7. Treatment of insomnia

### Questions to answer:

- What constitutes effective insomnia treatment?
- What are the most effective psychological therapies for insomnia?
- What are the most effective drugs for treating insomnia?
- Are there effective measures to prevent this disorder from becoming chronic?

The diversity of hypotheses about the origin, development and maintenance of insomnia mean a global view of it is required. So, before resorting to any treatment, it is essential to identify the type of insomnia and its causes, as sometimes it may be symptomatic of other disorders.

The main objective of Primary Care insomnia treatment is to improve the level of satisfaction with sleep, by focusing on interventions that promote it positively. It has to be an integrated therapeutic approach, which takes into account all contributing factors. This will lead to improving sleep quality and quantity, reducing sleep onset latency and nocturnal awakenings, increasing the total time asleep and improving day-time functioning.

A survey of general practitioners conducted in France (n = 6,043) stated that 60% of physicians do not prescribe medication at the start and, when prescribing hypnotics, 81.3% do so by suggesting sleep hygiene measures as well as the medication85.

In a US survey, the general population was asked about the different options used to help sleep and how often they are used. 8% of people said they drank alcohol at least two nights a week, 7% used pharmaceutical products from chemists, 3% took medication prescribed by their doctor and 2% preferred alternative therapies, such as acupuncture, melatonin, or other herbal preparations, such as valerian. These data are shown in Figure 45.
Figure 4. Frequency of Using Substances as “Sleep Aids”

**Frequency of Using Substances as “Sleep Aids”**
*(At Least a Few Nights a Week)*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol, beer or wine</td>
<td>8%</td>
</tr>
<tr>
<td>Non-prescription medicines</td>
<td>7%</td>
</tr>
<tr>
<td>Medicines prescribed by a doctor</td>
<td>3%</td>
</tr>
<tr>
<td>Alternative therapies or herbal supplements</td>
<td>2%</td>
</tr>
</tbody>
</table>

Total sample of general population, n = 1,000

**THERAPEUTIC INTERVENTIONS:**

Insomnia treatment interventions can be classified as follows:

- Health education
- Sleep hygiene education
- Psychological therapies
- Pharmacological therapy
- Other treatments

The types of outcome measures used to evaluate the efficacy and/or effectiveness of these interventions are summarised in Appendix 7.
7.1 Health education

As well as healing sick patients, Primary Care is also concerned with the health promotion of individuals and the community. One method used to achieve this goal is health education for both individuals and the whole population.

For patients with insomnia, this means providing information about both understanding the source of the problem (etiology, epidemiology) and learning the measures to be taken to resolve it (treatment and relapse prevention). It is an intervention that professionals usually put in place before starting any insomnia treatment, regardless of the therapeutic action chosen.

Patients need to receive adequate information about their health problems, so that they can also be involved in the decision-making process (shared decision-making). Studies have been unable to unequivocally confirm, however, the effectiveness of this intervention for the treatment of insomnia.

The practitioner seeks to correct misconceptions about the sleep cycle, its problems and therapeutic measures, which in some areas is known as “psychological education” (see Appendix 8). By taking into account the views of the patient regarding his sleep problem, the practitioner can make better use of the information obtained when implementing therapeutic interventions for insomnia.

The essential points on which to base the intervention are the following:

1. Sleep structure.
2. Influence of age on sleep structure.
3. The number of hours of sleep needed and individual variations.
4. The prevalence of insomnia.
5. Sleep as a reflection of daytime functioning and vice-versa.
6. The importance of conditioning.
7. The mental processes that cause a vicious circle to start.
8. The role and purpose of medication in the treatment of insomnia, and the effect of substances such as alcohol.
9. Clarification of the goals and objectives of the treatment to suit expectations.

Appendix 9 includes information about the therapeutic objectives of this intervention for both practitioners and patients.
Evidence on health education for insomnia

<table>
<thead>
<tr>
<th></th>
<th>1+,4, I. Qualit. R</th>
<th>Adequate information for patients about their health problems helps them get involved in the decision-making process (shared decision-making)\textsuperscript{76,87}.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4, I. Qualit. R</td>
<td>Adequate information for patients about their health problems helps them get involved in the decision-making process (shared decision-making)\textsuperscript{76,87}.</td>
<td></td>
</tr>
<tr>
<td>4, I. Qualit. R</td>
<td>The practitioner can help correct misconceptions about the patient's sleep cycle, its problems and therapeutic measures\textsuperscript{76,88}.</td>
<td></td>
</tr>
<tr>
<td>4, I. Qualit. R</td>
<td>Knowing the patient's conceptions of their sleep problems can help health practitioners optimise the therapeutic proposal to be followed\textsuperscript{76,88}.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Appropriate interventions in health education for insomnia should be based on: sleep structure, influence of age on sleep structure, number of hours of sleep needed and individual variations, the prevalence of insomnia, sleep as a reflection on daytime functioning and vice versa, the importance of conditioning, the mental processes causing a vicious circle to start, the role and purpose of medication in treatment, the effect of substances such as alcohol and clarifying the goals and objectives of the treatment to suit expectations\textsuperscript{79}.</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations on health education for insomnia

<table>
<thead>
<tr>
<th>Q</th>
<th>The ideas, concerns and expectations of the patient regarding sleep complaints should be discussed with the patient, in order to be able to give further information and correct any misconceptions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Health education for insomnia should be based on: the structure of sleep, influence of age, the number of hours required and individual variations, prevalence of insomnia, sleep as a reflection on daytime functioning and vice versa, the importance of conditioning and mental processes that lead to a vicious circle, the place of medication in treatment, the effect of certain substances and the clarification of treatment goals to adjust to expectations.</td>
</tr>
</tbody>
</table>

7.2 Sleep hygiene education

Sleep hygiene measures include a series of behavioural habits that facilitate falling and staying asleep and are the common denominator in all therapeutic interventions used for sleep disorders.

Sleep hygiene measures includes a series of recommendations that people with sleep problems can adopt to minimise the impact of their problem and promote normal sleep. The process consists of acquiring habits which are suitable for a general lifestyle (eg, physical activity) or of changing those that are known to interfere with sleep, such as using drugs or substances that make it harder to sleep.

Key sleep hygiene measures for insomnia are based on the following\textsuperscript{73,74,76,89}:

1. Going to bed only when sleepy.
2. Getting up every day at the same time, including weekends.
3. Avoiding staying in bed awake longer than necessary.
4. Avoiding daytime naps.
5. Reducing or stopping consumption of alcohol, caffeine, hypnotics.
7. Maintaining appropriate environmental conditions for sleep (regarding temperature, ventilation, noise, light).
8. Avoiding stressful activities in the hours before bedtime.
9. Doing some moderate physical exercise at the end of the evening.
11. Having a bath with the water at body temperature for its relaxing effect.

Appendix 9 expands on the information on these measures.

Studies published on the efficacy of sleep hygiene measures agree that by themselves these measures are unable to resolve chronic insomnia. There is also no information on their effectiveness in the treatment of acute insomnia. In fact, most of the time these measures were used in studies as an adjunct to other therapeutic interventions. They are included in the majority of treatments, despite their impact on sleep being minimum when used as the only intervention.

In terms of sleep efficiency, there are studies that compare sleep hygiene as monotherapy compared with a combination therapy (sleep hygiene plus stimulus control or plus more relaxation or more sleep restriction). In general, the study results show the combination therapy to be more efficient.

### Evidence of sleep hygiene education for insomnia

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++, 1+</td>
<td>Sleep hygiene measures alone are not able to resolve chronic insomnia.</td>
</tr>
<tr>
<td>1++/1+</td>
<td>There is no data on the efficacy of sleep hygiene measures for the treatment of acute insomnia.</td>
</tr>
<tr>
<td>1++, 1+</td>
<td>Sleep hygiene measures are often used as an adjunct to other therapeutic interventions.</td>
</tr>
<tr>
<td>1+</td>
<td>A combination therapy of sleep hygiene plus stimulus control, more relaxation or more sleep restriction has better results in terms of sleep efficiency than sleep hygiene as monotherapy.</td>
</tr>
</tbody>
</table>

### Recommendations on sleep hygiene education for insomnia

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Sleep hygiene education is recommended in the treatment of chronic insomnia as an adjunct to other psychological and pharmacological therapeutic interventions.</td>
</tr>
<tr>
<td>A</td>
<td>To achieve greater sleep efficiency, a combination therapy is recommended, that includes one of the following techniques in addition to sleep hygiene education: stimulus control, relaxation therapy or sleep restriction.</td>
</tr>
</tbody>
</table>

### 7.3 Psychological therapies

Psychotherapy is an interpersonal communication process between an experienced practitioner (therapist) and a subject in need of help for health problems (patient). The aim is to make changes to improve the health of the patient by removing or modifying existing symptoms, modifying or changing behaviour and/or promoting the growth and development of a positive personality. The psychotherapeutic approach of insomnia arises mainly from the viewpoint of behavioural interventions and cognitive behaviour. This guide focuses primarily on the models of behavioural interventions and cognitive behaviour as most applicable research concerns these fields.
**Behaviour therapy and cognitive behavioural therapy (CBT)**

**Behaviour therapy** considers the symptoms as a learning of maladaptive behaviour patterns and aims at correcting these through different intervention techniques.

**Cognitive behavioural therapy (CBT)** includes a set of techniques that incorporates elements of both behaviour therapy and cognitive therapy. It takes into account affective and cognitive processes (expectations, beliefs, thoughts), whose distortion leads to symptoms; and its objective is the identification and analysis of these dysfunctional thoughts and beliefs, their relationship with the symptoms, and the construction of more adaptive and functional behaviour patterns.

Cognitive behavioural therapy (CBT) is characterised by an active and direct method, with patient and therapist working together in a structured fashion, with tasks outside the meeting.

In the treatment of insomnia, both behavioural techniques - relaxation and breathing, stimulus control, sleep restriction and paradoxical intention - as well as cognitive behavioural therapy that combines cognitive restructuring as a cognitive element are used, with one or more behavioural interventions.

The main purpose of **behavioural techniques**, applied to the treatment of insomnia, is to change behaviours and cognitions learned with regard to sleep, which are factors that perpetuate or exacerbate sleep disturbances. These factors may be due to poor sleeping habits (such as staying too long in bed), irregular sleep-wake patterns (waking up at different times) or psychophysiological hyperactivation. **Cognitive techniques** are aimed at identifying and analysing thoughts and dysfunctional beliefs in relation to sleep or the consequences of insomnia. It also aims to reduce anticipatory anxiety (fear of not sleeping) that occurs before going to bed which prevents sleep from coming. Once the therapy is finished, the person may occasionally have some difficulty sleeping. The CBT then has another implicit goal which is to teach patients effective skills to cope with such problems after therapy.

Over the past decade, advances in the treatment of insomnia from the cognitive and behavioural perspectives have been significant and therapeutic interventions well accepted by patients. However, despite these advantages, this type of treatment is still largely unknown. Moreover, behavioural therapies and CBT for insomnia are used little in PC, and can be said to be under-used97.

At the level of treatment of insomnia, psychological interventions have focused on such behavioural techniques alone, or in combination with each other, and on cognitive behavioural therapy interventions.

CBT is a psychotherapy model that works with the ideas the patient has about sleep, its problems at bedtime and ideas about managing these problems76. In the treatment of insomnia, CBT combines cognitive techniques - cognitive restructuring, paradoxical intention - with one or more behavioural techniques.

