medical or psychiatric disorder able to account for complaint
- No other criteria for other sleep disorders able to cause difficulties in falling asleep (e.g. limit-setting sleep disorder)

f) *Nocturnal eating/drinking syndrome*

- Frequent and recurrent awakenings in order to eat or drink
- Following food or drink intake, sleep onset is normal

2. Associated with psychiatric disorders

a) *Psychoses*

- Complaint of insomnia or excessive sleepiness
- Clinical diagnosis of schizophrenia, schizophrenia-like disorder or some other functional psychosis

b) *Mood disorders*

- Complaint of insomnia or excessive sleepiness
- Complaint is temporally associated with diagnosis of mood disorder

c) *Anxiety disorders*

- Complaint of insomnia or excessive sleepiness
- Presence of long-term generalised anxiety disorder or some other anxiety disorder
- The sleep disorder has followed the course of the psychiatric problem without significant prolonged periods of remission

d) *Panic disorders*

- Complaint of sudden awakening or insomnia
- Presence of panic disorder with or without agoraphobia
- The sleep disorder has followed the course of the psychiatric problem without significant prolonged periods of remission

e) *Alcoholism*

- Complaint of insomnia or excessive sleepiness
- Diagnosis of alcoholism

3. Associated with environmental factors

a) *Environmental sleep disorder*

- Complaint of insomnia or excessive sleepiness
- Complaint is temporally associated with the introduction of an environmental stimulus or circumstance that alters sleep and is physically measurable
- The physical properties of the environmental factor explain the sleep complaint; the psychological significance of the environmental factor does not account for the complaint
- Withdrawal of the causal environmental factor leads to immediate or gradual resolution with a return to normal sleep
- The disorder has been present for more than three weeks
- Complaint of insomnia

b) *Food allergy insomnia*

- Complaint of insomnia
- Complaint is temporally associated with the introduction of a concrete food or drink
- Withdrawal of the agent restores normal sleep and waking, either immediately or in the course

of about 4 weeks. The diurnal behaviour may improve before the sleep model
- Recurrence of altered sleep and diurnal behaviour when the suspected allergen is reintroduced in the diet

c) *Toxin-induced sleep disorder*
- Complaint of insomnia or excessive sleepiness
- Complaint is temporally associated with the presence of an environmental or ingested toxic agent (e.g. heavy metals or organic toxins, etc.)
- No evidence of any other medical or psychiatric disorder, other than that associated with the toxicity accounting for the complaint
- The diagnostic criteria for any other sleep disorder causing complaints of insomnia or excessive sleepiness are not met.

4. Associated with drug dependencies

a) *Hypnotic-dependent sleep disorder*
- Complaint of insomnia or excessive sleepiness
- Use of hypnotics practically daily for at least three weeks
- Withdrawal of the hypnotic is associated with exacerbation of the primary complaint, which is often judged as being worse than the original sleep problem

b) *Stimulant-dependent sleep disorder*
- Complaint of insomnia or excessive sleepiness
- Complaint is temporally associated with the use or withdrawal of a stimulant medication
- Use of stimulant medication alters the habitual sleep period, or more than one attempt to withdraw the stimulant induces symptoms of excessive sleepiness

c) *Alcohol-dependent sleep disorder*
- Complaint of insomnia or excessive sleepiness
- Complaint is temporally associated with more than one attempt to withdraw alcohol consumption before bedtime.

5. Associated with sleep-induced respiratory impairment

a) *Obstructive sleep apnoea syndrome*
- Complaint of insomnia or excessive sleepiness. The patient may occasionally be unaware of clinical facts that are nevertheless apparent to others
- Frequent episodes of obstructed breathing during sleep
- The associated conditions include:

1. Heavy snoring
2. Dry mouth on awakening
3. Chest retraction during sleep in young children

b) *Central sleep apnoea syndrome*
- Complaint of insomnia or excessive sleepiness. The patient may occasionally be unaware of clinical facts that are nevertheless apparent to others
- Frequent episodes of shallow breathing or absence of breathing during sleep
- Polysomnography shows central apneic pauses lasting more than 10 sec (20 sec in infancy), with one of the following:

