Universitat de Girona

A COMPARATIVE STUDY ON THE EFFICACY OF AN EDUCATIONAL AND BEHAVIOURAL INTERVENTION FOR THE WITHDRAWAL OF LONG-TERM HYPNOTICS

A RANDOMIZED CONTROLLED CLINICAL TRIAL

FINAL DEGREE PROJECT
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ABBREVIATIONS

BZD: Benzodiazepines

BZRA: Benzodiazepine receptor agonist

EEG: Electroencephalogram

EMG: Electromyogram

EOG: Electrooculogram

NREM: Non-rapid eye movement

REM: Rapid eye movement

MnPO: Median preoptic area

VLPO: ventrolateral preoptic area

GABA: γ-aminobutyric acid

EES: Epworth Sleepiness Scale

ISI: Insomnia Severity Index

PSQI: Pittsburgh Sleep Quality Index

CBT-I: Cognitive behavioural therapy for insomnia

BTIs: Brief therapies for insomnia

CNS: Central nervous system

DSM-V: Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition)

ICSD-3: International Classification of Sleep Disorders 3

SL: Sleep latency

WASO: Wake time after sleep onset

TST: Total sleep time

TIB: Time in bed

PMR: Progressive muscle relaxation

ICS: Institut Català de la Salut

IAS: Institut d'Assistència Sanitària

BHA: Basic Health Area

BAU: Basic Assistance Unit

GP: General practitioner

PCC: Primary care centre

SIAP: Sistema d'Informació d'Atenció Primària

CEI: Ethics Committee of Investigation

ABSTRACT

Background: Long-term use of hypnotics, for the treatment of chronic insomnia, has increased in the last decades. This fact constitutes a health problem due to a chronic use of hypnotics do not present a favourable risk-benefits relation. First, there is no evidence of them being beneficial when the treatment lasts more than 4 weeks. And second, the use of a hypnotic, as almost all pharmacological treatment, implies a risk of side effects (such as daily somnolence, tolerance, dependence and increased risk of dementia, falling and bone fractures) that increases as long is the treatment.

Objective: To compare the efficacy of an educational and behavioural group intervention in contrast to a written educative intervention, at primary care, on the withdrawal of long-term hypnotics.

Design: A multicentre, randomized, parallel group, comparator-controlled clinical trial conducted in the 4 basic health areas of Girona.

Participants: Adults between 18 and 85 years old, living in Girona, under a daily treatment with hypnotics during a period of 6 or more weeks. A total of 100 patients will be recruited from each basic health area using a simple random sampling.

Intervention: First, participants will receive an educational and behavioural intervention or a written educative intervention, which will be randomly allocated by basic health areas. Then, all participants will be subjects of an evaluation of their stage on the Prochaska and DiClemente model, in order to decide whether a gradual tapering plan of hypnotics is offered to them.

Keywords: Long-term, hypnotics, withdrawal, educational and behavioural intervention

INTRODUCTION

BACKGROUND

Sleep physiology

Sleep is a low consciousness physiological state (1) that alternates with wakefulness, making the sleep-wake cycle which is one of human circadian rhythms.

The features (2) of this state are: being rapidly reversible, having a reduced arousal (the environmental stimulus response is reduced) and being subjected to a homeostatic regulation.

Sleep phases

Polysomnography is a test, based on a combination of electroencephalogram (EEG), electromyogram (EMG) and electroculogram (EOG), which allow for distinguishing two types of sleep (1):

- NREM sleep

  Non-rapid eyes movement sleep, also known as slow wave sleep, is characterized for high voltage cerebral waves and slow frequency, slow eye movements and the tonic activity on EMG (3).

  NREM sleep is composed of 3 stages with defined EEG patterns (1):

  -Phase I: It's transitory phase between wakefulness and sleep and usually doesn't take more than 7 min. Phase I is characterized for theta waves (4-6 Hz) predominance with a reduction of alpha waves (Wakefulness typical waves) in the EEG, a modest reduction of tonic activity in the EMG and presence of slow eyes movements in the EOG.

  In this phase, sleep can be easily interrupted and also, its duration increases when a person has a fragmented sleep.

  -Phase II: Represents 50% of sleep time in healthy adults. The EEG presents a low voltage and frequency basal activity combined with **sleep spindles** (High frequency and short duration waves) and **K-complexes** (Slow biphasic waves with high voltage). There is lower tonic activity and eye movements are unusual.

  -Phase δ or delta: Represents 15-25% of sleep time and it is the phase in which deep sleep is achieved. This phase presents slow waves (Frequency $\leq$ 2 Hz) with high amplitude in the EEG and low tonic activity in the EMG.

- REM sleep

  REM sleep represents 20-25% of sleep time and consists of short duration episodes (Between 5 to 30 min), every 90 minutes on average, which length increases gradually as the night moves forward (1,3)

  Polysomnography characteristics are: low voltage activity with the presence of sawtooth waves (Normally appear temporally close to eyes movements) in the EEG, episodes of rapid eye movements in EOG and generalized muscular atony in EMG.

  Also, REM sleep has vegetative changes such as pulse increase, hypopneas and apnoea, blood pressure increase and/or penile tumescence (1).

Sleep architecture

Sleep has a cyclic structure in which NREM and REM sleep alternate.

In healthy adults, the NREM sleep predominates at the first half of the sleep, whereas, in the second half, REM periods become longer. The phase sequence of every cycle use to be: phase I, as the initial phase, followed by phase II and after, phase δ. Then, phase II reappears and it is continued by a REM period (1).

However, the different phases of sleep change with age. In neonates, REM sleep represents 50% of the sleep and they don't have phase δ. Then, as they have grown up, there is an increase of NREM sleep (which causes a reduction of REM time) until childhood when phase δ has the longest duration. Finally, at an elderly age, NREM sleep is only constituted by the phase I (which tends to become longer and this change is related to sleep quality worsening) and the phase II. In relation with REM sleep, it stays without changes in comparison to adult sleep (1).

Sleep neurophysiology

Sleep is regulated by interaction between wake and sleep brain networks. The main wake-promoting systems are the ascending reticular activating system (with a tonic cortex stimulation), limbic network (which reinforces the stimulation system by suppressing the sleep promoting areas) and cognitive systems. Therefore, sleep initiates when the GABAergic neurons of the ventrolateral preoptic area (VLPO) and median preoptic area (MnPO) of hypothalamus inhibit the stimulation systems, and concludes with activation of arousal centres (4).

Basing on Borbely model, the activity of wake and sleep centres is regulated by 2 physiologic processes: process S, which is wake-dependent, and process C, a circadian rhythmicity that is wake-independent.

Process S stipulates that sleep need increases with the wakefulness time. In contrast, circadian sleep propensity (Process C) depends on the intrinsic circadian oscillations, regulated by suprachiasmatic nucleus, influenced by melatonin, social factors and exogenous light (1,2,4).

Sleep disorders classification

Based on the 3rd edition of the International Classification of Sleep Disorders (ICSD-3), published by the American Academy of Sleep Medicine in cooperation with other international sleep societies, sleep disorders can be classified in 7 major categories (5): Insomnia, Sleep-related breathing disorders, Central disorders of hypersomnolence, Circadian rhythm sleep-wake disorders, Parasomnias, Sleep-related movement disorders and Other sleep disorders.

Insomnia

Insomnia is defined as persistent difficulties on the sleep initiate or maintenance, early morning awakening, or nonrestorative sleep associated with impaired daytime functioning, such as fatigue, mood disturbance, social dysfunction or impaired cognitive functions (4,6–9).

The most important diagnostic criteria's for chronic insomnia is ICSD-3, shown in Table 1, and DSM-V, shown in Table 2.

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.

B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the night-time sleep difficulty:
    1. Fatigue/malaise.
    2. Attention, concentration or memory impairment.
    3. Impaired social, family, occupational or academic performance.
    4. Mood disturbance/ irritability.
    5. Daytime sleepiness.
    6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression).
    7. Reduced motivation/ energy/ initiative.
    8. Proneness for errors/ accidents.
    9. Concerns about or dissatisfaction with sleep.
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep.
D. The sleep disturbance and associated daytime symptoms occur at least three times per week.
E. The sleep disturbance and associated daytime symptoms have been present fort at least 3 months.
F. The sleep/ wake difficulty is not better explained by another sleep disorder.

Table 1. Diagnostic criteria for chronic insomnia according to ICSD-3 (6)

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms:
    1. Difficulty initiating sleep.
    2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.
    3. Early-morning awakening with inability to return to sleep.
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning.
C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

E. The sleep difficulty occurs despite adequate opportunity for sleep.

F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g. narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).

G. The insomnia is not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication).

H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specify if:

With non-sleep disorder mental comorbidity, including substance use disorders

With other medical comorbidity

With other sleep disorder

Specify if

Episodic: Symptoms last at least 1 month but less than 3 months.

Persistent: Symptoms last 3 months or longer.

Recurrent: Two (or more) episodes within the space of 1 year.

Table 2. Diagnostic criteria for insomnia disorder according to DSM-V (10)

Classification

Insomnia disorder, according to ICSD-3, can be classified in (5):

- Short -term insomnia disorder: Insomnia lasts less than 3 months. It's very frequent and not always needs a specific treatment (6).
- Chronic insomnia disorder: Insomnia that occurs at least 3 times per week during 3 or more months.
- Other insomnia

Epidemiology

The prevalence of the chronic insomnia disorder in high income countries oscillates between 6% to 10% of adults (6,7). The main risk factors are female sex, increasing age, medical or psychiatric comorbid, low socioeconomic status and low quality of life (QOL) (6,7,10,11).

In Europe, the prevalence varies from 5.7% in Germany to 19% in France (6). In Spain, there was a 6.4% of insomnia diagnosis at 2010 (12).

Insomnia symptoms affect 33-55% of the adult population and the most frequent symptom is the difficulty maintaining sleep (11). However, it reduces to 10-15% if we look for those who insomnia symptoms cause an impaired daytime functioning (7).

In the recent years, it has been an increase in prevalence of insomnia and in the use of hypnotic agents (6).

Finally, short term insomnia prevalence in United States adults is approximately of 9.5%, but 1 in 5 cases become chronic (11).

Aetiology and pathophysiology

Insomnia aetiology is explained by the "3P model of insomnia" by Spielman (6). It describes three types of factors that contribute to the development and maintenance of insomnia (4,6,11):

- Predisposing factors: They are those factors than make an individual more susceptible to insomnia, including age, sex, genetic or personality traits, etc.
- Precipitating factors: It refers to those factors that trigger insomnia, usually major stressors (such as traumatic events, unemployment, divorce, a new relevant medical diagnosis…)
- Perpetuating factors: They are behaviours, thoughts or adaptation strategies that maintain insomnia after the triggers are solved. For example, extending time in bed, daily napping…

The pathophysiology insomnia is explained by two processes, which can appear individually or combined: the neurophysiology hyperarousal and the psychological and behavioural processes (4).

The hyperarousal model establishes that insomnia is a disorder caused by an excessive activation of the wake promoting systems. So, the arousal levels of cognitive, emotional and physiological networks are increased. The basis of this model is that patients with insomnia show major voltage on fast EEG frequencies during NREM sleep (4,6).

The cognitive model emphasises the relevance of worry intrusive thoughts in patients with insomnia, especially about not getting enough sleep and their consequences. This could lead into a sleep-related anxiety that aggravates the sleep disruption. Also, in the

behavioural field of insomnia, the presence of inadequate sleep-promoting stimuli have an important role (4).