The following additional guidance is presented as a table describing CBT interventions that are often used in the treatment of insomnia.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulus Control</strong></td>
<td>– Based on the principles of classical conditioning: it associates the use of the bed with sleep. &lt;br&gt;– The main objective is to re-associate the bedroom with a rapid onset of sleep. &lt;br&gt;– Establishing a set wake-up time stabilises the sleep-wake rhythm. &lt;br&gt;– Activities acting as cues for staying awake are gradually restricted.</td>
</tr>
<tr>
<td><strong>Sleep restriction</strong></td>
<td>– Intervention to consolidate sleep, shortening the time spent in bed to increase the sleep efficiency of sleep. &lt;br&gt;– It involves restricting the allowed time in bed to match the average time people spend sleeping.</td>
</tr>
<tr>
<td><strong>Relaxation therapies and breathing</strong></td>
<td>– To reach a state of hypoactivation to counteract and help control anticipatory anxiety. It is presented and practised to reduce the somatic arousal levels of the person rather than as a method to induce sleep. &lt;br&gt;• Training in progressive relaxation. &lt;br&gt;• Training in breathing control. &lt;br&gt;– The main techniques include progressive muscle relaxation, diaphragmatic or abdominal breathing, relaxation in directed imagination and biofeedback.</td>
</tr>
<tr>
<td><strong>Cognitive restructuring techniques</strong></td>
<td>– To replace irrational or distorted thoughts with more rational ones. The work is structured in a skills training model to help patients develop the ability to identify maladaptive cognitions, to compare them with reality and defuse them by generating their own rational thoughts. &lt;br&gt;– Used to identify dysfunctional beliefs, attitudes, expectations and attributions a person may have about sleep, and to restructure them by replacing them with others of more adaptive value. &lt;br&gt;– In the long term, they can be used to overcome all the concerns relating to sleep and to eliminate the anxiety associated with poor quality and quantity of sleep.</td>
</tr>
<tr>
<td><strong>Paradoxical intention</strong></td>
<td>– This assumes that an important part of the sleep problem are the attempts to try to resolve it and the anxiety produced by failure to control sleep. &lt;br&gt;– The patient is asked to do the opposite, ie to strive not to sleep.</td>
</tr>
</tbody>
</table>
Studies in the field of Specialised Care

The Clinical Practice Guidelines revised for the preparation of this guide consider behavioural interventions and CBT as a treatment for primary chronic insomnia\(^73-75\).

The meta-analyses, systematic reviews and randomised clinical trials (RCTs) included in the HAS guide\(^73\) evaluate the efficacy and/or length of the effects of behavioural interventions, for the following types: stimuli control, sleep restriction, relaxation and biofeedback compared to a control group. The parameters studied were sleep onset latency, nocturnal sleep maintenance, total sleep time and in some cases the quality of sleep, daytime functioning and quality of life. The results were analysed separately, depending on whether they were obtained by subjective or objective methods. The conclusion was that behavioural intervention and CBT demonstrated their effectiveness in reducing sleep onset latency and maintenance of sleep at night, but not with total sleep time\(^73\).

When comparing CBT treatment with either a control group or an alternative drug treatment, the conclusion was that psychological intervention showed superior effectiveness in reducing sleep onset latency and the number of nocturnal awakenings as well as in improvement in daytime functioning and quality of life. But no significant change was found in total sleep time. The long term duration of the effects ranged between 6 months, 12 months and 2 years after treatment\(^73\).

CBT also helps in reducing the consumption of drugs and psychotropic substances, especially for older patients, and appears to contribute to more cost-effective, long-term drug treatment.

Among the various behavioural interventions, stimulus control is the most effective, followed by sleep restriction. There is controversy over the effectiveness of relaxation and the combination of behavioural interventions was no more effective than stimulus control and sleep restriction alone\(^73\).

For Canadian and American guidelines, the initial focus of insomnia treatment should include at least the following: a behavioural intervention such as stimulus control or relaxation therapy, or a combination of cognitive therapy, stimulus control, sleep restriction and/or relaxation: this is known as cognitive-behavioural therapy (CBT) for insomnia. These guidelines recommend that when the initial psychological intervention proves ineffective, it be replaced with a different one or by a combination of psychological techniques, and that pharmacological interventions are used as adjuvants for non-pharmacological treatment\(^74,75\).
There are other systematic reviews that provide additional information to support the use of stimulus control interventions, relaxation therapies, paradoxical intention, sleep restriction, cognitive restructuring and cognitive behavioural therapy. The outcome parameters were again sleep onset latency, the number of nocturnal awakenings, total sleep time, wake time after sleep onset, sleep efficiency and the quality of sleep. All treatment was performed using scales, questionnaires, sleep diaries and in some cases polysomnography and actigraphy (see glossary). The effectiveness of CBT was demonstrated both for patients with primary insomnia and for insomnia associated with other diseases^90,91.

It was found that the highly effective psychological interventions were latency and sleep quality, while they were moderately effective for the other parameters. Between 70% and 80% of patients with insomnia benefit from CBT treatment, although only between 20% and 30% achieved complete remission. A significant proportion of patients reached an inflexion point (plateau) in their recovery and continued having sleep difficulties after the therapy, which carries a risk of relapse.

This shows the limitation that exists with the outcome parameters used, because they focus on the symptoms of insomnia and do not assess, for example, other effects such as reduction of morbidity or other, more qualitative, ones, such as improving the quality of life of the patients^90,91.

There was another meta-analysis evaluating the effectiveness of some of the cognitive and behavioural techniques, such as progressive relaxation, sleep restriction, stimulus control, paradoxical intention and biofeedback against a control group. For latency parameters and sleep quality, all techniques showed similar effects. The effectiveness of relaxation was lower, but not significantly, in the wake time after sleep onset. However relaxation was significantly less sleep “efficient” when compared to other interventions. It can be concluded therefore that relaxation may be the least effective behavioural intervention for the treatment of insomnia. However, the authors of the study show that the sleep efficiency results should be interpreted with caution given the small number of studies assessed in each behavioural group intervention, and that future RCTs should use sleep efficiency as an outcome variable, as this would clarify the results^101.

In addition to studying the efficacy of stimulus control and relaxation for the treatment of insomnia, recent studies demonstrated the efficacy of the sleep restriction, alone or in combination with stimulus control therapy. Although it is unusual to provide a patient with insomnia with a single cognitive or behavioural technique, to be able to measure the relative effectiveness of each component, the comparisons made indicate that the sleep restriction, alone or in combination with stimulus control therapy, is more effective than relaxation alone. This in turn is more effective than sleep hygiene alone^90,91.
Although there are various psychological interventions that have proven effective in the treatment of insomnia, there is a clear tendency on the part of researchers to conduct studies that use a combination of two or more techniques. A systematic review evaluating the efficacy of a CBT programme (which includes stimulus control, sleep restriction of time, cognitive restructuring and relaxation and sleep hygiene) compared well with the following: a control group (placebo or waiting list); those undergoing a single intervention, cognitive or behavioural; and a pharmacological treatment. Sleep hygiene was also included in all RCTs, except one. The outcome variables were sleep onset latency, wake time after sleep onset, sleep efficiency, total sleep time, total wake time and sleep quality. An at-home sleep log was used for assessment, questionnaires and scales. The interventions were administered by psychologists, except in one RCT review where nurses were used. The included studies showed that CBT combined with different behavioural techniques produced statistically significant changes in all outcome variables, in comparisons with simple interventions such as relaxation, sleep hygiene, medication and with a waiting list control group92.

When the effectiveness of CBT was evaluated against combined CBT treatments and medication or medication alone, there was evidence of the superiority of CBT and combination therapy compared to drug treatment alone. It also concluded there was a reduction of medication used in combination therapies, without which a deterioration in sleep, anxiety or depression would have been found, as these results were also statistically significant92,102.

Although the reason for the change in trend of researchers towards the use of multicomponent intervention programmes is not sufficiently clear, according to some studies it could be related to the idea of better treatment of chronic insomnia factors90,91.

There is little evidence on the optimal duration of psychological treatment. The reviews found suggest between 6, 8 and 10 weeks91,92. However, a subsequent RCT achieved different results103. For 8 weeks, the patients included in the study were assigned treatment of behavioural techniques lasting 1, 2, 4 or 8 sessions, or put on a waiting list. Interventions included sleep hygiene, stimulus control and sleep restriction. Evaluation was done by sleep diaries, questionnaires, and actigraphy. The outcome parameters were sleep onset latency, total sleep time, wake time after sleep onset, total wake time and sleep efficiency. There were also additional quality of life indicators obtained from questionnaires. A follow-up was also carried out at 6 months. It was assumed that the treatment given with 8 week sessions would be most effective, but the results showed that the 4 biweekly sessions given was the optimal treatment. The authors conclude therefore that the optimal duration of treatment with these techniques is 4 sessions fortnightly. The fortnightly frequency favours adherence to therapy, because it allows the patient to implement the guidelines learned and come across difficulties, which can be solved in future sessions103.
More RCTs are needed to determine the optimal duration of therapy, and to see if the maintenance of long-term therapy improves the efficacy results for insomnia.

As insomnia may be a recurring problem, it is important to assess the result of the interventions after the initial treatment. There are not many studies that have monitored the effectiveness of this type of long-term treatment. However, those that exist show good results with short-term behavioural interventions and CBT, which are maintained over a longer time period. These can reach up to 24 months after completion of therapy in studies which were monitored up to that point91,92,104,105.

There are reviews that assess the long-term effectiveness of behavioural and CBT interventions (with or without relaxation or sleep hygiene) in comparison with drug treatments (temazepam and zolpidem). The benefits obtained in results such as sleep onset latency and sleep efficiency for patients treated only with psychological interventions are maintained between 3 and 12 months afterwards. In those using medication only, effectiveness was only short-term (lasting no more than 3 months)20,91,92.

As there is a significant proportion of patients with chronic insomnia who still benefit from short-term therapy, they are vulnerable to recurrent episodes. Further studies are needed to assess both the long-term efficacy of this type of treatment and the maintenance techniques to prevent or minimise the recurrence of insomnia.

Most of the studies cited so far have considered behavioural and CBT interventions done individually. In cases assessing the effectiveness of CBT applied individually and in a group, they concluded that the two methods yield similar results regarding significant improvement of sleep and secondary parameters, with no differences in effectiveness between the two types76,91. However, there are trials that suggest that group therapy can be a cost-effective alternative compared to individual therapy, and that it provides an incentive for greater patient motivation in difficult techniques, such as sleep restriction and withdrawal of the medication91,106-108.

**Studies in the field of Primary Care**

With only one exception, as outlined in previous studies92, all interventions were carried out in Specialised Care by psychologists and psychiatrists, who implemented the CBT for insomnia, following the Morin intervention model. According to this model, the therapeutic goals are: reducing hyperarousal (somatic, cognitive and emotional), modifying poor sleeping habits and changing dysfunctional beliefs about sleep and insomnia50.

Studies on the use of psychological interventions and their effectiveness for insomnia in Primary Care are scarce and have methodological weaknesses. There is one study of the effectiveness of interventions with combined behavioural techniques compared to the total absence of treatment, over a programme of six group sessions conducted by trained nurses.
A significant decrease in sleep onset latency and wake time after sleep onset were observed in the psychological intervention group versus the control group. A follow-up one year later showed the effects of psychological therapy persisted, although no comparison was made with the control Group\textsuperscript{76,109}.

There was another comparison of effectiveness between a short form of CBT (2 sessions) with sleep hygiene advice among patients with chronic primary insomnia. CBT was significantly better than sleep hygiene in the follow-up three months after treatment. Nearly half of the patients who received CBT experienced at least a 50% decrease in wake time after sleep onset \textsuperscript{76,110}.

According to some authors, CBT interventions for insomnia that include stimulus control, sleep restriction, relaxation training, and paradoxical intention are still underused in PC. This is probably because they are slow and require medical staff training to be effective\textsuperscript{111,112}.