1. Frequent awakening from sleep associated with apnoea
2. Bradycardia or tachycardia
3. Oxygen desaturation associated with the apnoeic episodes (criteria included in ICSD)
4. Multiple sleep latency test (MSLT) exhibiting a mean sleep latency of less than 10 min

c) *Central alveolar hypoventilation syndrome*
- Complaint of insomnia or excessive sleepiness. The patient may occasionally be unaware of clinical facts that are nevertheless apparent to others, such as hypoventilation during sleep
- Frequent episodes of shallow breathing or absence of breathing during sleep
- Absence of primary lung disease, skeletal malformations, or neuromuscular disorders affecting respiration
- Polysomnography shows episodes of shallow breathing lasting more than 10 sec, associated with oxygen desaturation and one or more of the following:

1. Frequent awakening from sleep associated with the breathing alterations
2. Bradycardia or tachycardia
3. Multiple sleep latency test (MSLT) exhibiting a mean sleep latency of less than 10 min

d) *Chronic obstructive pulmonary disease*
- Complaint of insomnia or excessive sleepiness

- Complaint is temporally associated with the presence of chronic obstructive pulmonary disease (COPD)

e) *Sleep-related asthma*

- Complaint of insomnia or excessive sleepiness, and cough or dyspnoea
- Complaint is temporally associated with the presence of asthma

f) *Altitude insomnia*

- Complaint of insomnia
- Complaint is temporally associated with elevations typically above 4000m

6. Associated with movement disorders

a) *Sleep starts (hypnic jerks)*

- Complaints of difficulties falling asleep, or of intense bodily movements at start of sleep
- Sudden, brief jerks at start of sleep, affecting mainly arms or legs

b) *Restless leg syndrome*

- Complaint of unpleasant sensation in legs at night, or difficulty falling asleep
- Unpleasant 'slipping' sensation within gastrocnemius region, often associated with generalised pain and leg pain
- Discomfort is calmed with limb movements

c) *Periodic limb movement disorder*

- Complaint of insomnia or excessive sleepiness. Occasionally the patient is asymptomatic, and the movements are observed by another person
- Repetitive and highly stereotyped limb muscle movements, characterised in the leg by extension of the big toe in combination with partial flexion of the ankle, knee and occasionally the hip

d) *Nocturnal leg cramps (nocturnal myoclonus)*

- Complaint of painful sensation in the leg associated with muscle stiffness or pressing feeling
- Recurrent awakenings associated with painful leg sensation

e) *Rhythmic movement disorder*

- Rhythmic body movements occurring during sleepiness period or actual sleep
- At least one of the following alterations is present:

1. The head moves strongly in an anterior-posterior direction ('head banging')

2. The head moves laterally when in dorsal decubitus ('head rolling')

3. The entire body moves in jerks while supported by hands and knees ('body rocking')

4. The entire body moves laterally when in dorsal decubitus ('body rolling')

f) *REM sleep behaviour disorder*

- Limb or body movements associated with dreaming
- At least one of the following:

1. Hazardous or potentially hazardous sleep behaviours

2. Sleep appears to involve 'acting'

3. The behaviours alter sleep continuity

g) *Nocturnal paroxysmal dystonia*

- Abnormal motor activity during sleep
- Dystonic or dyskinetic episodes occurring mainly during sleep
- Not associated with any underlying medical or psychiatric disorder capable of accounting for the symptom, e.g. frontal lobe epilepsy
- Does not meet the diagnostic criteria for other sleep disorders, such as REM sleep behaviour disorder or night terror.

7. Associated with alterations of the sleep-waking cycle temporal model

a) *Short sleeper*

- Possible complaints of insomnia
- Total daily sleeping time is less than 75% of what is considered normal for the age
- The sleep model must have been present for at least 6 months
- No excessive sleepiness

b) *Time-zone change (jet-lag) syndrome*

- Complaint of insomnia or excessive sleepiness
- Symptom started 1-2 days after air travel across at least two time-zones

c) *Shift-work sleep disorder*

- Primary complaint of insomnia or excessive sleepiness
- Primary complaint is temporarily associated with a work period (normally at night) taking place during normal sleeping period

d) *Delayed sleep-phase syndrome*

- Complaint of inability to fall asleep at desired time, or inability to spontaneously wake up at desired time, or excessive tiredness
- Delay in main sleep phase with respect to desired sleeping time
- Symptoms present for at least 1 month
- When no strict sleep model is required (e.g. during holidays), the patient:

1. Has a habitual sleep period that is deep and of normal quality and duration

2. Wakes up spontaneously

3. Maintains stable coupling to the 24-hour sleep-waking model, though with a phase delay

- Evidence of temporal delay of habitual sleep period in sleep diaries, for a period of at least 2 weeks

e) *Advanced sleep-phase syndrome*

- Inability to stay awake until the desired bedtime, or inability to continue sleeping until the desired waking up time
- The symptoms are present for at least 3 months
- Evidence of time-advance in habitual sleeping period, as evidenced by polysomnographic monitoring over a period of 24–36 hours
- The diagnostic criteria for any other sleep disorder causing inability to maintain sleep or excessive sleepiness are not met

f) *Non-24-hour sleep/wake disorder*

- Principal complaint of difficulty falling asleep or waking up
- Progressive delays in start and end of sleep, with inability to maintain stable entrainment of a 24-hour sleep-waking model
- Presence of the sleep-waking model for at least 6 weeks

g) *Irregular sleep/wake pattern*

- Complaint of insomnia or excessive sleepiness
- Irregular model of at least three sleep episodes in the course of a 24-hour period
- Presence of the sleep model for at least three months
- Evidence of altered chronobiological rhythmicity attributable to any of the following:

1. Demonstration of loss of normal sleep-waking model via continuous polysomnographic monitoring for at least 24 hours

2. Demonstration of normal temperature model loss via continuous polysomnographic monitoring for at least 24 hours

8. Associated with parasomnias

a) *Confusional awakenings (sleep drunkenness)*

- Complaint by patient or some observer of recurrent mental confusion with micro-awakening or full awakening
- Spontaneous confusional episodes can be induced by forced awakening
- Not associated with other medical disorders such as complex partial epilepsy
- The diagnostic criteria for any other sleep disorder causing the complaint (e.g. night-time fears, sleepwalking) are not met

b) *Night terrors (pavor nocturnus, incubus attacks)*

- A sudden episode of intense terror during sleep
- The episodes usually occur within the first third of the night
- Produces partial or total amnesia of the events during the episode

c) *Nightmares*

- At least one episode of sudden awakening from sleep with intense fear, anxiety and imperative harm sensation
- Immediate recall of terror contents of sleep
- Alertness is complete immediately after awakening, with little confusion or disorientation
- The associated conditions include at least one of the following:

1. Return to sleep after the episode is delayed and not rapid

2. The episode occurs during the last half of the habitual sleep period

d) *Sleep hyperhidrosis*

- Complaint of excessive perspiration during sleep.

9. Associated with disorders of the central nervous system

a) *Parkinsonism*

- Frequent awakenings or episodes of daily sleeping with or without motor activity during the sleep period
- Diagnosis of parkinsonism

b) *Dementia*

- Frequent awakening, daily sleeping episodes or nocturnal confusion
- Associated with the diagnosis of dementia (e.g. Alzheimer's disease)

c) *Degenerative brain disease*

- Complaint by patient or some observer of insomnia or excessive sleepiness. There may be abnormal body movements or alterations in the number of movements during sleep
- Associated with the diagnosis of degenerative central nervous disease (e.g. Huntington's disease)
- The symptom is not associated with psychiatric disorders

d) *Sleep-related epilepsy*

- Complaint of one of the following: sudden awakening at night, unaccounted urinary incontinence or abnormal movements during sleep
- Over 75% of the episodes occur at night
- At least two of the following conditions are present:

1. Generalised tonic-clonic movements of the limbs
2. Focal limb movement
3. Automatisms (lip sucking, sheet-grasping manoeuvres, etc.)
4. Urinary incontinence
5. Tongue biting
6. Forced expiratory 'epileptic crying'
7. Post-stroke lethargy and confusion

e) *Fatal familial insomnia*

- Insomnia complaint initially present
- Autonomous hyperactivity with pyrexia, excessive salivation, hyperhidrosis or anhidrosis, and cardiac and respiratory dysfunction
- Familial model present
- Progression to stupor, coma and death in about 24 months
- Not the result of some other medical or psychiatric disorder, e.g. Alzheimer's dementia, Creutzfeldt-Jakob syndrome or schizophrenia.