Finally, in a subgroup of individuals such as blind patient or undertake shift work, circadian factors are relevant (6).

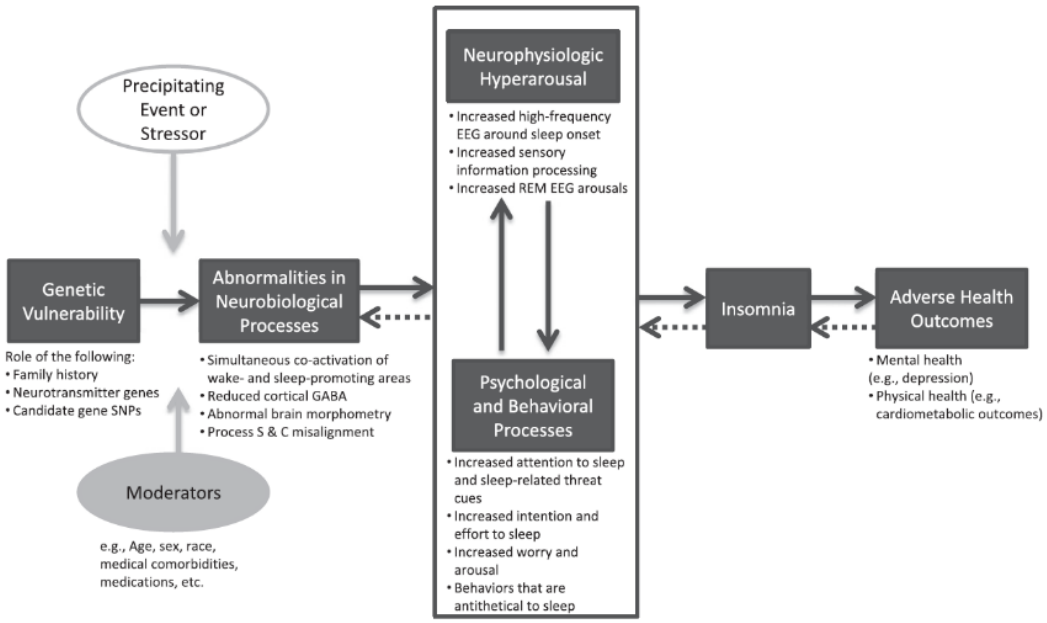


Figure 1 Model of pathophysiology of insomnia (4)

Diagnostic management

The diagnosis of insomnia is, basically, based on the medical history and a physical exploration.

1) Clinical history

It's important that the medical interview includes the patient and also, the bedroom partner. The main items to ask about are:

-Previous history: Including sleep disorders in family, medical diseases (which can be a somatic cause of insomnia, such as hyperthyroidism, prostatism, arthrosis…), psychiatric history (Mainly anxiety, depression, bipolar or psychosis disorders; insomnia increases the risk of suffering psychiatric disorders or can be an early symptom of them), pharmacological treatment (For example, corticoids, diuretics, thyroid hormones, antidepressant, etc.) and substance use (Especially those stimulating such as caffeine, alcohol, amphetamines…), social environment and lifestyle (6,8).

-Sleep history: Consist in enquire into the main complaint. The interviewer should make a characterization of the complaint type (onset sleep difficulties,

awakenings or unrefreshing sleep), evolution time, frequency (daily, weekends…), course (progressive, intermittent…), daytime symptoms (such as fatigue, cognitive dysfunctions…), nocturnal symptoms (for example snoring, kicking or vocalizations), factors that increase or reduce symptoms, possible precipitants and previous or present treatments.

Furthermore, bedroom environment and sleep habits (Such as napping, sleep schedule, pre-bedtime activities…) should be asked (7,8).

2) Physical examination

The main objective is to find signs that can reinforce our suspicions after the anamnesis. A general physical exploration should be done, including vital signs, BMI (to detect obesity), oropharyngeal examination (including Mallampati scale), cardiopulmonary, neurologic, etc. (7,8)

3) Complementary tests

Complementary test are not strictly necessary, but can be useful. The more used are:

-Blood test: Including hemogram, biochemical analysis, renal and liver function, thyroid hormones, toxics… (8)

-Sleep diary: The patient at home has to write down some measures during at least 15 days. This diary is useful to have an overview of the patient's sleep patterns. Some of the measures include are: bedtime, sleep latency, number and duration of awakenings, time in bed, total sleep time or nap times (number and duration)(7,8). There is an example in Annex 1.

-Sleep questionnaires: The more used are the Epworth Sleepiness Scale (EES), which makes a subjective assessment of sleepiness (normal <10), the Insomnia Severity Index (ISI), to assess the patient's perception of insomnia, and the Pittsburgh Sleep Quality Index (PSQI), which analyses sleep quality factors (a score >5 is considered poor sleep) (7,13).

-Others: Actigraphy (it is a test that records the gross motor activity during sleep and wakefulness, which can be a complement to sleep diary, mainly in the suspicion of circadian rhythm disorders) (13,14) or Polysomnography (Table 3 shows its indications).

a)Clinical suspicious of other sleep disorders (e.g. narcolepsy) b)Treatment-resistant insomnia c)Insomnia in high risk occupational groups (e.g. professional drivers) d)Clinical suspicion of large discrepancy between subjectively experienced and polysomnographically measured sleep
Table 3. Indications of polysomnography (Adaptation from European guideline (6))

Treatment

Insomnia treatment's aim is to improve sleep quality and to reduce dysfunctions caused by this disorder. In general terms, treatment is based on non-pharmacological treatments, pharmacological treatments or a combination of both (15–18). Also, insomnia management should include the treatment of medical or psychiatric comorbidities, the modification of those medications or substances than interfere with sleep and optimizing sleep environment (17).

- Non-pharmacological treatments

  Basing on European and USA insomnia guidelines, only cognitive behavioural treatment for insomnia (CBT-I) is strongly recommended in the treatment of insomnia. Brief treatments for insomnia (BTIs), due to insufficient evidence on adults, has a low to moderate strength evidence. Furthermore, single-component interventions based on cognitive therapy or sleep hygiene education are not recommended (6,19,20).

- Pharmacological treatments

  Pharmacological treatments are mainly based on hypnotics, which includes benzodiazepines (BZD) and benzodiazepine receptor agonist (BZRA). The strength of recommendation of these drugs is week, but the benefits outweigh possible harms. Hypnotics only have demonstrated being effective in a short-term treatment ($\leq$4 weeks). In long-term treatments aren't recommended because the lack of evidence and higher risk of side-effects. There are no differences in efficacy between BZ and BZRA and only those hypnotics with a short or intermediate half-life are recommended to avoid side-effects such as morning sedation (6,17,21)

Other treatments are sedating antidepressants, which could be effective in short-term treatment of insomnia (low evidence), or other treatments with insufficient evidence such as anti-histamines, melatonin, phytotherapy or antipsychotics (6,21).

Summarizing, the current recommendations on insomnia treatment prefer CBT-I as first-line therapy for chronic insomnia because long-term studies have demonstrated that CBT-I alone or combined with medication is more efficacy compared to only medication approaches. In addition, CBT-I does not expose patients to side-effects or drug interactions.

Pharmacological treatment with BZD or BZRA should be offered when CBT-I is not effective or available. However, if the clinical situation needs a quick response (e.g. daytime dysfunction or excessive anxiety) a combination of both treatments can be used, but planning withdrawing the medication over time (6,18,22).

Hypnotics

Hypnotics are a heterogeneous group of drugs with similar depressant effects over the central nervous system (CNS). There are two mainly used groups: benzodiazepines (BZD) and benzodiazepine receptor agonists (BZRA).

Mechanism of action

BZD and BZRA have the same mechanism of action. They work as an allosteric modulator of $GABA_A$ receptors, increasing the frequency of chloride ion (Cl^-) channel opening when GABA joins his receptor (23,24).

The stimulation of $GABA_A$ receptors by the GABA creates an influx of Cl^- into the postsynaptic cell producing a hyperpolarization of it which will reduce excitability of the cell in response to a next excitatory stimulus (23).

The main difference between these two groups is in the molecular structure, because BZRA don’t have a structure based on the benzene ring.

Epidemiology

The prevalence of benzodiazepine between 1996 and 2013, in noninstitutionalized adults from the USA, increased from 4.1% to 5.6% (25). BZD use was major in female sex and increased with the age, being the highest in women among 80 years old (26). Majority BZD prescriptions weren't done by a psychiatrist and short half-life BZD were the most prescribed type. Finally, the use of long-term benzodiazepines was

approximately of 31% in older than 65 years-old, while only represented a 15% of young people (18-35 years old) (26).

In Spain, there is a study in Lleida about BZD and BZRA consumption between 2002 and 2015. It shows a BZD use prevalence of 14% at 2015, in which the 9.7% were short-intermediate half-life BZD. Also, between 2002 and 2015, global BZD use prevalence decrease due to a lower intermediate-long half-life BZD prescription. However, the short half-life BZD use increased. Finally, they found that the most used BZD were lorazepam, diazepam and lormetazepam (27).

Furthermore, basing on ICS and IAS data from the SIAP ("Sistema d'informació d'Atenció Primària"), in the province of Girona, until September 2021, there were 55,592 people taking hypnotics. This represents an increment of more than 2,000 people since 2019 (the previous year to SARS-CoV2 pandemic), in which 53,128 people were under hypnotic treatment.

Efficacy

BZD and BZRA show low to moderate reduction in polysomnographic and subjective sleep onset latency, compared to placebo (28–31). Buscemi et al. (2007) did not find any difference on sleep onset latency between BZD and BZRA, but Winkler et al. (2014) showed that BZD are more effective than BZRA in subjective measured sleep onset latency (30,32).

Buscemi et al. (2007) showed an objective and subjective improvement on sleep quality and sleep efficacy (30). Furthermore, Winkler et al. (2014) and Holbrook et al. (2000) have found a small increase in total sleep time with objective measurements (28,32).

Finally, the different meta-analysis have obtained unalike results in other sleep measures such as number of awakenings or wake after sleep onset.

Pharmacokinetic characteristics

BZD and BZRA, in insomnia treatment, are principally administrated orally. Also, they have hepatic metabolism and renal excretion (23,24,33). Benzodiazepines have an important union to plasmatic proteins and, for insomnia treatment, are only used those with short and intermediate elimination half-life. Finally, about benzodiazepine receptor agonists, they have a short elimination half-lifes (23,24,34).

Side effects

The most common side effect, which derivate from their CNS depressant action, is somnolence. In high dose treatments, the patient could present dizziness, ataxia, dysarthria, diplopia or causing a confusion syndrome (23,33–35).

Benzodiazepines can produce anterograde memory disturbances, especially, in short half-life BZD used on the elderly or combined with alcohol. Also, in some cases, they cause a paradoxical reaction shown as the lack of behaviour inhibition, aggressiveness or psychomotor agitation (35). Furthermore, some studies have related BZD and BZRA with an increased risk of falling and fractures, dementia, cancer and mortality from any cause (36).