The proper implementation of psychological therapies usually requires more time than prescribing a hypnotic drug, which may represent a significant barrier to the use of such interventions in clinical practice. However, some interventions such as restricting time in bed and stimulus control require less time and can be implemented by PC practitioners. Some studies have reported benefits in terms of cost-effectiveness of implementing interventions carried out by trained nurses, in group therapy or with self-help materials to supplement intervention directed by a therapist (psychologist or psychiatrist). However, additional studies of the cost-effectiveness of different psychological interventions for insomnia are needed\textsuperscript{91,106-108,113}.

The treatment of insomnia with psychological interventions is based mainly on international studies, although some of these techniques can be performed in Spanish Primary Care. General Practitioners, nurses and social workers play an important role in the therapeutic management of insomnia in this first level of care. They can perform both individual and group approaches, using techniques that can be implemented provided that the practitioners have received the necessary training.

The general principles of psychological interventions have already been expressed as well as the importance of a professional attitude from the first interview. These PC interventions must be applied with some common features\textsuperscript{95}, differing from the usual support relationship found in PC, which can be summarised as follows:

- Structured: simple to learn and easy to apply
- Brief and with times established in the initial manual
- With specific goals, set after the evaluation
- Having a description of their effectiveness for treating the condition
Evidence on the treatment with behavioural therapy and cognitive behavioural therapy (CBT) for insomnia

Specialised Care

1++,1+ Behavioural techniques and CBT are effective in the treatment of primary chronic and secondary insomnia because they reduce the latency of sleep onset, and improve and maintain sleep throughout the night73.

1++,1+ Behavioural techniques and CBT are also effective for patients with insomnia associated with other diseases (medical conditions or mental disorders)91.

1++,1+ The most effective techniques for reducing sleep onset latency and the number of night time awakenings are stimulus control and sleep restriction73,75.

1++,1+ Relaxation seems to be the least effective intervention for the treatment of insomnia73.

1++,1+ The combination of several behavioural techniques has not proved more effective than stimulus control and sleep restriction alone73,91.

1++,1+ The revised CBT includes stimulus control, sleep restriction, relaxation and breathing, paradoxical intention and/or cognitive restructuring73,91.

1++,1+ Duration of the CBT in the studies varies between 4, 6 and 8 weeks. However, there is no evidence for the optimal duration of therapy nor for whether the maintenance of long-term therapy would improve effectiveness results for insomnia73,103.

1++,1+ The short-term efficacy achieved with behavioural interventions and CBT remains up to 24 months after completion of the therapy73,91,104,105.

1++,1+ With behavioural interventions and CBT alone, the benefits obtained in sleep onset latency and sleep efficiency are maintained from 3 to 12 months afterwards. However, the effectiveness achieved from medication (temazepam or zopiclid) lasts no more than 3 months73,92.

1++,1+ Behavioural and CBT interventions applied individually have a similar effect to group treatment for significant improvement in sleep and secondary parameters. However, it is suggested that group therapy can be more cost-effective, and may motivate patients more73,91,106-108.

Primary Care

1++,1+ There is evidence of the effectiveness of the implementation of behavioural interventions in PC, such as sleep restriction, stimulus control and relaxation73.

1+/1- Psychological interventions in a programme of six group sessions conducted by trained nurses compared with no treatment showed a significant decrease in sleep onset latency and wake time after sleep onset76,109.

1++,1+ Interventions carried out by trained nurses, group therapy or self-help materials to supplement intervention led by a therapist (psychologist or psychiatrist) have shown their benefit in terms of cost effectiveness. The sleep restriction and stimulus control can be implemented by professionals in PC73,104-108,113.

4 The following techniques could be used in PC to reduce symptoms associated with insomnia:
– Relaxation therapies: progressive relaxation training or breathing control
– Stimulus control techniques
– Sleep restriction
– Paradoxical intention
– Cognitive restructuring: replacing irrational or distorted thoughts with rational ones

4 The following common features were found in brief psychological interventions made in PC, individually or in groups, that achieved greater effectiveness85
• Carried out by trained practitioners
• Structured: simple to learn and easy to apply
• Brief and with times set in the initial manual
• With specific goals, set after the evaluation
• Describing their effectiveness in treating the clinical condition
7.4 Pharmacological interventions

Pharmacological treatment is an adjunctive measure in the comprehensive treatment model for insomnia. Before establishing drug therapy, the duration of the problem and the type of insomnia have to be taken into account73,76.

The selection of a drug for the treatment of insomnia is influenced by several factors: symptoms, treatment goals, responses to past treatment, patient preference, cost of the drug, availability of other treatments, comorbidity conditions, contraindications and interactions with other drugs and side effects74.

One goal of pharmacotherapy is to achieve a favourable balance between the potential therapeutic effects and side effects. The risk-benefit ratio of each drug used in the treatment of insomnia should be assessed bearing in mind: a) effectiveness, b) the development of tolerance, c) withdrawal symptoms; d) adverse reactions.

In addition, the individual characteristics of patients must be considered (personality and psychopathology). Certain personality types are predisposed to dependence on drugs or substances114. If this is the case, it must be considered as a contraindication for prescribing CNS depressants.

It is not uncommon for a patient who complains of chronic insomnia to be a chronic user of CNS depressants. Continued use of hypnotics should be avoided as far as possible, as there are studies that show there is an abuse of benzodiazepine prescriptions, and particularly so in PC in Spain115.
Between 23 - 25% of patients treated with benzodiazepines (BZDs) receive it because of insomnia. In 80% of cases, the first prescription was from the general practitioner, and the patient profile was mostly women over 65, 46% of whom had been under treatment for than a year\textsuperscript{115,116}. At these ages, the perception of the risks of the use of BZDs is lower in patients than practitioners\textsuperscript{117}.

In these cases, the gradual withdrawal of the drugs, or removing dependency, is a priority, and often requires the simultaneous use of non-pharmacological techniques (eg, cognitive behavioural therapy, standardised interviews with successive visits). These have proved successful in the Spanish PC\textsuperscript{118}. Appendix 10 includes a protocol for gradual withdrawal from BZDs proposed by the Spanish Agency of Medicines.

When drug therapy is the option best suited to the patient, it is important to follow up the intervention by checking for adverse effects, and to prevent long-term dependency by scheduling a drug reduction programme, as far as is possible. Although approximately one third of patients do not succeed in overcoming their addiction to hypnotics, it was seen that for those who took no medication for eight weeks, their insomnia and anxiety symptoms were less severe. They also had more positive perceptions of health and self effectiveness to avoid taking drugs in different situations. We must therefore take into account the problems arising from prolonged drug treatment\textsuperscript{119}.

Objective methods based on sleep polygraph records are chosen to study the effectiveness of different drug treatments, and they have clearly demonstrated their superiority over more subjective methods\textsuperscript{120}. One important aspect of effectiveness is their maintenance or loss over time for use on consecutive nights (or tolerance). Appendix 7 includes variables that are used to evaluate such effectiveness.

**Hypnotics**

Hypnotics used currently for the treatment of insomnia fall into two major groups according to their chemical structure: benzodiazepines and non-benzodiazepines. The latter in turn have three subgroups: cyclopyrrolones, imidazopyridines and pyrazolopyrimidines. Hypnotics are benzodiazepine receptor agonists (BRAs), and act on the GABA-benzodiazepine-receptor complex, although the different types act on different receptor subunits.

For about 30 years, the pharmacological treatment of insomnia has been dominated by the use of benzodiazepine hypnotics (BZDs). The most recent studies are based on the comparing the effectiveness of non-benzodiazepine drugs with BZDs.

**Benzodiazepines (BZDs)**

BZDs are nervous system depressants and promote mental and physical relaxation by reducing nerve activity in the brain (GABAergic action). They are a heterogeneous group of drugs with different chemical structures, pharmacokinetic properties and pharmacodynamic properties.

The chemical structure has two types: the 1,4 benzodiazepines and triazolobenzodiazepines. Both are different, as shown by the fact that there is no cross-tolerance between them and their different adverse reaction profiles. There are also marked differences in the pharmacokinetic and pharmacodynamic properties between them\textsuperscript{120}.
There have been no significant developments on the pharmacological characteristics of BZDs for about 20 years. Studies recommend their use only for occasional and short-term insomnia. At present, research is focused on the comparison of the effectiveness of this type of hypnotic with non-benzodiazepines\textsuperscript{73,74,76}.

There are several studies that assess either the effectiveness of the BZD or the benefits and risks of its use. Among these drugs are: flurazepam, estazolam, triazolam, quazepam, loprazolam, nitrazepam, midazolam, temazepam, flunitrazepam, brotizolam, diazepam and lorazepam. The comparison is with a placebo and the following outcome variables were used: sleep onset latency, number of nocturnal awakenings, total sleep time, sleep quality and daytime side effects (dizziness, drowsiness, numbness and weakening of daytime functions, such as memory). The evaluation is performed either by questionnaires and sleep diaries or by polysomnography\textsuperscript{73,76,121}.

Using the two types of evaluation, studies conclude that BZD versus placebo is more effective in the short term for sleep duration. The decrease in sleep onset latency is only seen in the subjective evaluation. Also, the importance of the side effects associated with these drugs should not be neglected. Further research could investigate the risk-benefit ratio of the treatments\textsuperscript{73,76,121}.

Side effects have been observed with the use of BZDs in relation to daytime drowsiness, headache, dizziness, nausea, fatigue and others. After 2 weeks of using a BZD, there is an increased risk of development of tolerance, physical and psychological dependence, and long-term use has been associated with increased risk of traffic accidents. In case of abrupt termination or stopping treatment, signs of withdrawal are produced. Moreover, effects such as memory loss and the risk of falls are also important as they mostly affect older people, who are major consumers of drugs and more sensitive to side effects. Clinically significant interactions with other drugs and with alcohol have also been reported\textsuperscript{20,75,76,122}.

As a unit, the drugs with a shorter half-life, greater power and a “triazolo” chemical structure (triazolam, brotizolam, estazolam and alprazolam) have a worse risk-benefit ratio. Triazolobenzodiazepines have certain pharmacodynamic properties, such as direct action on the noradrenergic system, increasing their potential to cause certain side effects\textsuperscript{123}.

Withdrawal symptoms are more likely and more intense with drugs of high potency and shorter half-life\textsuperscript{123}. These phenomena are associated both with dependency and the development of tolerance or loss of efficacy (the faster, the shorter the half-life, and the greater the affinity for the receptor/power).
Concern for BZD dependence has led to the following recommendations: the use of BZDs in the treatment of insomnia be restricted to acute insomnia only, treatment be done with the lowest dose possible for rapidly cleared drugs, those with a short half-life are not used and treatment to last for no more than 2-4 weeks73,74,124,125.

During pregnancy, there is insufficient evidence to determine whether the potential benefits for the mother offered by BZDs outweigh the potential risks to the foetus126-129. If they are needed to be used, the lowest effective dose of BZD for the shortest treatment time possible, and as monotherapy, should be adopted, to reduce the potential risk of birth defects. In advanced stages of pregnancy or during lactation, BZDs may cause adverse effects on newborns (neonatal hypotonia, withdrawal syndrome, sedation and hypothermia)130-133.

There are few studies on the long-term efficacy of these hypnotics. Some authors have studied the characteristics of long-term consumers of BZDs, as well as the perceptions and attitudes of patients and health practitioners. As for the perception of patients about the effectiveness of a drug, this was related to the choice on whether to continue or stop treatment, and this choice had been previously made. However, no conclusions could be drawn, due to the sample size, the methodological quality and subjective burden of the results73.

More RCTs are needed to assess the long term use of BZDs for insomniac patients.