10. Associated with indeterminate sleep disorders

a) *Sleep state misperception*

- Complaint of insomnia
- Normal duration and quality of sleep

b) *Sleep choking syndrome*

- Sudden awakening during sleep
- Frequent (almost daily) episodes of choking or suffocation during sleep
- The associated conditions include at least one of the following:

1. Tachycardia
2. Intense anxiety
3. Imminent death sensation

11. Idiopathic insomnia

- Complaint of insomnia, associated with complaint of diminished performance during waking hours
- Insomnia is of prolonged duration, typically commencing in early infancy or even after birth
- No evidence of any other medical or psychiatric disorder capable of accounting for the early onset of insomnia

12. Other causes of insomnia

a) *Sleep-related gastro-oesophageal reflux*

- Complaint of recurrent awakening. The disorder may occasionally be asymptomatic
- Episodes of chest discomfort or burning and substernal pain sensation during sleep
- Other conditions occurring during sleep include one or more of the following:

1. Sour or bitter taste in mouth
2. Cough or choking
3. Heartburn

- Polysomnographic monitoring shows:

1. Awakenings during sleep
2. The monitoring of pH reveals acid gastro-oesophageal reflux during sleep related to polysomnographic monitoring

b) *Fibrositis*

- Complaint of non-restorative sleep and muscle pain
- Muscle pain is not associated with other musculoskeletal disorders
- Hard and tender zones are palpated in the muscles, particularly in the neck and shoulders

c) *Menstrual-associated sleep disorder*

- Complaint of insomnia or excessive sleepiness
- Complaint of insomnia or excessive sleepiness is temporally associated with menstrual cycle, or insomnia complaint is temporally related to menopause
- The disorder is present for at least three months

d) *Pregnancy-associated sleep disorder*

- Complaint of insomnia or excessive sleepiness
- The sleep disorder begins with and is present during pregnancy

e) *Terrifying hypnagogic hallucinations*

- Sudden awakening at the start of sleep, with immediate recall of terrifying hallucinations
- Alertness is present immediately after awakening, with little confusion or disorientation

f) *Sleep choking syndrome*

- Complaint of sudden awakening associated with sensations of choking or suffocation, or insomnia
- Choking or suffocation during sleep associated with 'gargling' sounds from the upper airways
- No evidence of any other medical or psychiatric disorder capable of accounting for the symptoms (e.g. panic disorder)
- The diagnostic criteria for any other sleep disorder capable of causing the symptoms (e.g. obstructive sleep apnoea syndrome or sleep-related gastro-oesophageal reflux) are not met

g) *Sleep-related laryngospasm*

- Sudden awakening during sleep
- Stridor associated with laryngeal spasm.

9. Appendix 4. Brief Pharmacological Compendium

9.1 Pharmacokinetic Parameters of Benzodiazepines and Hypnotics

In order to understand the action and efficacy of benzodiazepines, and benzodiazepine and non-benzodiazepine hypnotics, the significance of parameters such as onset of action, duration of action, half-life, distribution volume and clearance should be understood.

9.1.1 Onset of Action

The speed of onset of hypnotic action is directly dependent upon the rate at which the drug reaches its action sites, and therefore on its rate of access to plasma, i.e. its **absorption**. Drugs with a rapid absorption are obviously preferred, so that sleep induction begins soon after nighttime administration of the active ingredient. Slowly absorbed substances would be confusing for the patient and could worsen his or her anxiety and concern over the sleep problem as time passes without production of the desired effect: sleep induction.

In any case, it should be remembered that when using the oral route, the presence of food in the gastrointestinal tract modifies drug absorption. In general, the absorption rate decreases when absorption takes place in the intestine (as is usually the case), and the maximum plasma concentration of the drug may therefore also be reduced. Rapidly absorbed hypnotics taken during or immediately after meals behave in the same way as slowly absorbed drugs. It is therefore advisable to take the drug without food, 2 hours after a meal.

9.1.2 Duration of Action

Hypnotics are usually classified based on their **half-life**,[38,39,42] but this is not always equivalent to the duration of action. The half-life defines the time required for elimination of half the amount of substance absorbed, i.e. for plasma levels to drop by 50%.[38] The action of a drug ceases when it disappears from its action site. This can occur by two mechanisms:

- By redistribution, the mechanism by which the drug is initially distributed to the action site (the brain), but is also subsequently distributed to peripheral storage areas, mainly fat tissue, skeletal muscle and liver.
- By drug elimination, including both excretion and metabolic inactivation of the active ingredient.

Once in plasma, all drugs start to be distributed to the different tissues. Drugs reach the tissues through arterial blood, from which they diffuse through capillaries to the interstitial and cellular structures of the organs. The **distribution volume** is the theoretical volume in which the drug is homogeneously distributed, and is basically dependent upon the lipid- or water-solubility of the drug and its particular affinity for given tissues or structures:

- A large distribution volume means that significant amounts of the drug have been removed from the bloodstream.
- A small distribution volume implies a low drug distribution to the tissues, as a result of which its plasma levels will remain high for longer periods of time.