Rare reactions include agranulocytosis, hypotension and syncope, skin rashes, lupus-like syndrome, blurred vision, nausea, constipation, sexual dysfunction, etc. (23)

Lastly, chronic use of benzodiazepines has the potential to produce tolerance and physical dependence, which is higher in short half-life benzodiazepine treatments. So, a sudden discontinuation could cause rebound effects (higher intensity insomnia and anxiety symptoms) or withdrawal symptoms (such as hallucinations, sweating, photophobia, seizure crisis… (23,35,36).

Interactions and contraindications

The combination of BZD with other CNS depressants (such as ethanol, other hypnotic agent, anti-histamines, antipsychotics or antidepressants) can have additive or multiply sedative effects. Other interactions are with those drugs that modify hepatic enzyme activity, by inhibiting them (increasing BZD plasmatic levels), such as isoniazid or erythromycin, or by inducing them (reducing BZD efficacy) as carbamazepine, phenytoin or rifampicin (23,35,36).

The BZD contraindications are hypersensitivity, myasthenia gravis, severe respiratory insufficiency, dependence history or sleep apnoea syndrome without CPAP (Continuous Positive Airway Pressure) treatment. Also, they are not recommended during pregnancy and lactation (23,35).

Cognitive behavioural therapies

Non-pharmacological treatments include educational strategies, such as sleep hygiene, cognitive therapy and behavioural treatments, including stimulus control therapy, sleep restriction or relaxation techniques.

- Sleep hygiene and education: Sleep education includes information about physiologic sleep and its changes related to aging and the sleep-hygiene rules (Table 4), which look for promoting behaviours and environmental factors that make get to sleep easier, and, also, eliminate those that interfere with sleep (6,14).

a) Maintaining a stable sleep schedule.
b) Keeping favourable sleep environmental conditions (e.g. quiet, darkness…).
c) Avoiding napping.
d) Having dinner minimum 2 hours before sleep and avoiding copious meals.
e) Not taking stimulating substances (e.g. coffee or nicotine) since the afternoon.
f) Moderate alcohol consume.
g) Doing regular exercise, but minimum 3 hours before sleep.
h) Avoiding electronic devices minimum 1 hour before sleep.
Table 4. Sleep hygiene rules recommendation (8,37)

- Stimulus control therapy: The aim of this therapy is to re-associate bed and bedroom with sleep and reinforce this relation, because the association bed-sleep can be conditioned with anxiety and arousal stimulus. The instructions agreed with the patient should include those shown in table 5.

1) Only going to bed when you are sleepy.
2) Using bed and bedroom only for sleep and sex.
3) Leaving the bed and the bedroom if unable to fall asleep after 15 to 20 minutes, only return when feel sleepy again.
4) Keeping a fixed wake time in the morning.
Table 5. Stimulus control instructions (9,14)

- Sleep restriction therapy: Therapy based on limiting the amount of time spent awake in the bed during the night. It consist of establishing how long can the patient stay in bed basing on the actual total sleep time, which is obtained from sleep diary. Then, every week the sleep window has to be adjusted basing on the sleep efficiency (If it is >85%, time in bed will be increased 15-30 min, between 80-85%, we will keep it stable, or sleep window will be reduced if sleep efficiency is <80%) until reaching an optimal sleep duration (6,9,14,38).

- Relaxation techniques: Based on learning relaxation techniques that help the patient to reduce physiologic and cognitive hyperarousal. These techniques can be used in several situations such as during the day, before going to sleep or after night awakening. Some examples are progressive muscle relaxation, meditation, diaphragmatic breathing, etc. (9,11,14)
- Cognitive therapy: It is type of psychological treatment that looks to identify and change faulty and negative beliefs, unrealistic expectations or worrying about sleep that generate anxiety, which also contributes to perpetuating insomnia. This therapy wants that patient generates more-adaptive beliefs and realistic expectations about sleep (e.g. the amount or the quality of sleep) (6,9,11,14).

Those approaches with more evidence to apply these therapies are cognitive behavioural therapy for insomnia (CBT-I), brief therapies (BTIs) or single-component therapies (20).

CBT-I combines cognitive therapy, behavioural therapies and sleep hygiene education. Consists of four to eight sessions in-person, which can be on an individual or group form, run by trained professionals. During the treatment, the patient's sleep diary is useful to adapt the treatment to his or her necessities. There are several meta-analysis, such as Trauer et al. (2015)(39) or Johnson et al. (2016)(40), that demonstrate efficacy of CBT-I on treatment of insomnia and co-morbid insomnia, so it is a strongly recommended treatment considered the first line (6,19,20).

BTIs is mainly based on behavioural therapies and sleep hygiene education. As CBT-I, use to be an individual or group therapy done by a clinician, but less duration (1-4 sessions). BTIs has demonstrated a significant improve of sleep quality. However, the recommendation is low due to the evidence is moderate. Its strong points are: requiring less resources and being preferable for the patient than CBT-I (6,19,20).

Finally, single-component therapies are those that only use one type of therapy. It could be sleep hygiene, relaxation techniques, stimulus control, sleep restriction or cognitive therapy. This type of approach doesn't have enough evidence to be recommended as an efficacy insomnia treatment, especially, sleep hygiene education (19,20).

Prochaska and DiClemente transtheoretical model

Prochaska and DiClemente (1982), in a retrospective study of the process of smoking cessation, found that the subjects were able to differentiate 4 stages of changes for which they passed through during their stopping smoking process. Basing on that, they developed a change model with different stages that represents the different phases a patient has to pass through to achieve a behavioural modification. These stages were represented in a circular way because, in the practice, as well patients can progress, they can step back to achieving a stable change (41,42).

The transtheoretical model developed in 1986 by Prochaska and DiClemente consists of 4 stages (precontamplation, contemplation, action and maintenance) (43), but it has progressed to a 6 stage model for which patient has to progress through to achieve the behaviour change (41,44).

Precontemplation is that stage in which the person has not any motivation or interest on changing in a close future. Usually they deny or don not perceive having any behavioural problem. One reason for being in this stage are lack of information or that they are misinformed. Another reason may be the demoralization because the lack of success on change attempts.

Contemplation is the stage in which the person starts considering the change. They use to be more aware about the advantages and disadvantages of changing, but they do not have the courage to do it.

Preparation is when people want to carry through the change in the immediate future (considered as next month). They use to have planned how are going to do it (e.g. looking for physician help).

Action stage is based on putting the planned decision into practice. It is the phase in which patents make their behaviour change. Only those total changes (e.g. abstinence) can be considered as an action.

Maintenance consists of working actively for preserving the change and consolidated. The person will have to deal with temptations for avoiding relapse.

Termination is that stage in which patients do not have any temptation to return to past habit, no mattering what can happen (e.g. depression, stress…). Finally, DiClemente and Prochaska did not consider relapse as a stage, it is just a form of regression. Relapse was

defined as returning from action or maintenance to an earlier stage. It is considered as a part of the process of change (41,44).

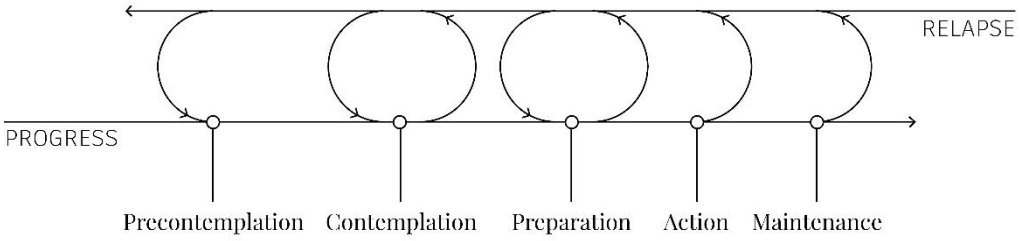


Figure 2. Prochaska and DiClemente transtheoretical model diagram (Adapted from Prochaska and DiClemente, 1982 (42))

STUDY JUSTIFICATION

Chronic insomnia represents a high prevalent health problem in high income countries, such as Spain (12) or other Europe's countries (6), and it has been demonstrated to be a risk health factor. Insomnia increases the risk of cardiovascular disease (45,46) and neurodegenerative diseases, especially dementia (47). Also, insomnia has been related to an increased risk of major depressive disorder (48), suicides (49), occupational accidents and traffic accidents (50). Therefore, insomnia not only has an impact on patients' quality of life, moreover, it represents a risk to their physical and mental health. However, chronic insomnia and its impact on the health and quality of life are not the only problem. Last decades, an increase of the chronic use of hypnotics for the treatment of insomnia has become a problem itself (26,27,51). As is written in hypnotics' epidemiology, data from ICS and IAS of the province of Girona, shows an increment of more than 2,000 people under hypnotic treatment between 2019 and 2021.

The significance of reducing the chronic use of benzodiazepine for insomnia treatment in the population is, basically, justified on an unfavourable risk-benefits relation (risks widely exceed the benefits).

Regarding the hypnotic treatment benefits, the only improvement of a sleep variable that the majority of meta-analysis have demonstrated is a low to moderate reduction of sleep latency (between 15-20 minutes) (28–30). In addition, some meta-analysis have found slight improvements of other sleep variables, such as sleep quality (29) or total sleep time (28,32). However, the evidence of these sleep benefits has been only demonstrated in short-term insomnia treatments (≤4 weeks) (6,7). In conclusion,

although short term treatments have demonstrated to provide sleep benefits, a chronic treatment (>4 weeks), which is our study subject, has not any high quality evidence of being beneficial.

In relation to the risks, it is important to underline that the probability of experiencing a side effect or an interaction increases with the treatments' duration. Benzodiazepines tend to generate tolerance and dependence, which is higher in short half-life BZD. The dependence phenomenon translates into rebound insomnia and withdrawal symptoms when the hypnotic treatment is interrupted (23,35,36). Due to the BZD mechanism of action, they cause CNS's depression symptoms such as daily somnolence (which increases the risk of traffic accidents) or confusional syndrome (23,35). Also, BZD and BZRA has been associated with an increased risk of dementia, cancer and mortality for any reason. Furthermore, mostly in older than 65 years old, hypnotic treatments increase risk of falling fractures, which in the elderly have a huge morbimortality (36). Finally, the pharmacological interactions, more frequent in polymedicated patients, such as elderly people, increase the probability and severity of side effects, mainly the sedative effects, which could have fatal consequences (e.g. respiratory depression, coma or death) (36).

Another reason for reducing use of BZD and BZRA in long-term insomnia treatments is the non-justified (because there is not any evidence of providing benefits) economic expenditure that these treatments represent to health public system. The public health spending is limited, so it's important to look for the maximum efficiency, reducing not justified treatment spends and investing in those with evidence and an important benefit for people's health.

Furthermore, all clinicians should base their medicine acts on the bioethical principles. In this case, the evidence shows that chronic hypnotic treatments have no benefits for patients, and in addition, they represent a high risk of producing other health problems. So, basing on beneficence and non-maleficence principles, clinicians have the ethical duty to try to withdraw them.

In the literature review, we found studies analysing different interventions to withdraw benzodiazepine long-term treatments, such as CBT with tapering off BZD (52,53), a brief advice (54) or an educational intervention with gradual BZD tapering (55,56). However,

we thought that CBT, although may achieve a huge BZD discontinuation, is an expensive and lengthy intervention, which reduces the feasibility of its implementation in primary care centres. Also, long interventions have more probabilities of abandonment, not only during the study, but in daily life. About the other interventions (e.g. educative interventions), although they have demonstrated being efficacious and feasible, we think that adding behavioural therapies (with evidence for treating insomnia), the benzodiazepine discontinuation will be higher and feasibility will be kept. We think that due to the relevance of the problem is important to keep searching for new and more effective ways to deal with it.