**Non-benzodiazepines**

In the past 20 years, several drugs belonging to three chemical groups: cyclopyrrolones (zopiclone and eszopiclone), imidazopyridine (zolpidem) and pyrazolopyrimidine (zaleplon), have entered the market. These hypnotics were developed with the aim of overcoming some of the side effect disadvantages of BZDs, for example, next day sedation, dependence and the effects of drug withdrawal.

Although insomnia is often a chronic condition, the only non-benzodiazepine drug approved by the FDA (US Food and Drug Administration) for use without a specific time limit is Eszopiclone (this drug has not been approved in Spain, and so is not marketed). The other non-benzodiazepines have been approved for a limited use of 35 days or less20.

When evaluating the effectiveness and safety of non-benzodiazepine versus placebo, the outcome parameters used were: sleep onset latency, wake time after sleep onset, sleep efficiency and total sleep time. Evaluation methods used were polysomnography and sleep diaries.
Non-benzodiazepine hypnotics produced a significant improvement in the treatment of chronic insomnia in adults. The results obtained by sleep diaries were statistically significantly more favourable than those obtained with polysomnography. The results are related to the short-term treatment of insomnia. It also concluded that adverse effects were significantly higher in the drug group than in the placebo.\textsuperscript{134}

A meta-analysis evaluating the effectiveness for insomnia of non-benzodiazepine hypnotics (zolpidem, zopiclone, zaleplon) was performed. It made comparisons between them and with BZDs. The outcome variables were sleep onset latency, total sleep time, number of nocturnal awakenings, sleep quality and side effects, which may or may not be related to the central nervous system (vertigo, drowsiness, nervousness, dizziness, headache, fatigue and gastrointestinal problems).\textsuperscript{125,135}

In the comparison of the non-benzodiazepines among themselves, the effectiveness of zaleplon was higher than zolpidem for sleep onset latency, and zolpidem was more effective than zopiclone. Zolpidem was more effective than zaleplon for sleep quality and duration results, while zaleplon was best for lack of rebound insomnia.

Effectiveness outcomes depend on the characteristics of each drug. Zaleplon is absorbed and eliminated more quickly, this leads to poor sleep onset latency and no increase in sleep duration, when compared with zolpidem. The “best hypnotic” depends on what aspects of sleep are problematic for a patient: not being able to sleep or waking up several times. And because the differences among these drugs are so small in absolute terms, the advantage of zolpidem over zaleplon needs to be established from further studies.\textsuperscript{125,135}

The results from this review should be interpreted with caution. The capacity of this review to reach a conclusion is hampered by the limitations of the RCT data. It was difficult to properly quantify the differences in effectiveness between the various non-benzodiazepine hypnotics and to evaluate the clinical significance of any difference. Many studies included did not have a high methodological quality and had potential conflicts of interest, making it difficult for the meta-analysis authors to extract and compare the data to answer the review question.

More RCTs without the existence of potential conflicts of interest and with a minimum of four weeks to allow direct comparisons between these drugs are needed to reach reliable conclusions.
The adverse effects found for non-benzodiazepine hypnotics are: daytime drowsiness, dizziness, fatigue, headache, hallucinations, nausea, disorientation and confusion, anxiety or panic attacks, weakness, trembling, palpitations, and tachycardia. Some studies have also described rebound insomnia, withdrawal syndrome (at both supratherapeutic and normal doses) and the danger of dependence, especially after prolonged use. They are therefore recommended for short-term use, and must be monitored if used in the long term. As with BZDs, zopiclone was recognised as a potential replacement for alcohol in people addicted to it, even with standard daily doses. Therefore, it is recommended to be prescribed cautiously in patients with alcohol and/or drug abuse\textsuperscript{125,136}. No specific studies have been carried out during pregnancy. Some studies also suggest an increased risk of traffic accidents with the consumption of these drugs (zopiclone, zolpidem)\textsuperscript{137}.

The most recent studies with non-benzodiazepine hypnotics focused on other treatment regimens, such as intermittent use, use “on demand according to patient’s needs” and the slow-release formulation.

Among alternative regimens to the daily use of hypnotics for insomnia, there is the expectation that intermittent treatment for patients improves their quality of life by reducing the possibility of drug dependence, as they are the ones who control the drug and not vice versa. There are several RCTs, some of them in the context of PC, which evaluate the efficacy of zolpidem used intermittently as compared with daily. Most of the studies show statistically significant efficacy for intermittent administration and favourable risk-benefit ratio compared to placebo. However, the daily treatment has a greater efficacy\textsuperscript{138-140}.

There are studies conducted in the PC field regarding the administration of zolpidem “on demand according to patient’s needs”. Some of these used the drug on demand with the support of behavioural stimulus control for the days when the medication was not used. These RCTs however did not conclude any proven, statistically significant effectiveness for this alternative form of administration\textsuperscript{138,141}. Some patients who alternated stimulus control with the drug did, however, manage to improve their quality of life and reduce medication use\textsuperscript{141}.

More RCTs are needed, especially in the long term, to confirm any results for these discontinuous zolpidem administration regimens, both intermittent and on demand. Moreover, any favourable results with zolpidem may not apply to other hypnotics.
According to RCTs comparing the efficacy and safety of zolpidem extended release against placebo, this formulation demonstrated its effectiveness by decreasing sleep onset latency and increasing both sleep maintenance and daytime functioning. However, more RCTs without the potential conflicts of interest, both short and long term, are needed to provide reliable information and general findings142,143.

Benzodiazepines (BZDs) versus non-benzodiazepines

The aim of some reviews and meta-analyses was to compare the effectiveness and/or safety of BZDs in the treatment of insomnia with non-benzodiazepine hypnotics. The drugs studied include zolpidem, zopiclone, zaleplon, diazepam, loprazolam, lorazepam, temazepam, nitrazepam and lormetazepam. The outcome variables used were latency and total sleep time124,135.

The results of these RCTs do not currently give convincing evidence of a clinically useful difference between the use of the non-benzodiazepine hypnotics and BZDs studied124,135. From the standpoint of efficacy, side effects and potential for dependence or abuse, there is no evidence to suggest that if a patient does not respond to one of the families of these hypnotics, he will respond to another. So changing from one hypnotic to another does not seem a useful strategy to follow124.

Despite the lack of consistency found in the description of the side effects of BZDs and non-benzodiazepine hypnotics, included in these reviews, there are no statistically significant differences regarding rates of adverse events between both drug families. The side effects found for the two types of drugs were mainly: vertigo, drowsiness, nervousness, dizziness, headache, fatigue and gastrointestinal problems. Except for a lower risk of aggravation of conditions that involve breathing, clinical practice has shown that non-benzodiazepine hypnotics may have the same drawbacks as benzodiazepine hypnotics of similar pharmacokinetic characteristics.

Also, there were no differences when the residual effects the following day were compared124,125.

The most prominent case is that of zolpidem, whose clinical use has shown that is associated with unwanted side effects in a similar way to, for example, triazolam. Moreover, although some early studies reported no rebound insomnia, the data demonstrate its presence144-148. These examples suggest the need for independent studies with appropriate methodology.
Regarding abuse and dependence, it should be noted that the BZDs were often used with higher doses and over longer periods than would be recommended today. This contributed to the addiction that a large number of patients developed due to taking BZDs. By contrast, the use of non-benzodiazepines is more recent, when attitudes towards the use of hypnotics and sedatives in general have changed. They may therefore be less likely to be used for long periods, as BZDs were, and there is less information about their addictiveness. As a result, researchers propose restrictions on prescribing, and recommend they be used only on patients with disabling insomnia\textsuperscript{125,136}.

According to the authors of the studies, patients are not sufficiently informed about the risks of potential addiction associated with the use or widespread use of hypnotics. In many cases, patients are directly prescribed non-benzodiazepines or have their treatment changed from BZDs to non-BZDs. This is due to the perception that the probability of dependence is less with non-benzodiazepines than with BZDs. However, there is no evidence to support this assumption regarding dependence. Therefore, the increasing abuse of non-benzodiazepines can be added to the abuse of BZDs\textsuperscript{124}. More short and long term RCTs without potential conflicts of interest are needed to understand these adverse effects, and in turn to make comparisons between benzodiazepine and non-benzodiazepine hypnotics.

In the reviews carried out, non-benzodiazepine hypnotics have not proven cost-effective compared to BZDs\textsuperscript{124,125}. There are economic models submitted by a pharmaceutical company based on the premise that the use of a particular non-benzodiazepine when compared with the use of another or with a BZD prevents traffic accidents or hip fractures caused by falls. The conclusions of these models were not accepted because it was considered that the tests used lacked robustness and additional assumptions proposed were not appropriate. Furthermore, it was considered that there was no reliable evidence to support the idea that the superiority of the price of non-benzodiazepines would be offset by reductions in the use of other medical resources\textsuperscript{124}.

In summary, comparisons between benzodiazepines and non-benzodiazepine drugs do not provide convincing evidence of superiority, in terms of clinical utility, of one group over the other\textsuperscript{125,135}. This is true both in terms of effectiveness and risk. The conclusion is therefore that unless it appears that a patient has side effects directly related to a specific hypnotic, the cheapest drug must be used as opposed to a more expensive alternative\textsuperscript{124}.
Table 11 shows the benzodiazepine and non-benzodiazepine hypnotics with their approved indication in Spain for insomnia, chemical structure, elimination half-life and potency/affinity for the receptor.

**Table 11. Hypnotics approved for insomnia treatment**

<table>
<thead>
<tr>
<th>Family</th>
<th>Substance</th>
<th>Average half-life / hours</th>
<th>Dose equivalent to 5 mg of diazepam</th>
<th>Daily dose/ mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short</td>
<td>Midazolam</td>
<td>1-3</td>
<td>7.5</td>
<td>7.5-15</td>
</tr>
<tr>
<td>Triazolam</td>
<td>2-3</td>
<td>0.25</td>
<td>0.125-0.250</td>
<td></td>
</tr>
<tr>
<td><strong>Average half-life</strong></td>
<td>Brotizolam</td>
<td>3-8</td>
<td>0.5</td>
<td>0.125-0.5</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>Lormetazepam</td>
<td>9-15</td>
<td>1</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>3-13</td>
<td>1</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td><strong>Long</strong></td>
<td>Flurazepam</td>
<td>70-100</td>
<td>15</td>
<td>15-30</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>9-30</td>
<td>1</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Quazepam</td>
<td>40-55</td>
<td>15</td>
<td>7.5-15</td>
<td></td>
</tr>
<tr>
<td><strong>Non-benzodiazepines</strong></td>
<td>Imidazopyridines</td>
<td>1.5-3</td>
<td>2.5</td>
<td>5-10</td>
</tr>
<tr>
<td>Zolpidem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cyclopyrrolones</strong></td>
<td>Zopiclone</td>
<td>1.5-3</td>
<td>2</td>
<td>3.75-7.5</td>
</tr>
<tr>
<td><strong>Pyrazolopyrimidines</strong></td>
<td>Zaleplon</td>
<td>1</td>
<td>2.5</td>
<td>5-10</td>
</tr>
</tbody>
</table>


*There are many other benzodiazepines used as hypnotics, but they do not have the indication noted in their technical data, eg, lorazepam, diazepam, alprazolam.

Nitrazepam and temazepam are benzodiazepine hypnotics which are not marketed in Spain.

**Eszopiclone, authorised in the U.S. for chronic insomnia, is not available in Spain. Zaleplon, in the pyrazolopyrimidine family, is no longer available.

Table 12 summarises the main side effects reported with the use of hypnotics. These side effects or adverse reactions are of two basic types according to their predictability: expected and unexpected. The first is an extension of the therapeutic action of the drug, while the second is not expected by the doctor or patient and are often anti-therapeutic in action.