Clearance quantifies the capacity of the body to eliminate the drug, and can be defined as the volume of blood or plasma that is cleared of a substance per time unit through elimination processes. The elimination rate of a drug depends on the excretory/biotransformation **capacity** of the organs and on its concentration in the plasma reaching these organs. In turn, and for a given amount of drug in the body, the plasma concentration depends on the distribution volume. Thus, the half-life can be regarded as the result of two primary processes:

- The distribution capacity of the drug, expressed by its distribution volume.
- The elimination capacity of the body, expressed by clearance, so that the elimination half-life increases with increasing distribution volumes and decreases with a decreasing clearance.

As an example, zolpidem, which has no active metabolites, has a short half-life (1.5–2.4 hours)[38] and a small distribution volume; this accounts for its duration of action (about 4–5 hours), an observation that would not be comprehensible if only the elimination-half life were taken into account.[39,41]

After administration of a single dose, the distribution volume is more important than clearance for explaining the duration of the effects. Thus, drugs with long half-lives have very short effects after a single dose because of their extensive distribution. In contrast, less lipophilic drugs with smaller distribution volumes have longer lasting effects after administration of a single dose.[39]

Following repeated administration, drugs with long half-lives undergo slow and significant accumulation during repeated administration intervals of 24 hours or less, since the degree of accumulation of these substances is mainly dependent upon the half-life in relation to the interval between administered doses. When treatment is discontinued, the drug also slowly disappears from the body. However, for drugs with a very short half-life, such as certain hypnotics (e.g. zolpidem), total disappearance from the body may occur in the interval between doses.[38] Each dose should therefore be regarded as a single dose. It is important to remember that on passing through the liver, drugs are converted into metabolites, some of which are active, i.e. also exhibit hypnotic action. Therefore, drug action is not terminated as a result of passage through the liver and can even increase in terms of duration as a result of a prolonged half-life of these secondary products. Thus, the half-lives of these metabolites can range from somewhat less than a few hours to 200 hours, for example, for a diazepam metabolite.[40,41]

9.2 Untoward Effects and Complications, Alertness during Wakefulness

When the untoward effects and complications of hypnotics are evaluated, a number of drug- and patient-dependent parameters should be taken into account.[48,49,51-55]

9.2.1 Drug-Dependent Parameters

Pharmacokinetic characteristics: These are related to the half-life of the hypnotic used following repeated administration and to the administered dose. Short-acting hypnotics do not pose such prob-

lems, because they are rapidly eliminated from the body. In the case of drugs with a long half-life, however, these sedative effects may be highly evident. Regardless of the half-life, if the dose is higher than the recommended dose, even short half-life substances give rise to residual effects. Because of the different pharmacokinetic characteristics of drugs in elderly patients, these effects are more marked in such individuals and can lead to immobility, restlessness and even confusion.

Potency: As regards the potency of hypnotics (affinity, i.e. receptor binding capacity, and intrinsic activity or the capacity to trigger a response), all hypnotics bind to a specific portion of the GABA receptor complex (GABA-A type receptor), promoting binding to the latter and its consequences: opening of the chlorine ionophore bound to the complex, with the consequent repolarisation of the postsynaptic membrane.

The central regional distribution of receptor density can account for the different pharmacological effects. Thus, anxiolytic activity would be related to receptors located in the limbic system and frontal cortex. The presence of receptors in the ascending activating reticular formation and other structures of the pons and medulla oblongata could be related to the sedative/hypnotic action of hypnotics, while the high concentration of receptors found in the brain cortex, hippocampus and amygdala may be associated with anticonvulsant activity.

These receptors have been called benzodiazepine receptors, and three types have been described: θ_1, θ_2 and θ_3. Each of these could be closely related to some specific effect of these drugs. This designation has replaced the terms benzodiazepine 1, 2 and 3, since non-benzodiazepine ligands exist for these receptors. θ_1-receptors are related to the hypnotic-sedative effect, and perhaps also to anxiolytic effects, while θ_2-receptors are associated with anxiolytic, anticonvulsant, muscle relaxant and amnesic actions, and θ_3-receptors are related to anxiolysis. There are differences between benzodiazepines as regards their affinity for the different receptors, the number of receptors occupied, and their intrinsic activity, i.e. the potency of the biological consequence of receptor binding. While benzodiazepines exhibit binding that may be defined as nonspecific, zolpidem and zaleplon specifically bind to θ_1-receptors, as a result of which their residual effects are non-existent at therapeutic doses. Zopiclone would be slightly less specific, since it maintains a discrete anticonvulsant and myorelaxant action.