Therefore, we have designed an intervention (combining educative and behavioural components) to be compared with an educational intervention (inspired from previous study interventions (56), both followed by a gradual BZD tapering, in order to evaluate if the new one could show better results. To maintain the feasibility, our intervention will be carried out in a group and will consist of 3 sessions. In addition, the study's behavioural therapies can be performed by general practitioners, without the need for a specific professional (for example, a psychologist). Finally, unlike other studies, before doing the gradual BZD tapering, we will include an assessment of the motivation for change (based on Prochaska and DiClemente transtheoretical model) to ensure a definitive discontinuation. We think that is important to identify who will get profit from a BZD tapering plan and avoid pressing those who are not prepared.

In conclusion, due to the high prevalence of chronic insomnia, there has been an increase of long-term treatments with hypnotics. This fact represents a problem because there isn’t evidence about their benefits, but much their risk (including mortality increase). Therefore, there is the necessity of having more efficacy, but feasible tools to deal with this relevant health problem.

HYPOTHESIS

The principal hypothesis is that the educational and behavioural group intervention will achieve a moderately larger incidence of hypnotics' discontinuation in comparison to a written educative intervention in chronic insomnia population on long-term hypnotic treatment, at 12 months of follow-up.

The secondary hypothesis are:

-People who receive the educational and behavioural intervention will show a major improvement in patients-reported sleep quality, sleep onset latency, total sleep time and wake time after sleep onset regarding the baseline than written educative intervention at the end of the follow-up.

-The incidence of benzodiazepine discontinuation after the educational and behavioural intervention will be lower in those patients with a more severe insomnia at baseline.

-The percentage of patients that will modify their motivation state to change based on the Prochaska and DiClemente's transtheoretical model, at the end of the specific intervention, will be higher in the group subjected to the educational and behavioural intervention.

OBJECTIVES

The main objective is to compare the efficacy of a short educational and behavioural group intervention in contrast to a written educative intervention, at primary care, on the withdrawal of long-term hypnotics, in adults with insomnia from Girona city under a chronic hypnotic treatment, at 12 months of follow-up.

Secondary objectives are:

- To study and compare how both study interventions modify patients-reported sleep related variables (such sleep quality, sleep onset latency, total sleep time and wake time after sleep onset) regarding the baseline.
- To analyse how insomnia severity at baseline interacts on the incidence of benzodiazepine discontinuation after the educational and behavioural intervention.
- To evaluate differences of progress in the Prochaska and DiClemente's transtheoretical model between study and comparison groups, at the end of the intervention.

MATERIALS AND METHODS

STUDY DESIGN

This study will be a multicentre, randomized, parallel group, comparator-controlled clinical trial. It will be conducted in the 4 basic health areas of Girona. This clinical trial will last approximately 2 years and 7 months.

POPULATION

Inclusion criteria

- Patients with insomnia diagnosis in their clinical history or under treatment with hypnotic drugs.
- Daily use of benzodiazepines or analogues during at least 6 weeks (independent of treatment duration).
- Age between 18 and 85 years old.
- Residing in the city of Girona (≥5 days per week).
- Basic education (minimum primary education).
- Spanish or Catalan oral and written comprehension.

Exclusion criteria

- Severe psychiatric disorders.
- Alcohol or other drugs (e.g. cocaine, heroin…) abuse history.
- Pregnancy (confirmed by a pregnancy test or an echography).
- Severe medical disease.
- Convulsions related with previous benzodiazepine withdraw.
- Incapable person (sentenced by a judge).
- Dementia (diagnosed by a clinician and included in the patient's clinical history).
- High risk occupations (e.g. professional drivers).

SAMPLING

Sample size

The sample size estimation has been done with the free online GRANMO calculator configured for two independent proportions.

Assuming an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, GRANMO estimates that 192 subjects are necessary in each intervention group (384 in total) to find statistically significant a proportion difference of 15%.

This calculation is based on an expected proportion of benzodiazepine discontinuation of 60% in the educational and behavioural intervention group (based on the results of two studies that have used a CBT-based intervention plus gradual benzodiazepine reduction, which we consider could be the most similar to our intervention (52,53) and 45% in the control group (based on a study that evaluates an intervention that is very similar to our control intervention (56). Also, we estimate a drop-out rate of 10%, basing on previous studies with 12 month follow-up period (53,56).

Sample selection

The sample's selection will be done from the population of the city of Girona and we will use a two-stage sampling.

First, we will select, using a convenience sampling, the four basic health areas of Girona: Santa Clara's BHA (Girona 1), Can Gibert del Pla's BHA (Girona 2), Montilivi/Vila-roja's BHA (Girona 3) and Taialà's BHA (Girona 4).

Secondly, the GPs of the 4 basic health areas will be requested to provide a list of those patients, from their BAU, which accomplish the selection criteria. Using this data, a list of selectable patient for each BHA will be done. Then, from each BHA's list, 100 participants will be selected by a simple random sampling (using a computerised program).

Finally, the 400 selected participants, will be distributed in groups of 10 people maximum each. These groups will be done based on the basic health areas and their basic assistance units. The groups will be preferably assigned to their general practitioners as long as they want to participate in the study, in order to keep the clinician-patient relationship.

During the selection, an identification (ID) code will be assigned to every participant.

The selection process will be coordinated by a researcher (a study coordinator) only involved in the selection, recruitment and intervention allocation (so, he/she won't participate in other study phases). In the process of simple random sampling and the participant distribution in groups will be helped by a computer expert.

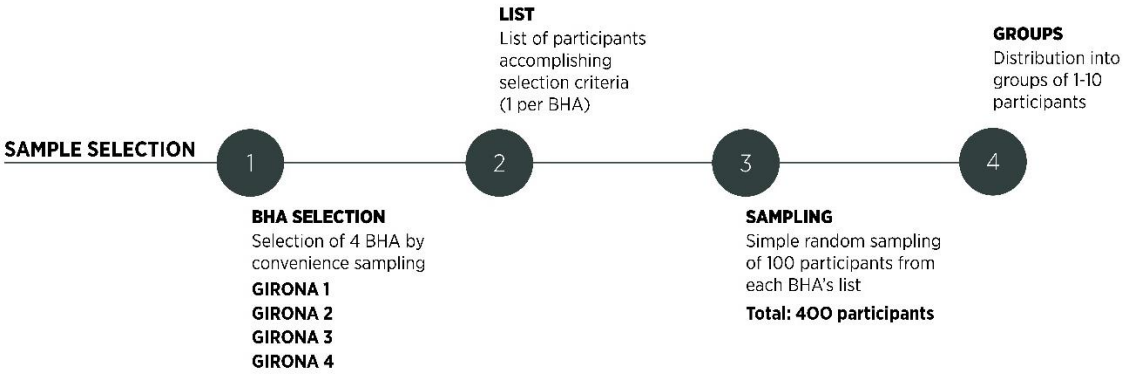


Figure 3. Sample selection diagram

RANDOMISATION AND MASKING

The allocation of the interventions will be done per basic health areas. Therefore, two BHA will do the educational and behavioural intervention, and the other two, the written educative intervention. The reason is to avoid a contamination bias.

The assignment process will have two parts:

- First, we will stratify the 4 basic health areas according to their socioeconomic status, obtaining two stratums: more well-off status (Girona 1 and Girona 3) or less well-off status (Girona 2 and 4).
- Secondly, for each stratum, we will randomly assign the interventions.

The stratification and intervention randomisation program will be prepared by the computer expert and the results will be only revealed to the researchers involved in this study phase.

The main research team will be necessarily unblended.

The general practitioners involved in study will not know which intervention are doing, whether the study intervention or the comparative one (they will be only aware of their assigned intervention).

The participants will know that we are investigating two interventional programs based on demonstrated strategies to know if there is an efficacy difference between them. However, they will not know which intervention have been assigned to. Also, participants will be asked for no sharing intervention's details with anyone external from their interventional group.

The baseline and outcome assessment will be externally evaluated by 2 different groups of nurses not involved in the study that will be masked about patients' intervention.

Finally, the biostatistician will be blinded about patients' allocation.

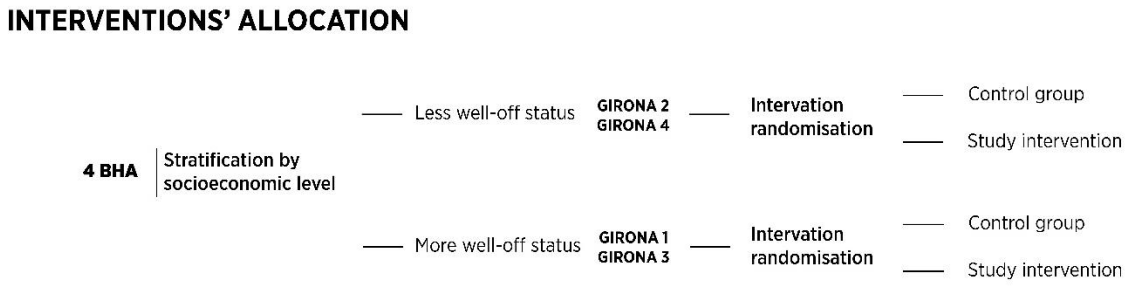


Figure 4. Interventions' allocation diagram

INTERVENTION

The intervention, in general terms, is composed for a specific and a common phase (summarized by a diagram in Annex 4). Week 1 will be considered as the one of the intervention start and week 0 as the one of baseline assessment.

Specific phase

Specific phase represents the initial stage of the intervention and it will take 3 weeks. In this phase, the two compared groups (study and control group) will receive a different intervention: the educational and behavioural intervention in the study group and the written educative intervention in the comparison group.

Educational and behavioural intervention

The objective of this educational and behavioural intervention is to provide participants with tools that facilitate withdrawing of chronic hypnotic treatment with the least effects on sleep variables, such as sleep quality or sleep latency.

The intervention is inspired on a brief therapy for insomnia (57). It will consist of 3 face-to-face group sessions, conducted by a general practitioner (GP), aimed to the participants included in the study from him/her quota. These sessions will be done within a period of 3 weeks (1 session per week) at the participants' primary care centre (PCC).

The specific structure of each session (briefly summarized in Annex 5) is explained below:

Session 1

This first session will present, mainly, the education part of the intervention. The duration will be between 60-75 minutes and before starting, the participants will

receive a short-written summary of the session (Annex 6 shows an example). The aim of this summary is to facilitate the session understanding and as a reminder of the most important topics discussed.

The 3 principal themes talked about will be normal sleep (approx. 25 minutes), insomnia (approx. 20 min) and hypnotics (approx. 20 minutes).

The session will begin by talking about normal sleep. Patients will first be encouraged to discuss what they think normal sleep is for 5-10 minutes, while the GP will act as a moderator and take notes on the relevant points made. Next, in a simplified way, the sleep phases (REM and NREM sleep) and age-related sleep changes (e.g. the lengthening of the phase I, which is a more superficial sleep, and deep sleep disappearance) will be explained. Furthermore, the GP will give an overview of the model of two sleep regulation processes (process S, which is the need to sleep due to waking time, and process C, which is the circadian propensity to sleep) and about sleep regulation brain networks (the ascending reticular activating system and GABAergic neurons of VLPO and MnPO).