**Table 12. Most common adverse reactions to hypnotics**

<table>
<thead>
<tr>
<th>Expected*</th>
<th>Unexpected**</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CNS depression</td>
<td></td>
</tr>
<tr>
<td>- Excessive daytime sleepiness</td>
<td></td>
</tr>
<tr>
<td>- Impairment of psychomotor task performance (driving)</td>
<td></td>
</tr>
<tr>
<td>- Amnesia with maximum drug concentration</td>
<td></td>
</tr>
<tr>
<td>- Poor motor co-ordination</td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td></td>
</tr>
<tr>
<td>• Hyperexcitability</td>
<td></td>
</tr>
<tr>
<td>- Pre-awakening sleeplessness</td>
<td></td>
</tr>
<tr>
<td>- Daytime anxiety</td>
<td></td>
</tr>
<tr>
<td>• Amnesia the following day</td>
<td></td>
</tr>
<tr>
<td>• Psychiatric</td>
<td></td>
</tr>
<tr>
<td>- Confusion</td>
<td></td>
</tr>
<tr>
<td>- Psychotic symptoms</td>
<td></td>
</tr>
<tr>
<td>- Lack of inhibition</td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td></td>
</tr>
</tbody>
</table>

*Depend on the half-life, potency and dosage.

**Especially with drugs like triazolam and zolpidem.
There are two other aspects to be considered in the pharmacological treatment of insomnia: withdrawal symptoms or rebound phenomena, which occur when the drug is no longer used; and those that appear while the drug is still being used, or hyperexcitability phenomena. The latter occur in association with the development of tolerance. Table 13 summarises these phenomena.

**Table 13. Rebound/hyperexcitability phenomena**

<table>
<thead>
<tr>
<th>Rebound phenomena*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebound insomnia</td>
<td>– Significant increase in night time awakenings compared with baseline values.</td>
</tr>
<tr>
<td></td>
<td>– May occur after very short periods of use.</td>
</tr>
<tr>
<td>Rebound anxiety</td>
<td>– Analogous to rebound insomnia: increased anxiety.</td>
</tr>
<tr>
<td></td>
<td>– Appears in both hypnotics and sedatives (used at night and/or during the day).</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
<td>– In addition to aggravating initial symptoms (insomnia or anxiety), other symptoms appear: motor, sensory, vegetative, emotional, cognitive.</td>
</tr>
<tr>
<td></td>
<td>– Appear after prolonged use, at either therapeutic or supratherapeutic doses.</td>
</tr>
</tbody>
</table>

**Hyperexcitability phenomena**

<table>
<thead>
<tr>
<th>Hyperexcitability phenomena**</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early morning awakening insomnia</td>
<td>Significant increase in wakefulness in the final hours of the night, after one or two weeks of administration.</td>
</tr>
<tr>
<td>Daytime anxiety</td>
<td>Progressive increase in anxiety in the days after administration.</td>
</tr>
</tbody>
</table>

*These are more intense with more powerful drugs (benzodiazepines and non-benzodiazepines) and those with a shorter half-life. These can be the source of dependency.

**Appears with benzodiazepine and non-benzodiazepine drugs with short or very short half-life.

**Evidence for treatment with benzodiazepine and non-benzodiazepine hypnotics for insomnia**

**Benzodiazepine hypnotics**

<table>
<thead>
<tr>
<th>Effectiveness Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>++, ++</td>
<td>The benzodiazepine hypnotics flurazepam, triazolam, quazepam, loprazolam, midazolam, flunitrazepam, brotizolam, diazepam, lorazepam, nitrazepam, estazolam and temazepam have proven effective in sleep duration.</td>
</tr>
<tr>
<td>++, +</td>
<td>BZDs have greater short-term effectiveness compared with placebo for sleep duration and latency, but they also have more frequent side effects.</td>
</tr>
<tr>
<td>++, ++</td>
<td>There is no evidence for effectiveness in the long-term use of BZDs for insomnia.</td>
</tr>
<tr>
<td>+</td>
<td>BZD use is associated with an increased risk of daytime sleepiness, tolerance, traffic accidents, physical and psychological dependence, memory loss, fall hazards and effects after withdrawal, as well as interactions with other drugs and with alcohol.</td>
</tr>
</tbody>
</table>
Drugs with high potency, shorter half-life and “triazolo” chemical structure have a worse risk-benefit ratio. Withdrawal symptoms are more likely and more intense with drugs of a high potency and shorter half-life and, in turn, are associated with the development of tolerance and dependence.

During pregnancy, the evidence is insufficient to determine whether the potential benefits of BZDs for the mother outweigh the potential risks to the foetus.

There are adverse effects in newborns when prescribed in advanced stages of pregnancy or during lactation (neonatal hypotonia, withdrawal syndrome, sedation and hypothermia).

Non-Benzodiazepine hypnotics

- Non-benzodiazepine hypnotics zolpidem, zopiclone, zaleplon have proven short-term effectiveness in the treatment of insomnia.
- Non-benzodiazepine hypnotics show significant short-term improvement in the treatment of insomnia compared with placebo; with the results obtained from sleep diaries being more favourable than those obtained with polysomnography. Also, side effects were more frequent.
- There is no evidence for the long-term effectiveness of the use of non-benzodiazepines for insomnia.
- The use of non-benzodiazepines is associated with an increased risk of daytime sleepiness, dizziness, fatigue, headache, hallucinations, nausea, disorientation and confusion, anxiety or panic attacks, weakness, trembling, palpitations and tachycardia; as well as rebound insomnia, withdrawal syndrome, dependence and an increased risk of traffic accidents.
- Zolpidem used intermittently compared to daily use suggests a favourable risk-benefit ratio for discontinuous treatment. These results cannot be extended to other hypnotics.
- RCTs of zolpidem given “as needed” do not show any significant effectiveness for this alternative form of administration. Although patients alternating the drug with stimulus control managed to improve their quality of life and reduce medication use.
- Delayed-release zolpidem compared with placebo appears to decrease sleep onset latency and increase both sleep maintenance and daytime functioning, but more short and long-term RCTs are needed.

Benzodiazepines (BZDs) compared with non-benzodiazepines

- There are no clinically significant differences between the use of non-benzodiazepine and BZD hypnotics in the treatment of insomnia.
- There are no statistically significant differences between non-benzodiazepine and BZD hypnotics in side effects, including next day residual effects, abuse and dependence.
- There is no evidence (effectiveness, side effects, dependence or abuse) to suggest that if a patient does not respond to a family of hypnotics he may respond to another.
- Non-benzodiazepine hypnotics have not proven cost-effective compared to BZDs.

Recommendations on the treatment with benzodiazepine and non-benzodiazepine hypnotics for insomnia

- If hypnotics are to be used for treating insomnia, it is recommended that treatment is short-term (not more than four weeks) and at the lowest possible dose.
- Long-term use of hypnotics is not recommended. If doing so, it should always be monitored, with a diagnosis and at a specific regimen.
- To prevent dependence on BZDs, it is recommended that use be restricted to acute insomnia, at the lowest dose possible and for no longer than 2-4 weeks.
As first choice hypnotics for insomnia, either a benzodiazepine or non-benzodiazepine can be chosen, as no significant differences in clinical or adverse effects have been demonstrated between the two types. 

If a patient does not respond to treatment with a hypnotic, it is not recommended to change to another, unless there are side effects directly related to a specific hypnotic drug.

It is recommended to use the hypnotic which is most efficient and responsive for the patient, unless side effects directly related to the chosen hypnotic are observed.

If a BZD is needed during pregnancy, it should be used at the lowest effective dose and for the shortest time possible to avoid the risk of birth defects.

The new discontinuous zolpidem treatment regimens, either intermittent or on demand according to the patient's needs, supported by stimulus control techniques, can be used in the short term as an alternative to continuous dosing.

When prescribing hypnotics, patients should be informed of the therapeutic objectives, the duration of treatment and possible side effects, including tolerance and dependence problems associated with their use, as well as the lack of studies reporting long-term efficacy.

When prescribing hypnotics, the following parameters must be considered: age, previous treatment, tolerance, potential pregnancy, side effects, patient preferences and costs of equally effective choices.

Other medicines
Other drugs that may be considered in the treatment of insomnia are:

Antidepressants
Antidepressants with a sedative profile are the tricyclics (doxepin, trimipramine and amitriptyline), trazodone and mirtazapine. The sedative effects in the tricyclics appear to be associated with antihistamines and possibly with the antagonistic effects of the alpha-1 adrenergic receptor. In the trazodone, they seem to be related to the antagonism of 5-HT2 receptors and possibly the alpha-adrenergic (ref). Another possible mechanism of action in the case of trazodone, trimipramine and doxepin would be by reducing the hypercortisolaemia that chronic insomniacs have.

These drugs are used as hypnotics at lower doses than when used for the treatment of depression. Their use for the treatment of insomnia has grown substantially over the last ten years in some countries, which is striking if one considers that there are few objective studies in the sleep laboratory on the hypnotic effects of these drugs for insomnia.

Therefore, the frequency of use of antidepressants, their possible action on the pathophysiology of insomnia and the frequency of chronic insomniacs presenting anxiety and depression psychopathology, even at sub-threshold, mean the above studies are necessary.

Sedating antidepressants are used in the treatment of insomnia, however, they were not originally approved for this essential purpose. The most obvious indication for antidepressants in the treatment of insomnia is when it is a symptom of a depressive syndrome. This is so because there is little evidence of the effectiveness and safety of antidepressants for the treatment of insomnia which is not associated with depression disorders.
Trazodone:

Research with trazodone emerged in the 1990s and lasted for a decade with the expectation that it was one of the best pharmacological alternatives for the treatment of insomnia. The results of studies conducted mainly in patients with insomnia associated with depression, showed clinical improvements in parameters of sleep quality and number of nocturnal awakenings, but data related to latency, total sleep time and wake time after sleep onset failed to give statistically significant results.

Due to the scarcity of studies for insomnia not associated with depression, and because the doses used would be smaller than those for treating depression, no definitive conclusions can be drawn on the severity of side effects. These and others are associated with daytime sleepiness and “difficulty in awakening”. More RCTs are needed to evaluate the effectiveness of trazodone, both objectively and subjectively, to determine its efficacy in the treatment of insomnia not associated with depression\(^{50}\).

Doxepin:

Studies with doxepin have shown clinical improvement for the first nights, but there are no significant differences by the fourth week of treatment. Researchers have envisaged the possibility of using it for the treatment of acute insomnia, although more RCTs are needed for its short and long-term safety and effectiveness\(^{151-153}\).

Amitriptyline and mirtazapine:

The hypnotic and clinical efficacy of amitriptyline and mirtazapine for primary insomnia has not been investigated. Effectiveness data available for these drugs are for patients with psychiatric illness (mainly depression) and insomnia complaints. There is no evidence to support its use in acute and chronic insomnia\(^{154,155}\).

In short, studies of antidepressants in the treatment of insomnia are few, which together with their low methodological quality does not provide convincing evidence for the treatment of insomnia with these drugs. Researchers agree that although some antidepressants are known for their sedative effects, such as amitriptyline and trazodone, there is little information on their use for treating non-depressive insomnia\(^{154,155}\).

Moreover, due to the importance of their adverse effects, the use of antidepressants as sleep inducing agents, in the absence of symptoms of depression, remains a source of controversy. Therefore, taking into account their potential toxicity, the guidelines selected conclude that they should be reserved only for their more specific indication, depression\(^{73}\).
**Ramelteon**

Ramelteon is a synthetic receptor agonist of MT1 and MT2 melatonin. In 2005, the FDA (US Food and Drug Administration) approved its indication (with a recommended dose of 8 mg taken within 30 minutes of bedtime) for treatment of “insomnia characterised by difficulty in falling sleep”. However, the European Medicines Agency (EMEA) has not yet approved its use for Europe and has issued a negative opinion for its use as a hypnotic, due to the need for more studies to confirm efficacy and safety.