9.2.2 Patient-Dependent Parameters

Age and underlying disease: Elderly patients require the administration of approximately one-half the dose indicated in younger adults, to avoid residual effects when using short-acting hypnotics. Long-acting hypnotics are contraindicated in elderly patients and patients with liver or kidney insufficiency.

Drowsiness, fatigue and alertness (objective and subjective measures): The presence of these symptoms is an indication for the use of short-acting hypnotics.

Daily family, social and work activity: These aspects are particularly important in situations where occupational activity requires special alertness, as in the case of drivers for example, as well as in professions requiring decision making. In such cases a short-acting hypnotic should always be administered, to avoid the possible residual effects.

9.3 Rebound Insomnia

The following parameters should be considered when evaluating rebound insomnia:[58-60]

9.3.1 Pharmacological Characteristics of the Hypnotic

The elimination rate and receptor occupancy of hypnotics are also involved in the appearance not only of therapeutic effects, but also of untoward effects such as rebound insomnia and anxiety. This rebound insomnia results from a decrease in receptor sensitivity caused by continuous administration of the hypnotic. Rebound insomnia has generally been associated with short half-life hypnotics. However, other aspects such as the distribution volume and potency must also be taken into account. Hypnotics with a short half-life, small distribution

volume and high potency cause rebound insomnia more easily (e.g. triazolam). By contrast, drugs with a short half-life, greater distribution volume and selective action show only a minimum tendency to cause rebound insomnia (e.g. zolpidem[60,67] or zaleplon[67]). If the elimination half-life is long, the effect will appear later, and its severity will depend on the potency of the hypnotic.

9.3.2 Impairment of Sleep Parameters

An evaluation must be made of the parameters included in the definition of rebound insomnia, comparing them with the pretreatment parameters: sleep latency, nocturnal awakenings, total sleep time, reparatory sleep sensation, diurnal fatigue, and anxiety. Objective measurements are required in some cases.

9.3.3 Time of Appearance of Rebound Insomnia

If rebound insomnia appears a few days after treatment discontinuation, it may easily be related to the latter; however, if rebound insomnia appears later, as in the case of long half-life and highly potent hypnotics, it is often considered a new process. For this reason it is necessary to define in the anamnesis whether the patient with insomnia has taken a hypnotic substance in the previous month.

9.3.4 Rebound Insomnia and Anxiety

The occurrence of rebound insomnia can cause marked anxiety, since the patient may think that the problem has recurred. In such situations, treatment should be restarted and then tapered, while at the same time explaining the process to the patient. However, rebound may also appear as diurnal anxiety in the case of ultrashort- and short-acting hypnotics. This is explained by the rapid disappearance of these drugs from their corresponding receptor site.

9.3.5 Diurnal Wellbeing

If rebound insomnia occurs, the waking quality of life of the patient will obviously be impaired. Therefore, appropriate measures should be immediately taken (i.e. treatment should be restarted).

9.4 Possibility of Withdrawal Effects

Although benzodiazepines are usually thought to cause less abuse and dependency than other psychotic drugs,[19] these may occur with long-term treatment. In fact, slight dependency may result in patients treated with benzodiazepines for long periods of time, and withdrawal syndromes can intensify the causes that led these patients to receive benzodiazepine treatment. For this reason, gradual dose reduction is advisable when treatment discontinuation is decided. In general, patients who follow the instructions of the physician do not experience these difficulties. The problem arises in individuals with a history of drug abuse and alcoholism, who tend to abuse these substances by administering high doses. As a result, withdrawal of treatment leads to severe symptoms such as restlessness, depression, panic, paranoia and muscle contractions.

The occurrence of withdrawal effects is a result of adaptive changes taking place following long-term administration of the drug; such phenomena consist of the appearance of tolerance to the behavioural effects of benzodiazepine, and the occurrence of physical symptoms or behavioural changes after drug discontinuation.