Secondly, to justify the usefulness of sleep hygiene rules and behavioural techniques (explained in session 2), insomnia physiopathology (the interaction between physiologic hyperarousal, worry and intrusive thoughts and sleep unhealthy behaviour, supplemented with examples) will be briefly explained. In this part, the patients will have 10 minutes to ask questions and share to the other their worries.

Finally, hypnotics will be the last point of session 1. In this part, the benefits and risks of hypnotics will be discussed. About benefits, the GP will explain the weak evidence of these meds (e.g. they reduce sleep latency about 10 minutes (30), which is even lower in chronic (>4 weeks) treatments, and the European insomnia guideline recommendation (basically, use hypnotics only in treatments lower than 4 weeks (6). For ending, hypnotic risks will be exposed including: daily somnolence, risk of falling, memory disturbances, physical dependence, tolerance or increased mortality from any cause.

<u>Session 2</u>

At the second session, the participants will be trained in relaxation techniques, stimulus control and sleep hygiene rules. It will last between 60 to 75 minutes and at

the end of the session, they will receive a summarized leaflet of the practised behavioural techniques (Annex 6) to make easier their daily application.

About relaxation techniques, the session will only deal with the explanation and practice of the progressive muscle relaxation (PMR), the single one relaxation technique with enough evidence supporting (14), during 25 minutes. First, in order to establish a connection with the first session, the GP will explain that the relaxation techniques' aim is to reduce the physiological hyperarousal (one of the physiopathology basis of insomnia). The participants will be encouraged to apply PMR minimal once a day, especially before bedtime and after a night awakening. PMR is based on alternately contract and relax the different body's muscle groups (e.g. arms, neck, hands…), comparing the tension and relaxation feelings after and before the process (9,14). The GP will explain the PMR process (58,59), asking for a volunteer that will be shown as an example and, then, all participants will practice it whereas the GP resolves doubts and helps to learn the technique. The session summarized leaflet will show a PMR short version, which we think will prevent from not applying the technique because of lack of time.

The session 2 will continue with stimulus control therapy for 20 minutes. First, the technique's objective will be discussed, which is breaking the association between bedroom and non-sleep related activities that can contribute perpetuating the insomnia. At this part, the GP will ask for doing a together brainstorming to identify which activities done in the bedroom, could promote insomnia. Finally, in an interactive way between the GP and the participants, they will debate the instructions to reinforce bed-sleep relation (shown in Table 5).

Finally, during 20 minutes, the sleep hygiene rules (Table 4) will be explained and justified (basing on sleep regulation, especially on circadian rhythm, exposed in session 1).

Session 3

The third session will be the last one with an approximate duration of 20-30 minutes. This session will be used to solve problems, worries or doubts and to do a brief review about the previous sessions (focused on the participants' doubts and looking that they help each other to find the answer).

Control intervention: A written educative intervention

The comparative intervention will consist of providing an educational leaflet that will include information about: age-related sleep changes, benefits and risks of hypnotic drugs and sleep hygiene recommendations. Participants included in the control group will be contacted by phone, during the week 1, to making an appointment with their GP to pick up the educative leaflet, at their primary care centre during the following week. An example (inspired on ICS leaflets about benzodiazepines (60,61)) of the written educative intervention is included in Annex 7.

Common phase

The common phase will be developed since week 5 to week 9.

The aim of the phase is to evaluate the motivation for leaving BZD, basing on Prochaska and DiClemente model stages, as a criteria for offering a gradual benzodiazepine tapering plan.

This part of the intervention will consist of an individual assessment in one or two (the second one only if it is needed) interviews conducted by the participants' general practitioners. In the first interview, done between weeks 5-6, the GP will ask the participant about his/her opinion related to BZD discontinuation. Depending on the answer, if participant is considered to be ready (he/she is in the preparation stage of Prochaska and DiClemente model), he/she will be offered by a gradual tapering plan. However, if the participant is considered to be on the pre-contemplative or contemplative stage, the GP will only do an educational support, emphasising on the risks and the lack of benefits of hypnotic drugs used in chronic treatments for insomnia. After the first interview, pre-contemplative and contemplative participants will have a two weeks reflection period (week 7-8) followed by a second interview, in order to re-evaluate their motivation state, at week 9. The functioning of this new interview will be the same as the first one, so GP will only offer the BZD discontinuation plan to those participants that have changed their motivation stage of preparation. Therefore, we will not attempt to discontinue BZD in those participants who remain in the pre-contemplative and contemplative stage.

The gradual BZD tapering plan will consist of switching the hypnotic med to an equivalent dose (Table 6) of a long half-life benzodiazepine (diazepam) and providing an

adapted (depending on the starting dosage) dose reduction schedule of 8 weeks length (which represents a total reduction of 2,5 mg every 4 weeks) (62) (Annex 8 shows a reduction dose schedule example). There will not be follow-up visits, but participants will have contact phone numbers and e-mails from getting in touch with a clinician if any problem appears during benzodiazepine reduction process.

-Alprazolam 0,25-0,5 mg	-Lorazepam 0,5-1 mg
-Bromazepam 3-6 mg	-Lormetazepam 0,5-1 mg
-Midazolam 7,5 mg	-Nitrazepam 2,5-5 mg
-Oxazepam 15 mg	-Temazepam 10 mg
-Triazolam 0,25 mg	-Zopiclone 7,5 mg

Table 6. Equivalent doses to 5 mg of diazepam (Adapted from (62))

OUTCOME VARIABLES

Primary outcome variable

The main outcome variable is benzodiazepine discontinuation that is defined, basing on Vicens et al., 2014 (56), as an occasional (fewer than 4 doses) or non-consumption of benzodiazepines in the previous month. The benzodiazepine discontinuation assessment will be based on patient-reported non-consumption and corroborated with the data from pharmacy dispensing records, at 6 and 12 months of follow-up.

Secondary variables

Secondary outcome variables are: the sleep outcomes improvement at 6 and 12 months of follow-up and the progress through the stages of the Prochaska and DiClemente transtheoretical model after doing the study compared interventions (week 5-9).

The sleep related variables that will be studied are:

-Sleep latency (SL): is the time, in minutes, since the person tries to go to sleep until he/she falls asleep.

-Wake time after sleep onset (WASO): are the time (minutes) the awakenings last after the onset of persistent sleep.

-Total sleep time (TST): is the result (in minutes) of subtracting the SL and the WASO to the time in bed (TIB), considering TIB as the time between getting in and out of bed.

-Sleep quality (SQ): is a variable that includes quantitative aspects, such as sleep duration or sleep latency, as well subjective facets. So, basing on Buysse et al. (1989) we defined as poor sleep quality a PSQI global score >5, and as good sleep quality, when the PSQI global score is ≤ 5. The PSQI instrument is explained in the measurement tools section.

Regarding to SL, WASO and TST, we will measure the mean time (in minutes) of each variable on a previous two week sleep diary (Annex 1). About sleep quality, we will assess it using the PSQI global score from the past month (from 0 to 21).

The SQ, SL, WASO and TST will be evaluated at the baseline (week 0) and at 6 and 12 months of follow-up. The improvement for each sleep outcome is a dichotomous variable (there is or is not improving) defined as:

- A reduction of 10 minutes or more in the mean of sleep latency and wake time after sleep onset between the baseline and after 6 and 12 months of follow-up.
- An increase of 30 minutes or more in the mean of total sleep time between the baseline and after 6 and 12 months of follow-up.
- Change from a poor to a better sleep quality between the baseline and after 6 and 12 months of follow-up.

The transtheoretical model of Prochaska and DiClemente presents different stages that we define, basing on Prochaska et al. (1997) (44), as:

- Precontemplation: in this stage, the person does not have the motivation or intention of changing in a nearby future. Interviewee perceives benzodiazepines as useful. One reason can be that for them the benefits of this pharmacological treatment exceed the cons or that they have not been informed about the advantages and disadvantages of BZD.
- Contemplation: the study's participant is aware of the lack of benefits of BZD in the treatment of chronic insomnia and the huge number of possible side effects. He/she is considering to leave benzodiazepines, but does not feel ready for it.

- Preparation: the interviewee has clearly defined the date he/she will start withdrawing from benzodiazepines. Perhaps, He/she is looking for clinician advice for knowing how doing it.
- Action: the participant has started with benzodiazepine discontinuation basing on proposed gradual benzodiazepine reduction.
- Maintenance: the interviewee has not used benzodiazepines again for insomnia, and usually, he/she uses other strategies to deal with insomnia.

The progress through the stages of the Prochaska and DiClemente transtheoretical model will be measured as a dichotomous qualitative variable: Progress or Non-progress. We will consider as progress any change from a prior motivation stage to one of the following (e.g. moving forward from contemplation to preparation stage) between the assessment done at the baseline and that one done in the interviews of the intervention's common phase. However, relapse (understood as going from a stage to the previous) won't be considered as a progress.

Covariates

The covariates will be evaluated only at the baseline (Week 0), after having signed the informed consent, in an individual interview supplemented with the computerised medical history. These covariates are:

- Age (in years) and Sex (male or female)
- Cohabiting:
  - Cohabit (sharing the living place with someone else $\geq$ 50% of the week days)
  - No cohabit (living alone more than 50% of the week days)
- Employment (based on Eurostat (63) and OECD (64)):
  - Employed (person over 16 years old that has performed work 1 or more hours in the last week)
  - Unemployed (person considered active population without work in the last week, available to start working in the next two weeks that has actively searched for an employment the last four weeks)
  - Inactive (active population that is not classified as employed or unemployed)
  - Retired (person who benefits from a pension)

- Education status:
  - Primary education
  - Basic secondary studies (ESO)
  - Higher education (Baccalaureate, university degree or postgraduate education)
- Time taking hypnotics (time, in months, since the hypnotic prescription was done)
- Hypnotical active substance (e.g. lorazepam, lormetazepam, Zopiclone…)
- Hypnotic dose
  - Equivalent dose $<$10 mg of diazepam
  - Equivalent dose $\geq$10 mg of diazepam
- Insomnia severity (measured by the Insomnia Severity Index/ ISI instrument, which is explained in measurement tools section)
  - No clinically significant (ISI score of 0-7)
  - Mild (ISI score of 8-14)
  - Moderate (ISI score 15-21)
  - Severe (ISI score 22-28)
- Alcohol consumption (average of standard alcohol units per week)
- Other non-severe diagnosed psychiatric disorders
  - Depression disorder
  - Anxiety disorder
  - Bipolar disorder
  - Eating disorders

MEASUREMENT TOOLS

Pittsburgh Sleep Quality Index (PSQI) (65)

PSQI is a questionnaire used for sleep quality assessment that is formed by 19 self-rated questions and 5 bedpartner or roommate rated question (see on Annex 2). Question 10 and the 5 bedpartner rated questions are not included in global PSQI score.

The 19 self-rated questions are grouped into 7 sleep aspects: duration of sleep (question 4), sleep disturbance (questions 5b to 5j), sleep latency (questions 2 and 5a), day dysfunction due to sleepiness (questions 8 and 9), sleep efficiency (questions 1, 3 and 4), overall sleep quality (question 6) and need meds to sleep (question 7). Every of these

7 sleep aspects are weighted on a 0-3 scale, trying to replay the majority of days and nights in the past month.

The global PSQI score is obtained by summing the result of the 7 sleep aspects. Its score range is 0-21, considering poor sleep quality those scores >5.