When evaluating the efficacy and safety obtained with ramelteon against placebo for the treatment of insomnia, there were small, but statistically significant, decreases in sleep onset latency for the drug, although with no clear clinical significance. The total time and sleep efficiency of sleep effects are less marked and were not reviewed.

Adverse effects associated with the use of ramelteon included headache, drowsiness, dizziness, fatigue and nausea. There were no significant rates for cognitive impairment, rebound insomnia, withdrawal effects or abuse.

More research without the existence of potential conflicts of interest and with a larger sample size is needed, to determine the clinical significance of the changes that have had significant results in RCTs conducted thus far. RCTs are also needed on the long-term use of ramelteon compared with other drugs to determine their relative efficacy for insomnia, compared with other pharmacological options.

**Others**

Other drugs that have been considered in the treatment of insomnia include:

**Gaboxadol:**

Gaboxadol is a selective GABA<sub>A</sub> agonist, and was originally developed in the 1970s as a possible anticonvulsant. It has shown some effectiveness in treating insomnia.

When evaluating the efficacy of gaboxadol (with different doses: 5, 10, 15 and 20mg) compared with placebo, the superiority of the drug was demonstrated for maintaining sleep, such as in wake time after sleep onset and total sleep time. The most effective dose turned out to be 20 mg. There were no significant improvements in regard to sleep onset latency.

Gaboxadol was generally well tolerated, although it was found that the incidence and severity of adverse effects were dependent on increasing the dose. The use of gaboxadol was not associated with residual effects the next day. The small sample size of the studies mean more RCTs are necessary to study both the short and long-term effectiveness of gaboxadol in the treatment of insomnia, and to establish the appropriate dose.

**Reviews of different types of studies**

\[1+, 1\-\]

**RCT 1+**

**RCT 1-**
Atypical antipsychotics and anticonvulsants:

The evidence for efficacy in the treatment of insomnia, (as well as potential side effects) of drugs like gabapentin, tiagabine, quetiapine and olanzapine is insufficient\(^75\).

**Not recommended**

Drugs such as chloral hydrate, meprobamate and barbiturates, approved by the FDA for insomnia, are not recommended, due to their low therapeutic index and significant adverse effects (which include the likelihood of tolerance and dependence)\(^75\).

### Evidence for other drugs in the treatment of insomnia

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1++,1+</strong></td>
<td>The effectiveness and safety of antidepressants for insomnia associated with depression disorders has been demonstrated(^73,78).</td>
</tr>
<tr>
<td><strong>1++,1+</strong></td>
<td>There is little evidence on the effectiveness and safety of antidepressants in the treatment of primary insomnia(^73,78).</td>
</tr>
<tr>
<td><strong>1+,1-</strong></td>
<td>Trazodone has shown efficacy in the clinical improvement of the quality of sleep and in the number of nocturnal awakenings in patients with insomnia. For latency, total time and wake time after sleep onset, no statistically significant results were found. More RCTs are needed to determine its efficacy in the treatment of insomnia not associated with depression(^15).</td>
</tr>
<tr>
<td><strong>1+,1-</strong></td>
<td>Doxepin has demonstrated some efficacy in the treatment of acute insomnia, but there are no significant differences by the fourth week of treatment. More RCTs are needed for short and long-term safety and effectiveness(^151,152).</td>
</tr>
<tr>
<td><strong>1+,1-</strong></td>
<td>There are insufficient studies to draw conclusions about the efficacy of amitriptyline and mirtazapine for the treatment of insomnia(^154,155).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ramelteon</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1+,1-</strong></td>
<td>Ramelteon compared to placebo has small but significant decreased sleep onset latency, but without clear clinical significance. The effects on total time and sleep efficiency of sleep are less marked(^157,158).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1++,1+</strong></td>
<td>There is insufficient evidence on the effectiveness (as well as potential side effects) of drugs such as gaboxadol, gabapentin, tiagabine, quetiapine and olanzapine(^75).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not recommended</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1++,1+</strong></td>
<td>There is evidence of low therapeutic index and significant adverse effects (most notably the likelihood of tolerance and dependence) in drugs like chloral hydrate, meprobamate and barbiturates(^75).</td>
</tr>
</tbody>
</table>
Recommendations for other drugs in the treatment of insomnia

<table>
<thead>
<tr>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>B  There is enough evidence to recommend the use of antidepressants for insomnia associated with depressive disorder, but not for primary insomnia.</td>
</tr>
<tr>
<td>B  There is insufficient evidence to recommend the use of trazodone and doxepin until results from long-term studies are obtained.</td>
</tr>
<tr>
<td>B  There is insufficient evidence to recommend the use of the antidepressants amitriptyline and mirtazapine in the treatment of insomnia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>B  More long-term comparative studies are needed to recommend the use of ramelteon in the treatment of insomnia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>B  The use of chloral hydrate, meprobamate and barbiturates are not recommended for the treatment of insomnia.</td>
</tr>
</tbody>
</table>

7.5 Other treatments

7.5.1 Melatonin

It has been suggested that exogenous melatonin can be used as a hypnotic, but this issue is controversial. Melatonin is a natural hormone produced by the pineal gland. Its nocturnal secretion and suppression during the day due to the effect of sunlight regulate the sleep-wake (chronobiotic) circadian rhythm. It is also associated with a hypnotic effect and increased sleep propensity. There are some substances such as tobacco, alcohol and some drugs that decrease the production of melatonin.

The secretion of melatonin decreases with age and may contribute, in part, to the etiology of sleep disorders of older people.

It is not currently commercially available in Spain, although its indication is approved for people over 55 years with insomnia.

There are two meta-analyses that suggest there is sufficient evidence to propose the use of melatonin as a hypnotic. One evaluates the safety and efficacy of melatonin compared to placebo for short-term treatment of insomnia. It included studies with patients with insomnia and sleep phase delay syndrome (SPDS). Among the results found was that there were no statistically significant differences in the parameter of wake time after sleep onset or the sleep efficiency, total time and quality of sleep. Melatonin did lead to a shortening of sleep onset latency in both types of patients, but this shortening was five times higher in patients with SPDS than those with insomnia, which suggests a more chronobiotic effect than hypnotic. The most common associated adverse effects were headache, pharyngitis, back pain and fatigue, although there were no differences between melatonin and placebo.\textsuperscript{161,162}
The second meta-analysis included studies with subjects ranging from healthy volunteers to patients with schizophrenia and insomnia, and patients with Alzheimer’s disease. The observed changes in sleep onset latency, sleep efficiency and total sleep time were clinically irrelevant\textsuperscript{163}.

As the results were based on a small number of studies, more research is needed in this area, with RCTs of greater sample size to determine the efficacy, withdrawal effects and adverse reactions of melatonin in patients with chronic insomnia, properly selected and belonging to various age groups. In addition, any appropriate dosages would need to be determined.

Some studies conducted in the PC field have focused on whether the use of melatonin may facilitate the discontinuation of BZDs in patients with insomnia. There were two RCTs where patients with insomnia had been taking a BZD (diazepam) for more than three months. The dose of benzodiazepine was gradually reduced over a fortnight and supplemented with melatonin or placebo. As the sample size of both studies was small and the mean dose of BZD used in the treatment group was low, the results were not conclusive in indicating whether melatonin is useful for stopping the use of BZDs\textsuperscript{164}.

More studies with larger samples taking into account the possible influence of dose on the facilitating effect of melatonin to stop the use of BZDs are required.

\textbf{Evidence for melatonin use in the treatment of insomnia}

\begin{center}
\begin{tabular}{|l|l|}
\hline
\textbf{1+} & Melatonin significantly decreased sleep onset latency, but not the parameters for wake time after sleep onset, sleep efficiency, total time and sleep quality\textsuperscript{161-163}. \\
\textbf{1+} & The usefulness of melatonin for the discontinuation of prolonged use of BZD has not been shown\textsuperscript{164}. \\
\hline
\end{tabular}
\end{center}

\textbf{Recommendations on treatment with melatonin for insomnia}

\begin{center}
\begin{tabular}{|l|l|}
\hline
\textbf{B} & There is insufficient evidence to recommend the use of melatonin in the treatment of insomnia until good quality methodological trials demonstrate its effectiveness. \\
\textbf{B} & There is not enough evidence to recommend the use of melatonin for the interruption of prolonged use of BZDs. \\
\hline
\end{tabular}
\end{center}

\subsection*{7.5.2 Acupuncture}

Acupuncture is a therapeutic procedure in which specific body areas (meridian points) are injected with fine needles. It is one of the main forms of treatment in traditional Chinese medicine.

Aside from traditional acupuncture with needles, other forms of acupuncture have been developed, including electroacupuncture, laser acupuncture, acupressure, auricular therapy and transcutaneous electrical nerve stimulation (TENS).
A review evaluating the efficacy and safety of acupuncture in people with insomnia was performed for various types of acupressure therapy, auricular magnetic seed acupuncture and transcutaneous electrical nerve stimulation (TENS). The review concluded that although the results of individual studies indicated that these acupuncture interventions could improve results for sleep quality, efficacy data on other outcome parameters such as latency, total sleep time, number of nocturnal awakenings, wake time after sleep onset, total wake time and sleep efficiency were inconsistent or not measured. A review of auricular therapy was performed to evaluate its effectiveness. The intervention compared well with western medicine (diazepam), placebo, and false auricular therapy. The review concluded that auricular acupuncture therapy is more effective than control treatments, manages to increase sleep maintenance (up to 6 hours more) and increases sleep efficiency. However, it also stressed that, due to the weak methodological quality of the RCTs and their short duration, more studies are needed to obtain definitive conclusions. Some studies have shown that acupuncture can be useful in the treatment of comorbid insomnia, associated with psychiatric or medical disorders, for example. So if standard treatments of pharmacotherapy, psychotherapy or a combination of the two are not effective for one type of secondary insomnia, patients could be referred for acupuncture intervention. There is very little information on adverse effects associated with the use of acupuncture. Only one trial of the reviews mentioned above includes an adequate description of adverse effects. These are usually types of pain, infections, inappropriate needle placement, tissue ischaemia or necrosis. Current evidence on the use of acupuncture is still not rigorous enough to allow conclusions about the extensive application of any form of acupuncture for the treatment of insomnia, from any cause and for any age group. Also, the long-term effects of acupuncture and/or its variants and their potential adverse effects are still not completely clear.

Randomised, double-blind, larger sample size RCTs of high quality and a longer follow-up are required, in addition to investigating the efficacy and safety of acupuncture for the treatment of insomnia.

### Evidence for acupuncture treatment for insomnia

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+,1-</td>
<td>There are no studies of sufficient methodological quality to draw conclusions about the efficacy or safety of acupuncture for the treatment of insomnia.</td>
</tr>
<tr>
<td>1+,1-</td>
<td>The long term effects of acupuncture and/or its variants are not known.</td>
</tr>
<tr>
<td>1-</td>
<td>Auricular acupuncture therapy appears effective in treating insomnia, increasing sleep maintenance (up to more than 6 hours) and sleep efficiency, however, more methodologically rigorous RCTs are needed.</td>
</tr>
<tr>
<td>1+</td>
<td>Acupuncture may be effective in the treatment of comorbid insomnia associated with psychiatric or medical disorders.</td>
</tr>
</tbody>
</table>
7.5.3. Herbal medicines

The use of herbal medicines to treat sleep disorders, including insomnia, is very old. Herbal medicines are popular, are used globally and could be considered a treatment option for insomnia if they were shown to be effective and safe. The healthcare practitioner must be able to acknowledge both the benefits and risks that these preparations have. This will prevent a rejectionist attitude that can lead patients concealing their use and masking possible adverse effects.