One of the aspects deserving mention is the definition of the type of symptoms that appear after the sudden withdrawal of medication. Three groups of symptoms should be distinguished:

- Reappearance of symptoms resulting from non-resolution of the cause of insomnia.
- Rebound phenomena: the same symptoms, caused by sudden treatment suppression.
- Withdrawal syndrome: the appearance of totally different symptoms such as seizures, delusions, hallucinations, etc.

Focusing on the first two groups, these phenomena are also seen with other drugs such as clonidine or β-blockers, among others. The timing of symptoms (if they do occur) depends on the pharmacokinetic characteristics of benzodiazepines. Thus, symptoms appear rapidly with short-acting benzodiazepines (even between doses), and later when long-acting benzodiazepines are given. Another important factor in determining the appearance of symptoms and their timing is the existence and proportion of active metabolites.

Tolerance (decreased effect after repeated administration, or the need to increase the drug dose to achieve the same effect after repeated treatment) need not be present for withdrawal effects to occur.

Dependence only develops in a limited number of patients (approximately 15%) receiving long-term treatment. In relation to the number of prescriptions made, the risk of excessive use, dependence and addiction is very low. On the other hand, benzodiazepine addiction preferentially appears in treatment lasting over 6 months. Nevertheless, despite this risk, many patients do require long-term therapy. In this sense, attention should be drawn to the fact that extreme attitudes deprive many patients of adequate treatment.

The risk factors for physical and/or psychological addiction to benzodiazepines are:

- High doses for long periods of time (>6 months)
- Drug-abusing patients.
- Elderly patients.
- The presence of psychiatric disease.
- Type of hypnotic.

The parameters to be considered in evaluating the potential for withdrawal effects are:

- Dose.
- Whether treatment is long-term and continuous.
- Risk population (history of addictive behaviour).
- Tolerance.
- Abuse potential.

There appear to be differences between the different benzodiazepines. Dependence has been reported most frequently for lorazepam and alprazolam. Theoretically, the benzodiazepines having a greater potential to cause dependence at high doses are those with greater potency and a short half-life, although clinical observations suggest that two benzodiazepines of similar potency and pharmacokinetic profile show different capacities to induce dependency. Moreover, many studies in animals suggest that reinforcement capacity differs between the benzodiazepines, regardless of their kinetics or potency. Thus, a possible selective action upon different receptor subtypes might also contribute to the differential profiles of these substances: one or more receptor subtypes specifically related to dependence could exist.

Action upon other neurotransmitters may also afford an explanation for the differences seen in terms of dependence. Thus, the action of triazolobenzodiazepines upon the central α_2- and 5-HT_{1A} receptors, as well as their pharmacokinetics (a very short half-life and no active metabolites), could be the cause of marked rebound phenomena that are mistaken for withdrawal symptoms, and which can be resolved by new drug presentations such as the delayed-release formulations. The occurrence of these rebound effects does not preclude consideration of alprazolam as one of the benzodiazepines most easily capable of inducing tolerance and dependence.

With zolpidem, a specific agonist of benzodiazepine θ_1-receptors, no tolerance or suppression symptoms are seen when treatment is discontinued suddenly. Dependence occurs only occasionally. Insufficient data are available for zopiclone[48] and zaleplon.

9.5 Effects on Memory and Psychomotor Performance

The effects of treatment upon memory may be very important in the case of pre-existing cognitive deficits, as in certain handicapped patients. Anterograde amnesia results, but the specific effects on memory include:

- Treatment decreases acquisition of new knowledge, but exerts very little effect upon what has already been learned.
- Attention and immediate recall are greatly reduced.
- Semantic memory is not affected (recall of concepts, words or objects).
- Event memory is affected (i.e. things that have happened) and effort is required, but automatic recall is less influenced.
- The sensation of being sure of what is remembered or not is not affected.

Impairment of psychomotor performance and memory, lethargy, confusion and disorientation depend upon the dose and patient susceptibility, and

are more evident in elderly patients or when some deficit exists, e.g. in disabled patients.[47] However, in situations of marked anxiety, benzodiazepines may even improve performance and memory. Nevertheless, activities requiring special attention and which imply risk to others (driving, flying aircraft, etc.) should be avoided.[69,71]

All these effects upon memory and psychomotor performance are very important during the waking hours, but not during sleep. The fact that a hypnotic impairs memory and psychomotor performance during the period in which it exerts its hypnotic effect is entirely consistent.[47,50,67,124] If a drug fails to cause these effects during the sleep period, it is a substance that induces sleep but does not maintain it.

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