It is a brief (≤10 minutes) and simple questionnaire validated in Spanish (66).

Insomnia Severity Index (ISI) (67,68)

ISI is a self-report instrument composed of 7 items (see on Annex 3). Its aim is to measure the perceived severity basing on the experienced nocturnal and diurnal insomnia symptoms.

ISI assessment includes: difficulties initiating sleep and staying asleep, too early morning awakening, satisfaction with present sleep pattern, interference with daily functioning, third people's perception of life quality impairment attributed to the sleep problem and degree of distress caused by the sleep problem.

The scoring of ISI is obtained of rating each of the 7 items on a scale from 0 to 4 basing on the severity (from less to more severe). At the end, a total ISI score is obtained between 0 to 28, considering a 0-7 score as no clinically significant insomnia, an 8-14 score as a mild to moderate insomnia severity, a 15-21 score as moderate severity of insomnia symptoms and a 22-28 score as severe insomnia with daytime functioning impairments.

It is a brief assessment and has been validated in Spanish (69).

DATA COLLECTION

All data collected will be introduced into an online database (with all data codified to preserve safety) using the ID code of each participant.

In order to guarantee a correct data collection, we will hire a data quality control service that will supervise this process.

If any participant misses a data collection appointment, the coordinator in charge of data collection will contact him/her by phone in order to reschedule the appointment as soon as possible.

The data collection process is summarised in table 7 and will have 3 phases:

Phase 1: Baseline measurements

Phase 1 will consist of an individual interview in the participants' primary care centre during the week 0 (the previous week to the interventions' start). The interview will be conducted by a nurse from an external outcome assessment team. The interviewer will proceed to collect the baseline data, which correspond mainly to the covariates, verifying the data provided by participants with their computerised medical history (ECAP). Also, the nurse will assess the participant's initial stage on the Prochaska and DiClemente model. Finally, the nurse will introduce the mean time of sleep latency, total sleep time and wake time after sleep onset from a previous two weeks sleep diary, and will evaluate the previous month sleep quality using the PSQI instrument.

Phase 2: Intervention phase

Phase 2 of data collection will be done by the general practitioners involved in the study between weeks 5 to 9. At this phase, once the specific interventions will have finished, GPs will evaluate the participants' stage on the Prochaska and DiClemente model. This assessment will be done in an individual interview between weeks 5-6. Those participants that in the first interview are in a pre-contemplative or contemplative stage, will have a second assessing interview at week 9.

Phase 3: Follow-up phase

During the follow-up, patient will have two scheduled interviews for assessing the primary outcome and the sleep variables at 6 and 12 months after the last intervention (week 9). These individual interviews will be performed by nurses from an external outcome assessment team (different from the baseline assessment team), at the participant's primary care centre.

The primary outcome, as it is explained in outcome variables section, will be assessed based on the patient-reported non-consumption and corroborated using the data from pharmacy dispensing records.

The data about the meantime of SL, TST and WASO will be obtained from a previous two weeks sleep diary and the sleep quality of the previous month will be assessed in situ using the PSQI instrument.

	DATA COLLECTED	RESPONSIBLE
Baseline *(week 0)*	-Covariates data -Sleep variables (SL, TST, WASO and SQ) -Stage on the Prochaska and DiClemente model	External nurse team 1
Intervention *(weeks 5-6 and 9)*	-Stage on the Prochaska and DiClemente model	General practitioners
Follow up *(6 and 12 months)*	-Primary outcome (BZD discontinuation) -Sleep variables (SL, TST, WASO and SQ)	External nurse team 2

Table 7. Summarizing table of data collection process

STATISTICAL ANALYSIS

UNIVARIATE ANALYSIS

In the sample description, qualitative/categorical variable results will be measured as proportions (with their 95% confidence interval). For continuous quantitative variables, if they have a normal distribution, they will be expressed as means +/- standard deviation (SD), but if they follow a non-normal distribution, we will use median and interquartile range.

BIVARIATE ANALYSIS

For comparing proportions (qualitative variables), we will use Chi Square test. However, the comparison of continuous variables will be done using Student's T-test (for quantitative variables with a normal distribution) or Mann-Whitney U test (for those with non-normal distribution).

MULTIVARIATE ANALYSIS

Finally, a multivariate logistic regression analysis will be performed, in order to analyse the relationship between the independent and dependent variable and to adjust it for the co-variables (those variables that are possible confounders or interactions). We will consider a P value <0.05 as a significant difference.

ETHICAL AND LEGAL CONSIDERATIONS

This protocol will be carried out guided by the ethical principles set up by the "*Declaration of Helsinki: ethical principles for medical research involving human subjects*" of the World Medical Association. Furthermore, this clinical trial will under the regulation of the "*Law 14/2007, July 3rd, of Biomedical research*" which is the Spanish applicable legislation in terms of biomedical research, as the study intervention (composed of psychological and educational parts) is a low risk invasive procedure.

The study will follow the four basic bioethical principles established in the Belmont Report:

- Autonomy: this principle is based on the respect to the capacity of the patients for taking all clinical decisions related to them. The autonomy of the patients in Spain is regulated by the "*Law 41/2002, of 14th November, regulating patient autonomy and rights and obligations regarding information and clinical documentation*". To respect this principle, all the study participants will receive a study information sheet (see Annex 9) in which the study characteristics will be detailed, such as the study aiming and hypothesis, the voluntary nature of study participation, a description of the interventions, the possible risks and benefits, alternative treatments, the possibility of withdrawing at any time, management of personal data, etc. The participants will have all time needed to read and understand the provided information and for asking any question related to it. Then, the participants will be requested to sign the informed consent form (see Annex 10) in order to express understanding of the information and agreement in getting involved in the study.
- Beneficence: the aim of the intervention is to reduce the chronic use of hypnotics, which have not demonstrated being effective at long-term and, in addition, present relevant side effects such as physical dependence, higher risk of dementia, falling and fractures of falling or mortality from any cause. Therefore, just the hypnotic drug withdraw offers several benefits for participants. Furthermore, the study intervention is based on behavioural and educative techniques with proven evidence in the treatment of insomnia, so we consider that could be beneficial for achieving hypnotic meds discontinuation. And finally, in relation to the control

intervention, it is based on an intervention with proven benefits for the participants.

- No maleficence: the protocol has been designed using those interventions that we considered could provide the participants the maximum benefit, but also reducing as much is possible the risks. Also, the interventions will be realised by experienced GPs, which will be trained for it. Finally, we have excluded those patients that we consider that the study could not benefit or even could harm (for example, pregnant women, severe psychiatric illness ...)
- Justice: in order to avoid injustice on the selection, we will use a simple random selection between those patients that accomplish with the selection criteria. Also, the inclusion and exclusion criteria have been established pretending to obtain a sample as much representative as possible of the population that will potentially benefit of the intervention, but protecting the population that could be harmed. Finally, the intervention will be randomly allocated to ensure equal chances for all participants.

Regarding to the use of personal data, the study will be conducted obeying the European ("*Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data"*) and Spanish ("*Organic Law 3/2018, 5th of December, of protection of personal data and guarantee of digital rights*") applicable laws. All data will be confidential and only used on research and educational purpose. Finally, all analyses will be performed with anonymised data.

Lastly, the study protocol will be presented to the IDIAP Jordi Gol ethics committee to guarantee ethical requirements obey. Also, the permission of the management of primary care centres included in the study will be requested.

LIMITATIONS OF THE STUDY

This protocol has several limitations that have to be considered in the execution of the clinical trial and the extrapolation of results.

- As the interventions' assignment will not be made on an individual basis (the interventions will be randomly allocated among the four basic health areas), we cannot guarantee that all confounders will be controlled for. In order to minimise the effects of confusion above the study results, we will adjust them for several covariates.
- In our study design, the study's control intervention is a proven efficacy strategy, but not the usually used in the clinical practice. There is the possibility of not finding statistically significant differences between the two interventions compared in the study, and as we will have not compared our proposal intervention with the usual clinical practice, we will neither known if our intervention represents an effective alternative approach strategy for benzodiazepine withdraw. A possible solution could be to include, in the protocol, a third arm to be compared, which will consist of doing the usual hypnotic discontinuation strategy in current clinical practice.
- There may be inter-professional variability, among the GPs that participate in the study, in conducting the intervention and assessing the participant's stage on the Prochaska and DiClemente model. To reduce the mistake that variability could generate, the main investigator will do a training for the GPs about the intervention assigned to their BHA, in order to try to standardise the evaluation criteria and the intervention's steps.
- Due to the type of interventions done in the study, we cannot assure a double-blind design. In order to reduce the observer bias, the outcome assessment will be performed by external professionals not involved in the study. Furthermore, for reducing the performance bias, the GPs involved in the study will only be instructed for conducting the intervention allocated to their BHA.
- Another limitation is the loss of participants to follow-up. We have estimated a drop-out rate of 10%, but if at the end of the study the loss of participants is greater, it could compromise the statistical power of the study to detect differences between the compared interventions. In addition, a selection bias could appear if the drop-out occurs distinctly in the comparison groups. In order to reduce it, we

try to build loyalty in the participants using the clinician-patient relationship with their GPs.

- Not achieving enough GPs that want to voluntarily participate in the study could suppose a limitation for executing the study. It would represent more workload for those enrolled and probably the work plan could not be fulfilled. To minimise this possible situation, the main investigator will promote the study, emphasizing the current problem with the chronic hypnotic use, to all the GPs of the four BHA included in the study.
- Finally, another limitation could be not having enough response rate. As the participants' selection will be done using a random simple sampling, exists the possibility that those participants selected would not want to get involved in the study. In order to achieve the maximum response rate, we will ask the GPs to promote the study among their patients and, also, the study will be advertised using the communication means and social media.

WORK PLAN AND CHRONOGRAM

WORK PLAN

The study length estimated will be approximately of 2 years and 7 months (January 2022 to July 2024). The work plan is structured in 6 stages:

Stage 1: Preparation – 4 months (January to April 2022)

- Protocol elaboration: Main investigator will be the responsible of elaborating the study's protocol. We expect it will take 2 months.
- Ethical committee approval: As it is a biomedical research that involves human subjects and their clinical data, our protocol will need the authorisation of the Ethics Committee of Clinical Investigation (CEIC) of the IDIAP Jordi Gol. We estimate a 2 month length to achieve the protocol approval and to make the CEIC requested modifications.
- Database creation: An external service specialized in databases will be hired, by the main researcher, to develop an online codified database and to supervise the data quality.

Stage 2: Promotion and coordination – 3 months (May to July 2022)

- Coordination meeting: The entire main research team (main investigator + 2 study coordinators) will meet to discuss and ensure the comprehension of the protocol. Also, each coordinator will be designated as responsible of a stage.
- Centres' management approval: The principal investigator will contact with the management of the four basic health areas of Girona (selected by convenience) to briefly explain the aim of the project, set up an in-person meeting (to thoroughly explain the study) and send the protocol.

  We estimate that getting the management approval of the 4 BHA will take 2 months.
- Study promotion: Once the management approval is achieved, the study will be explained (without specifying the interventions) to all general practitioners of each centre for encouraging them to participate and promote the study among their patients (in order to have an adequate response rate). Also, the study will be promoted in the media. We estimated these processes will take 1 month.

Stage 3: Sample selection, recruitment and intervention's allocation – 3 months (August to October 2022)

This stage will be managed by one study coordinator with the main investigator's help.