Valerian (Valeriana officinalis)

Valerian, for its attribution of sedative and sleep-inducing properties, is one of the most commonly used medicinal herbs for insomnia. It is used as a dried herb, extract or tincture.

Various reviews have investigated the effectiveness and safety of valerian for the treatment of sleep problems and insomnia. With a number of exceptions, comparing it with a BZD or another herb, the studies included in the review evaluated the effectiveness and safety of valerian compared to placebo\(^{167,168}\).

These reviews suggest that valerian may be effective in improving sleep quality, but the methodological problems of the studies limited the ability to draw firm conclusions about it. Valerian was found to be safe, with few reported side effects and, when they did appear, were no different from those associated with the use of placebo, and less than those associated with the use of BZDs\(^{168}\).

The reviews conclude that there is insufficient evidence to establish the effectiveness of valerian compared with placebo for treating insomnia. RCTs involving larger samples and comparing valerian with placebo or other interventions used for treating insomnia are needed. Also, those products on the market containing valerian need to be determined, as well as for the doses at which they may be effective.

Recent studies focused on evaluating the effectiveness of a combination of valerian with other plants. One RCT compared the administration at night for 28 days of two tablets of valerian combined with hops (Humulus lupulus L) against placebo. Both sleep outcome parameters and quality of life were assessed using sleep diaries and polysomnography\(^{169}\).

The study concluded that the combination of plants showed a greater (albeit modest) hypnotic effect than placebo; associating improved sleep above all with an increased quality of life. No significant secondary or residual effects were found, and no rebound insomnia was found after discontinuation. The treatment could be useful in cases of mild to moderate insomnia\(^{169}\).
Another RCT compared administration over 4 weeks of valerian, a valerian and hops combination and placebo. Both valerian preparations were superior to placebo, but only with the combination of plants was the superiority significant.

More RCTs of greater sample size to evaluate the sedative activity of this or other plant combinations are needed, however.

Other herbs:
Passion Flower (Passiflora incarnata L.), California poppy (Eschscholtzia californica Cham), lavender (Lavandula angustifolia Mill), melissa (Melissa officinalis L.), linden (Tilia cordata Mill).

These plants are often combined with other medicinal plants with sedative properties. In the review conducted for the preparation of this guide, however, no studies evaluating specific efficacy in insomnia of these herbal treatments were found.

### Evidence on herbal treatment for insomnia

| 1+,1- | There are insufficient studies to draw conclusions on the effectiveness of valerian for treating insomnia.

| 1+ | The combination of valerian and hops has demonstrated some efficacy in treating mild-moderate insomnia, however, RCTs with larger sample sizes are needed to confirm the results.

### Recommendations on treatment with herbal medicines for insomnia

| B | There is not enough evidence to recommend the use of valerian alone or in combination with hops for the treatment of insomnia.

| ✓ | Professionals should ask patients about any herbal product they are taking or have taken.

### 7.5.4 Self-help treatments

Self-help programmes can be an alternative for the treatment of insomnia in Primary Care. The alternatives currently used are those of bibliotherapy and support via programmes online.

### Bibliotherapy

Bibliotherapy is defined as the guided use of reading for therapeutic aims. It basically consists in the acquisition of knowledge and therapeutic practices by reading specific selected literature, recommended by the therapist. Manuals are used for this, which explain methods that are easy to learn and implement.

There are few studies evaluating the effectiveness of bibliotherapy for considering this type of self-help as an additional method and facilitator for the treatment of insomnia.
One RCT, however, compared three interventions: bibliotherapy alone based on CBT principles, bibliotherapy with consultation/weekly telephone follow-up and a waiting list control group. For 6 weeks, patients were sent a weekly treatment brochure, and half of them also received minimal professional follow-up via a weekly phone consultation of 15 minutes duration. During the same period, participants in the control group continued to monitor their sleep with sleep diaries. Participants who received bibliotherapy obtained significant improvement in the major outcome variables after treatment (total wake time and sleep efficiency). This improvement was enhanced in those with the telephone follow-up, although both treatments were comparable in the follow-up. The results suggest that bibliotherapy may be an effective approach for treating primary insomnia.[17]

On-line programmes

Self-help programmes on-line, based on the principles of CBT, may be a valid alternative for the treatment of insomnia in primary care. Recipients of this type of therapy may be patients with some kind of personal or geographic isolation with limited access to face-to-face psychological consultation, or people who have moved away or travel frequently. Alternatively, they may be individuals who are familiar with using the Internet and find that this gives them the freedom to control the time devoted to treatment and the advantage of anonymity.[113]

Self-help interventions via the Internet are similar to bibliotherapy programmes relying on telephone follow-up, however, the Internet has other advantages. It can provide support without having to keep telephone appointments, the therapist can save time by collecting previous questions and answers and setting up a Web page with frequently-asked questions, with answers, and treatment can be controlled time-wise to a regimen, with automatic advice.[113]

As happened with bibliotherapy, studies evaluating the effectiveness of self-help programmes via the Internet for the treatment of insomnia are scarce. One RCT evaluated such a programme, where the evaluation, treatment and monitoring were performed over the Internet. It compared a sleep management intervention based on the Morin manual, which included sleep restriction, stimulus control, sleep hygiene, cognitive restructuring, applied relaxation and/or information about withdrawal from medication, compared with a waiting list control group. The therapists were psychologists and the programme lasted 5 weeks, although all participants had previously filled in an at-home sleep log for two weeks as well as a series of different questionnaires.[113]

The premise was that self-help intervention via the Internet could be a potential alternative treatment for chronic insomnia. However, the control group, who only received information about the study and completed an at-home sleep log and questionnaires, also improved in most outcome parameters.

The study concluded that the Internet could serve as a means of psychological treatment of insomnia. However, further RCTs are required to investigate the effectiveness and efficiency of this novel form of self-help, as well as the possibilities of its implementation.[113]
Evidence on self-help treatment for insomnia

| 1+ | A self-help programme with bibliotherapy, based on CBT, with or without a weekly 15-minute telephone follow-up, proved effective in the treatment of patients with insomnia by reducing the total wake time and increasing sleep efficiency [17]. |
| 1+ | There is insufficient evidence to draw any conclusions about the effectiveness of on-line self-help programmes, based on CBT, for the treatment of insomnia [113]. |

Recommendations on self-help treatment for insomnia

B The application of bibliotherapy based on CBT principles via self-help manuals and guided by professionals is recommended in health centres

7.6 Treatment of the elderly

Therapeutic recommendations for the elderly with primary insomnia do not show marked differences with respect to the foregoing. However, it is also necessary to remember the features of sleep in the elderly (Table 4) and to make some special considerations.

As a general rule, the treatment of the elderly involves assessing a therapeutic level, and taking into account the possible diseases, both somatic and psychiatric, which often occur together within the same person. Also, the possibility of modifying lifestyle factors that may affect sleep quality need to be considered. Another factor not to be ignored is that many patients will be taking a number of drugs, so the contribution that some drugs have on the problem of insomnia must also be considered.

Psychological interventions:

The interventions of cognitive behavioural therapy (CBT), as presented in the previous paragraphs are also applicable to the treatment of insomnia in older people.

There are several reviews that assess the effectiveness of CBT in the quality, duration and sleep efficiency of sleep in people over 60 years. Outcome variables included in studies measure the difficulties in falling and staying sleep, the sleep efficiency and sleep onset latency, problems of delayed sleep and poor daytime functioning. The types of interventions were sleep hygiene, stimulus control, muscle relaxation, sleep restriction and cognitive therapies. Primary and secondary results, sleep quality and quality of life measurements were considered.

The conclusions of these studies show that the effectiveness achieved by treatment with CBT was lower in the elderly than that achieved in younger people, however, this treatment was still particularly beneficial in the short term. The effects, however, are not always long-lasting and, as already emphasised in previous sections, more long-term studies are needed [73,101,172].
After further analysis of the different outcome parameters included, the only clinically important improvement obtained is the wake time after sleep onset. Improvements were seen in latency and sleep maintenance, but they were not clinically significant and decreased over time. Sleep efficiency results also showed a modest benefit at first, but faded with time\textsuperscript{172}.

The most effective interventions are stimulus control (either individually or in a group) and the sleep restriction \textsuperscript{73,91,173}. Some studies emphasise the importance of sleep hygiene as an adjunct to these techniques\textsuperscript{73}.

A later RCT, taking into account the findings of the studies cited above, compared CBT with zopiclone for treatment of insomnia in older people. CBT was given by psychologists in individual weekly sessions of 50 minutes and included: sleep restriction, stimulus control, cognitive techniques, and progressive relaxation. The comparison was made against drug treatment of zopiclone or placebo. The duration of the intervention was 6 weeks with a follow-up of the active treatments at 6 months. Using sleep diaries and polysomnography, the parameters evaluated were total wake time, total sleep time, sleep efficiency and delayed sleep problems.

CBT showed a statistically significant clinical efficacy compared with zopiclone or placebo for sleep efficiency, delayed sleep problems and total wake time, both short and long-term. With polysomnography, there were no significant changes in effectiveness among the three treatments for total sleep time, but on the assessment made by the sleep diaries, participants showed greater improvement with CBT\textsuperscript{174}.

This study adds further evidence for the effectiveness of CBT in both the short and long term to treat insomnia in older people.

**Pharmacological treatment:**

Drug therapy for insomnia in the elderly should take into account a number of factors that can modify the response to these drugs. These factors can be summarised as follows:

- **Social and cultural:** A large number of the elderly manage their own medication. Circumstances associated with old age can affect compliance with treatment, such as memory loss, loss of vision, making it difficult for them to read the names of drugs, and hearing loss, which may impede their understanding of how to use the medication.

- **Comorbidity and polypharmacy:** The elderly suffer multiple conditions to a greater extent than the young, and tend to combine hypnotics with other substances. This association may be the cause of occurrence of interactions and side effects\textsuperscript{73}.

- **Pharmacodynamic changes:** These refer to the number of receptors for the drugs, once the special sensitive of the CNS to such substances has been objectified\textsuperscript{73}.

- **Pharmacokinetic changes:** The different phases of the drug through the body can be modified. Changes in absorption do not influence significantly. Changes in the liver result in a reduction of the effect of the first phase, increasing drug bioavailability. The distribution volume is determined by the degree of plasma protein binding and body composition, which in older people are modified. Hepatic metabolism and renal elimination are also slowed\textsuperscript{73,175,176}.
**Hypnotics:**

Given that hypnotics, and especially the BZDs, are the drugs most commonly used for older people with insomnia, all the changes mentioned above, may lead to drug accumulation and a resulting increase in adverse effects. Especially those linked to a loss of balance and increased risk of falls and fractures.\(^{73,177-180}\)

There is little evidence to quantify and compare the potential benefits and risks of using hypnotics for patients over 60 years. A meta-analysis confirmed that the drugs are significantly superior to placebo, although their effect is very small. However, at the same time, adverse effects are significantly higher in the group of patients with drug treatment than for placebo. The conclusion is, therefore, that the risk-benefit ratio for treatment with hypnotics is unfavourable.\(^{180}\)

However, it is difficult to draw conclusions from this study due to its methodological limitations: the heterogeneity in terms of half-life, the strength and dosage of hypnotics grouped in the meta-analysis, the difference in outcome measures used and lack of homogeneity of patient characteristics.

There is insufficient information on the comparison between the use of benzodiazepine and non-benzodiazepine hypnotics in older people. A review clarifies that the non-benzodiazepine are safer because they do not seem to cause a deterioration in daytime performance according to cognitive and psychomotor tests, and their interruption does not cause rebound insomnia, agitation or anxiety. However, more RCTs with good quality methodology are needed, to make comparisons between the two families of drugs.\(^{134}\)

**Antidepressants:**

Studies are needed to be carried out in patients with insomnia not associated with depression regarding the use of antidepressants such as trazodone, mirtazapine, and escitalopram.\(^ {73,75}\)

Regarding trimipramine, the lack of methodological quality of studies carried out does not allow any meaningful conclusion for its effectiveness.\(^ {181}\)

**Clomethiazole:**

Although the use of clomethiazole is indicated for adults with insomnia by the Spanish Drug Agency, there are insufficient studies to reach conclusions about the effectiveness of this drug in the treatment of insomnia for this group of people.\(^ {182}\)
Other drugs:

Because of their significant adverse effects, other drugs such as barbiturates and antipsychotics are not recommended, especially in the elderly. The same applies to some antihistamines such as diphenhydramine, hydroxyzine, doxylamine which, although they have hypnotic properties, are not recommended for elderly patients due to their strong anticholinergic action.

Moreover, there are some internationally accepted expert consensus criteria (Delphi modifiers) for the use of medication in the elderly, known under the name of the “Beers criteria”. These describe the drugs whose use would be potentially inappropriate in the elderly. The criteria have been used during the last decade for their usefulness in reducing problems associated with drug treatment in the elderly. After updating, the inappropriate drugs for older people with insomnia are listed in Table 14. It outlines the drug, the reason its use is inappropriate, and a severity index if it is used.

Table 14. Updated Beers criteria, for potentially inappropriate drug use in the elderly with insomnia, regardless of diagnosis or condition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concern</th>
<th>Severity Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long half-life benzodiazepines</td>
<td>Possibility of prolonged sedation and increased risk of falls and fractures.</td>
<td>High</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>This benzodiazepine hypnotic has extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fractures.</td>
<td>High</td>
</tr>
<tr>
<td>Doses of short-acting benzodiazepines:</td>
<td>Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.</td>
<td>High</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients.</td>
<td>High</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients.</td>
<td>High</td>
</tr>
<tr>
<td>Anticholinergics and antihistamines:</td>
<td>All nonprescription and many prescription antihistamines may have potent anticholinergic properties. Diphenhydramine may cause confusion and sedation. Should not be used as a hypnotic, and when used to treat emergency allergic reactions, it should be used in the smallest possible dose.</td>
<td>High</td>
</tr>
</tbody>
</table>

Modified from Fick et al
In a Dutch observational case-control study, the clinical value of the Beers criteria for the use of BZDs was investigated; and, in particular, an observational association between inappropriate use and risk of fracture. The results suggest that the inappropriate use of BZDs according to the Beers criteria is not associated with increased risk of fracture. There was, however, a greater risk with the use of high doses and in treatments exceeding 14 days.\textsuperscript{184}

There are two RCTs that evaluate the effectiveness of various methods of BZD drug treatment interruption in patients over 60 with insomnia. The methods compared were: gradual reduction of the drug, CBT and a combination of the two methods. The average age of people included in the studies was relatively low (63-67 years). Both RCTs concluded that the practice of gradual reduction of the drug in combination with CBT is more effective in helping people over 60 with insomnia to reduce or stop their consumption of BZDs. More RCTs with older patients and a placebo group are needed before any formal conclusions can be drawn.\textsuperscript{185,186}

In the process of discontinuation of hypnotics in older people, questions such as the following should be considered: the role that patient motivation takes in minimising the problems (side effects) associated with these drugs; and the overstatement, on the part of physicians, of the difficulties that withdrawal of the drug can lead to.\textsuperscript{187}

The French National Health Authority (HAS) prepared a programme with global and cross-actions for reducing the consumption of prescription hypnotics in older people. It was proposed from an improvement in the diagnosis of sleep problems (including insomnia) for reduction and interruption of the consumption of these drugs.\textsuperscript{188}

Other treatments:

\textit{Melatonin:}

There are other types of treatment evaluating the effectiveness of treating insomnia in the elderly.

There were reviews that tried to assess the effectiveness of melatonin in older people with insomnia, whose endogenous melatonin levels were lower. The results obtained (significant reductions in sleep onset latency, but no change in sleep maintenance) suggest that treatment with melatonin may be effective for these patients. However, the review opined that more conclusive RCTs of a larger sample size were needed.\textsuperscript{189}

A more recent RCT, with patients aged 55 or older, diagnosed with primary insomnia according to DSM-IV, excluded patients with insomnia associated with other sleep disorders or other pathologies. The study compared the effectiveness and safety of slow-release melatonin against pla-
cebo. Patients were divided into two groups according to the severity of their insomnia. The study lasted seven weeks, with three weeks of a nocturnal use treatment diary. The results showed that melatonin administration improves the quality of sleep, as well as daytime sleepiness indices compared with placebo. This improvement was statistically significantly more pronounced in the most serious group190.

There was no significant evidence of rebound insomnia or withdrawal effects after discontinuation of the treatment. The study concluded therefore that melatonin may prove to be effective and safe for the elderly with primary insomnia190.

Currently, in Spain, melatonin has been approved for use in people over 55 years with insomnia. However, it is not yet commercially available.

**Physical exercise:**

Some recent research was done based on the assumption that physical exercise may have benefits for sleep problems. It concerned anxiolytic (anti-anxiety) and antidepressant effects, and their role in the changing circadian cycle.

There was a review that evaluated the effectiveness of active participation in exercise programmes designed for patients over 60 years of age with sleep problems. Only one trial was found, with 43 patients over 60 with insomnia. It compared endurance training with moderate exercise (4 weekly sessions of 30-40 minutes, with gentle aerobic exercise and a brisk walk) with a control group waiting list, and lasted 16 weeks.

Significant results were obtained for latency, duration and sleep quality and a slight improvement in the sleep efficiency parameter. The review concluded that due to the small sample size, the results could not be generalised, pointing to the need for future research191.

**Bright light therapy:**

Another technique evaluated was treatment with bright light therapy. There was a review that evaluated the effectiveness of this intervention in improving the quality of sleep in adults over 60 years. In fact, the RCTs reviewed did not meet the criteria for inclusion of patients with primary insomnia, because they were for patients with other disorders like dementia (including Alzheimer’s) and depression. For these patients, treatment with bright light therapy was effective in synchronising uneven sleep timing and reducing the frequency of behavioural disorders27.

Considering the lack of evidence, the review concluded that bright light therapy treatments could not be recommended for the treatment of sleep problems among older adults without associated pathology. However, in view of the promising results obtained with other disorders, it concluded that future research in patients with primary insomnia was justified27.
A subsequent RCT evaluating the efficacy of bright light therapy for sleep onset problems in older persons with insomnia compared daily exposures of 10,000 lux intensity for 60 days, for either 20 minutes or 45 minutes. An assessment of the results was made after 3 and 6 months of treatment. The results showed a significant and lasting improvement for the parameters of latency and total sleep time in the 45-minute group. However, the methodological quality of the trial, with no control group, as well as the finding that the effects obtained did not necessarily result from the therapy, require the implementation of more RCTs to recommend this treatment192.

### Evidence on the treatment of insomnia in the elderly

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1++,1+</td>
<td>The effectiveness of behavioural therapy and CBT techniques for the elderly in the short term is demonstrated, although the benefits achieved are lower than those achieved in younger persons. Long-term studies are required113,122.</td>
</tr>
<tr>
<td>1++,1+</td>
<td>The best results with behavioural techniques and CBT are obtained for wake time after sleep onset, followed by latency, sleep maintenance and sleep efficiency. However, they diminish over time122.</td>
</tr>
<tr>
<td>1++,1+</td>
<td>The most effective behavioural and CBT interventions for the elderly are stimulus control (individually or in a group) and sleep restriction. Sleep hygiene is important as an adjunct to these techniques113,121.</td>
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<tr>
<td>1++</td>
<td>Compared with zopiclone or placebo, CBT showed statistically significant clinical efficacy for sleep efficiency, delayed sleep problems and total wake time, both short and long-term112.</td>
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<tr>
<td>1+</td>
<td>For older people, adverse effects of hypnotics compared with placebo, outweigh the benefits. The risk-benefit ratio is unfavourable for treatment with hypnotics114.</td>
</tr>
<tr>
<td>1+</td>
<td>There is insufficient information on the comparison between the use of benzodiazepine and non-benzodiazepine hypnotics in older people114.</td>
</tr>
<tr>
<td>1+</td>
<td>Studies are needed in older patients with insomnia not associated with depression, to demonstrate the efficacy of antidepressants such as trazodone, mirtazapine and escitalopram73,75.</td>
</tr>
<tr>
<td>4</td>
<td>Studies are needed for the use of clomethiazole to demonstrate efficacy in the treatment of insomnia for older people182.</td>
</tr>
<tr>
<td>1+</td>
<td>The treatment in older persons of barbiturates, antipsychotics, and certain antihistamines, such as diphenhydramine, hydroxyzine, and doxylamine, has significant adverse effects122.</td>
</tr>
<tr>
<td>1+</td>
<td>The practice of gradually reducing hypnotics combined with CBT is the most effective way to help people over 60 with insomnia to reduce or stop consumption of BZDs. More RCTs are needed with older patients and a placebo group to reach conclusions113,115.</td>
</tr>
<tr>
<td>1+</td>
<td>Slow-release melatonin is safe and effective (improving sleep quality and daytime sleepiness rates) for people of 55 or older with primary insomnia182.</td>
</tr>
<tr>
<td>1+</td>
<td>Participation in physical exercise programmes is effective for latency, duration, sleep quality and sleep efficiency. However, RCTs, with larger sample sizes are needed to draw conclusions191.</td>
</tr>
<tr>
<td>1+/1-</td>
<td>The use of bright light therapy appears effective in latency and total sleep time. However, more methodologically rigorous RCTs are needed in older patients with insomnia which is not associated with other pathologies27,182.</td>
</tr>
</tbody>
</table>
**Recommendations on the treatment of insomnia in the elderly**

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<table>
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<tbody>
<tr>
<td>✓</td>
<td>Any concurrent conditions, the possibility of modification of lifestyle factors affecting sleep quality and the contribution that some drugs can have on insomnia must first be taken into account.</td>
</tr>
<tr>
<td>✓</td>
<td>The use of hypnotics in older people is generally not recommended, due to the unfavourable risk/benefit ratio.</td>
</tr>
<tr>
<td>✓</td>
<td>There is insufficient evidence to recommend the use of clomethiazole in the treatment of insomnia in older people.</td>
</tr>
<tr>
<td>✓</td>
<td>When prescribing any hypnotic in the elderly, it is recommended to start with half the usual adult dose.</td>
</tr>
<tr>
<td>✓</td>
<td>Slow-release melatonin* may be used in patients aged 55 or over with primary insomnia, as it improves sleep quality and daytime sleepiness.</td>
</tr>
</tbody>
</table>

* Melatonin is approved for use in Spain for people over 55 with insomnia, however, it is not commercially available.

**Either behaviour therapy or cognitive behavioural therapy (CBT) is recommended in older people with insomnia; especially stimulus control and sleep restriction, supported with sleep hygiene education**

**The use of hypnotics in older people is generally not recommended, due to the unfavourable risk/benefit ratio.**

**There is enough evidence to recommend the use of antidepressants for insomnia associated with depressive disorder, but not for primary insomnia.**

**The use of barbiturates, antipsychotics or antihistamines, such as diphenhydramine, hydroxyzine, and doxylamine, is not recommended for older people with insomnia.**

**For elderly long-term users of hypnotics, a gradual reduction of the drug combined with CBT is recommended, to help slow or stop the consumption of BZDs.**

**More long-term comparative studies are needed to generalise the use of exercise in the treatment of elderly patients with insomnia.**