- Sample selection: The coordinator will request to all the GPs of each BHA to provide a list of those patients that accomplish the selection criteria of their BAU. Then, computer expert will randomly select a 100 participant sample for each basic health area (as is explained in "Sample selection" section). Participants will be distributed to groups depending on their general practitioner. We estimate it will take 1 month.
- Intervention's allocation: The randomly assignation of the specific intervention to each BHA will be requested to a computer expert (it will be done as it is explained on "Randomisation and masking" section).
- General practitioners formation: Simultaneously to the process of recruitment, for each BHA, the principal research will make a formation to standardise the way to make the intervention tasks. The GPs of the 4 BHA will receive the same formation about the common phase of the intervention. However, in relation with specific phase, the general practitioners of each BHA will only receive formation about the specific intervention assigned. We estimate that the formation will take 1 month.
- Recruitment: It will be structured in two phases with a 2 months total duration. At the first part of recruitment, the stage coordinator and the main researcher, will send a study inviting letter to the 400 selected participants. Then, after 2 weeks, they will contact the participants by phone to briefly explain the project and to invite them to an in-person meeting with their general practitioner to evaluate their participation in the study. This first part will take 1 month and will be done at the same time of the GPs formation.

  The second part of the recruitment will be the in-person interview with their general practitioner at their primary centre care. The GPs will explain the convenience of taking part of the study and will provide the study's information sheet (Annex 9) to the participants, which will have all time needed to read it and asking any question about it. Once they have understood what the study will consist of, those that agree to participate will be required to sign the informed consent form (Annex 10) and will be asked to complete a daily sleep diary (which functioning will be detailed by the GP) until the baseline interview. This second part will have 1 month duration.

- Coordination meeting: This meeting will be used to provide the necessary information (e.g. intervention allocation) that the intervention and data collection coordinator must know.

Stage 4: Intervention and data collection – 1 year and 2 months (November 2022 to December 2024)

This stage will be managed by the other study coordinator under the main investigator's supervision. The coordinator will be the responsible for scheduling the interventions and data collection and will be the reference person to contact if a problem appears.

- Baseline data collection: An external assessment team composed by 4 nurses will be hired (1 nurse for BHA) to collect the baseline data. It will be done during the previous week to the interventions' start.
- Interventions: The interventions will be managed by the GPs included in the study, supervised by the coordinator and the main researcher. Between week 5 to 9 (considering week 1 as the intervention's starting week), they will collect the data related to the evaluation of the participants' stage on the Prochaska and DiClemente model. The interventions length will be about 2 months.
- Data collection of the follow-up: Another external assessment team composed by 4 nurses will be hired (1 nurse for BHA) to collect the data at the 6 and 12 months of follow-up. The month previous to the assessment, the study GPs will contact their participants to request them to complete a daily sleep diary until the assessment (the coordinator will be in charge of remembering GPs about this task).
- Data monitoring and quality control: The company in charge will do a periodically data monitoring and quality control tests.

Stage 5: Data analysis and interpretation – 4 months (January to April 2024)

- Statistical analysis: Once all data have been collected, the statistical analysis will be performed by a blinded biostatistician. We estimate a 1 month duration.
- Results interpretation and discussion: The main research team will analyse, interpret and discuss the results obtained.
- Final report elaboration: The final report will be elaborated by the main researcher and reviewed by the rest of the main research team. The definitive version will be sent to the rest of the research team. We consider it will take 3 months.

Stage 6: Publication and divulgation – 3 months (May to July 2024)

- Report publication: The main investigator will send the report to different primary care journals. We estimate a 3 month period to achieve the publication.
- Divulgation: Results will be exposed in primary care conferences and congresses.

STAFF INVOLVED IN THE RESEARCH

Main research team: The team will be composed by the main investigator and two study's coordinators, all of them clinicians specialised on family medicine.

- Main investigator: he or she will be the responsible person of the protocol elaboration and achieving the CEIC's approval, of contacting and involving the selected basic health areas and their general practitioners in the study, GPs training, supervision of the study and coordination with the other two members of the main research team. Also, he/she will be in charge of the interpretation of results and final report elaboration.
- Study's coordinators: each coordinator will be responsible for the management of one the following stages: the selection and recruitment stage or the intervention and data collection stage. In addition, they will participate in the results' interpretation and will review the final report.

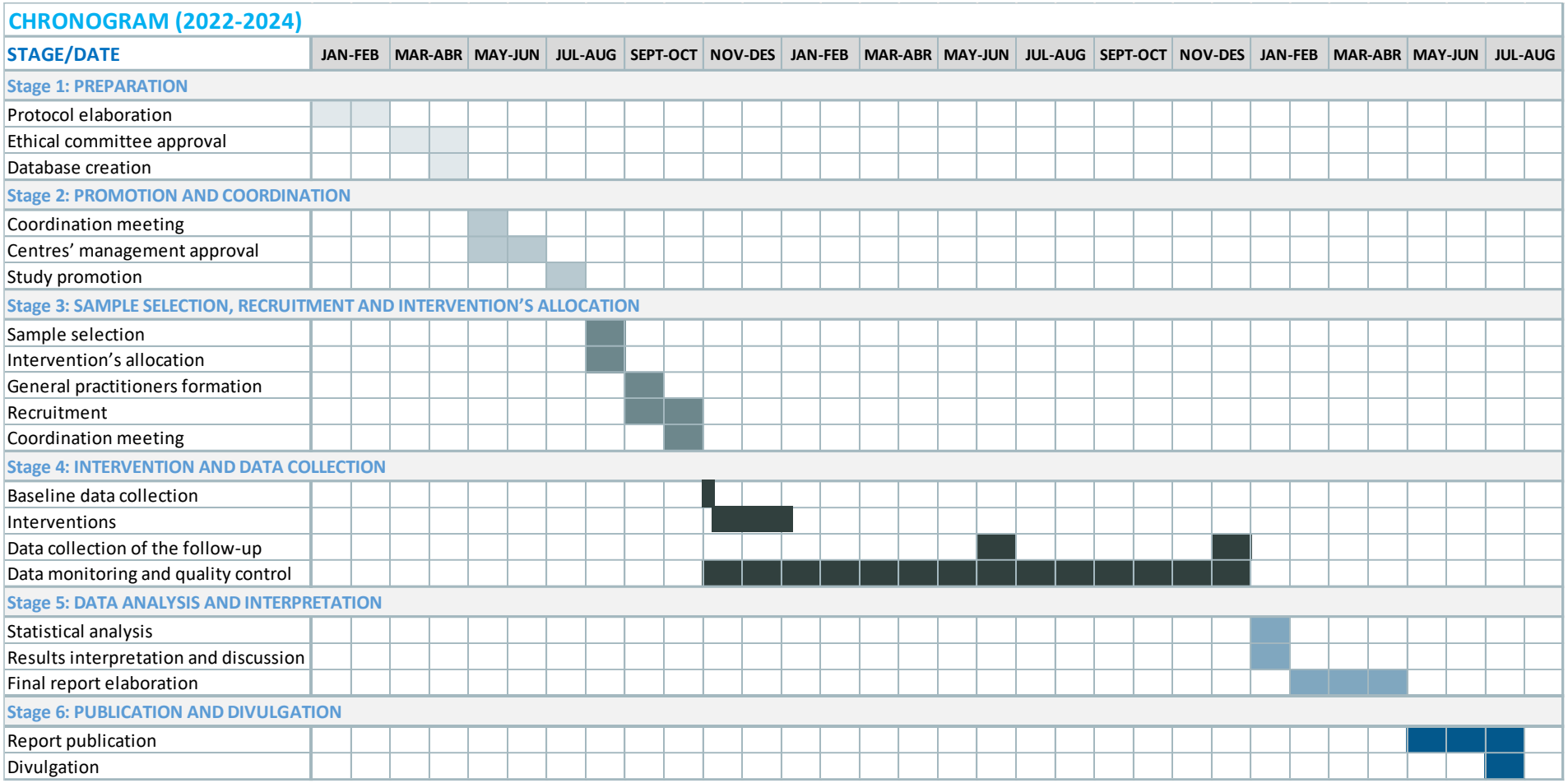
Co-investigators:

- General practitioners (GP): they will be responsible for providing, to the main research, team all those patients, of their basic assistance unit (BAU), that accomplish with selection criteria. Also, GPs will be in charge of giving the study's information sheet to the selected patients from their BAU, solving their doubts and requesting them to sign the informed consent. Finally, they will carry out, for the group of patients selected from their BAU, the intervention assigned to the basic health area (BHA) where they work.
- Computer expert: he/she will be requested to do the simple random sampling of 400 people (100 for each BHA), from the patient lists provide by the GPs. Also, will be responsible of the interventions' allocation randomisation. Finally, he/she will be available for solving any computer problem that any member of research team could have.

External services:

- Biostatistician: the person in charge of doing the statistical analysis of the data collected during the study.
- External assessment teams: two external evaluation team, composed by 4 nurses each (one nurse for each BHA), will be hired for doing the baseline assessment (one team) or the data collection of the follow up (the other team).
- Data monitoring and database creation company: an external company will be hired to create the research database and for monitoring and evaluating data quality.

CHRONOGRAM (2022-2024)



BUDGET

This budget includes an estimation of the cost that the study could suppose, basing on the possible expenses.

Not included costs

The following items are not considered as costs:

- Research team staff cost: the main investigator, study coordinators and the co-investigators (GPs and computer expert) will not be paid for their participation on the study to avoid an economic motivation. Their reward will be the scientific prestige, medical progress and the satisfaction of trying to improve population health.
- Available resources in the primary care centres: such as computers, telephones, consultation rooms or other work spaces.
- Questionnaire licenses: the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) are open licensed for research.
- Liability insurance: as the interventions of this clinical trial are considered as non-invasive procedures, we consider that hiring a liability insurance is not necessary. However, if the CEIC decides the opposite, we will comply with the ethical committee request and will adjust the budget in relation to the new expense.

Included costs

- Printing costs: we will need to print 45 pages for each participant in the study group and 43 pages for those in the comparative group. The total cost, considering a cost per unit of 0.05€/page, will be about 880€. The printed material needed is detailed below:
    - Printed material for all 400 study participants: the study's information sheet (2 units of 5 pages each), informed consent (2 units of 1 page), PSQI instrument (3 units of 4 pages each), ISI instrument (1 page), sleep diary for 1 month (3 units of 5 pages each) and the gradual benzodiazepine tapering schedule (1 page).
    - Printed material for the 200 participants assigned to the study group: session 1 summary sheet (2 pages) and session 2 summary sheet (2 pages)
    - Printed material for the 200 participants assigned to the comparison group: the leaflet of the educational intervention (2 pages).

- Travel costs: we budgeted 150€ destined for those justified costs derivative from possible displacements (e.g. in car, train, bus...) of the main research team.
- External services expense:
  - Statistical analysis: we estimate that the biostatistician will need 120 hours of work for doing the data analysis. Considering a salary of 40 euros/hour, the estimated cost will be about 4,800 €.
  - Data monitoring and database creation: this task will be carried out by an external company. We estimate, due to the duration of the study, that the service will cost 9,000 euros (300 hours of work paid at 30€ per hour).
  - Baseline assessment: this evaluation will be done by 4 external nurses during 5 days (20 participants per day). Considering an 8 hour work journey paid at 30€ per hour, the budgeted expense will be approximately of 4,800€
  - Follow-up data collection: this evaluation will be done by another 4 external nurses during 10 days (10 participants per day) at the 6 and 12 months of follow-up. Considering a 4 hour work journey paid at 30€ per hour, the estimated cost will be approximately of 9,600€.
- Divulgation costs:
  - Publication costs: we estimate that 2,000€ will be expended for the publication of the study's results in a journal article.
  - National and international congresses: in order to spread the study's results, we assume an expense of 3,000€ to attend to two congresses (one national and the other at international level), considering the inscription cost and the expenses derived from the trip.

	COST PER UNIT	HOURS/UNITS	TOTAL
MATERIAL COSTS			
-Printing costs	0.05€/page	45 pages × 200 participants (study group) 43 pages × 200 participants (control group)	880€
TRAVEL COSTS			
-Main research team displacements	0.1€/Km	500 Km × 3 members	150€
EXTERNAL SERVICES COSTS			
-Statistical analysis	40€/hour	120 hours	4,800€
-Data monitoring and database creation	30€/hour	300 hours	9,000€
-Baseline assessment	30€/hour	40 hours × 4 nurses	4,800€
-Follow-up data collection	30€/hour	80 hours × 4 nurses	9,600€
DIVULGATION COSTS			
-Publication expenses	2,000€/ publication	1 publication	2,000€
-Inscription and trip cost of the national congress	1000€/congress	1 congress	1,000€
-Inscription and trip cost of the international congress	2000€/congress	1 congress	2000€
TOTAL			**34,230€**

Table 8. Budget

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ANNEXES

ANNEX 1: SLEEP DIARY

Consensus sleep diary developed by Carney et al., 2012 (70).

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. If possible, the sleep diary should be completed within one hour of getting out of bed in the morning.

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency) you may make brief notes on your diary.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary.

Date: Write the date of the morning you are filling out the diary.

1. *What time did you get into bed?* Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.

2. *What time did you try to go to sleep?* Record the time that you began "trying" to fall asleep.

3. *How long did it take you to fall asleep?* Beginning at the time you wrote in question 2, how long did it take you to fall asleep.

4. *How many times did you wake up, not counting your final awakening?* How many times did you wake up between the time you first fell asleep and your final awakening?

5. *In total, how long did these awakenings last?* What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15= 70 min or 1 hr and 10 min).

6. *What time was your final awakening?* Record the last time you woke up in the morning.

7. *What time did you get out of bed for the day?* What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g. you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)

8. *How would you rate the quality of your sleep?* "Sleep Quality" is your sense of whether your sleep was good or poor.

9. *Comments* If you have anything that you would like to say that is relevant to your sleep feel free to write it here.

Sample **Consensus Sleep Diary-Core** ID/Name:________________________

Today's date	4/5/11						
1. What time did you get into bed?	10:15 p.m						
2. What time did you try to go to sleep?	11:30 p.m						
3. How long did it take you to fall asleep?	55 min.						
4. How many times did you wake up, not counting your final awakening?	3 times						
5. In total, how long did these awakenings last?	1 hour 10 min.						
6. What time was your final awakening?	6:35 a.m.						
7. What time did you get out of bed for the day?	7:20 a.m						
8. How would you rate the quality of your sleep?	☐ Very poor ☑ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good
9. Comments (if applicable)	I have a cold						

ANNEX 2: PSQI (65)

Subject's Initials_____ID#_____Date_____Time_____AM PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

ANNEX 3: ISI (67,68)

Insomnia Severity Index (ISI)

Subject ID: _____ **Date:_____**

For each question below, please circle the number corresponding most accurately to your sleep patterns in the **LAST 2 WEEKS**.

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood)?

Not at all Interfering	A little Interfering	Somewhat Interfering	Very Interfering	Extremely Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

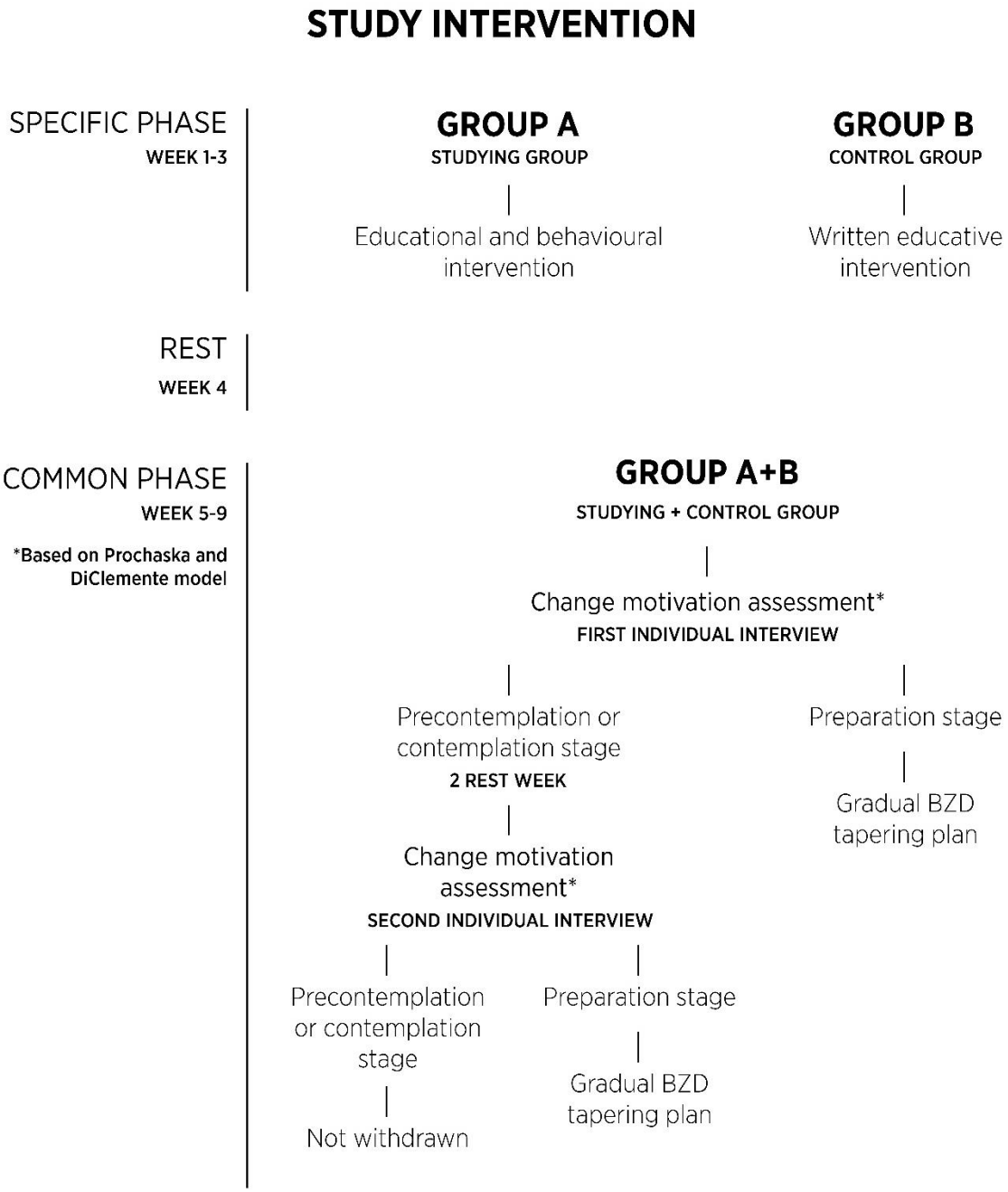
Not at all Noticeable	A little Noticeable	Somewhat Noticeable	Very Noticeable	Extremely Noticeable
0	1	2	3	4

7. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A little	Somewhat	Very	Extremely
0	1	2	3	4

ISI – United Kingdom/English - Version of 10 Sep 15 - Mapi.

ANNEX 4: STUDY INTERVENTION DIAGRAM



ANNEX 5: SUMMARY OF THE EDUCATIONAL AND BEHAVIOURAL INTERVENTION

SESSIONS	*CONTENTS*	*DURATION*
Session 1 (60-75 min)	-Physiologic sleep (sleep phases, age-related sleep changes and sleep neurophysiology) -Insomnia physiopathology -Hypnotics (Benefits and risks	25 minutes 20 minutes 20 minutes
Session 2 (60-75 min)	-Progressive muscle relaxation -Stimulus control therapy -Sleep hygiene rules	25 minutes 20 minutes 20 minutes
Session 3 (20-30 min)	-Solution of doubts or problems about session 1 or 2 -Brief intervention review	

ANNEX 6: EXAMPLE OF THE SUMMARY LEAFLETS OF THE EDUCATIONAL AND BEHAVIOURAL INTERVENTION

SESSION 1 SUMMARISING SHEET

>WHAT IS SLEEP?

·Sleep is a **life-necessity** and it is a biologic process that alternates with wakefulness ("being awake").

·**REM sleep** and **Non-REM sleep** are the two principal components of a sleep cycle and human sleep is formed by approx. 5-6 sleep cycles.

- Non-REM sleep → Composed by:
  - *Phase I*: is the transition period from being awake to be slept. At this phase, we talk about superficial sleep because you can easily wake up.
  - *Phase II*: is the longest phase.
  - *Phase delta*: is the deep sleep period.
- REM sleep → Phase name comes from its main characteristic that is **rapid eye movements**. Also, is the phase in which dreams occurs.

→*Is sleep a non-change process*?

-**NO**, it changes throughout life. Two examples are:

- In new-borns, there isn't phase delta and REM sleep is the longest phase
- In elderly, neither there is phase delta and phase I tends to be longer (so, night awakenings are more common)

→*How sleep is regulated*?

-At the brain, there are systems that promote being awake (because they stimulate the brain) and others that facilitate sleep onset (by inhibiting those brain stimulation systems).

-However, this brain regulation is modulated by two processes:

- **Process S**: establishes that as more time we stay awake, more will increase our sleep necessity.
- **Process C**: it is independent from the time we stay awake. It's based on that our bodily processes are regulated by a **biologic clock** (circadian rhythm) which is influenced by several factors such as environmental light (we tend to be sleepy when is dark outside).

>WHY INSOMNIA OCCURS?

·Long-term insomnia is explained by 3 factors:

A) Individual predisposition: some people have characteristics that make them more **vulnerable** to suffering insomnia such as being a nervous person, having low economic resources…

B) Triggering: usually an **adverse situation** that causes stress. In these situations, we tend to be more nervous and our brain stimulation systems are more activated, so is more difficult to inhibit them and fall sleep.

C) Insomnia persistence: there are **behaviours** or **thoughts**, such as being worried about not sleeping enough, that **make insomnia last** even when the trigger has been solved.

>SLEEP MEDICATION BENEFITS AND RISKS

·The sleep medication are **not** a **curative treatment**.

·Sleep meds can be useful, for a **short** period of time (approx. 1 month), to help you to get to sleep.

·*How they work*? These drugs help to inhibit the brain stimulation systems, so they facilitate the sleep onset.

·However, a **long-term use is not beneficial** and could imply risks.

·*Which are the risks*?

- Dependence: Is based on getting used to the sleep pills and needing them to sleep. Also, when these meds are suddenly left, you can experience unpleasant symptoms such as anxiety, more insomnia, sweating, irritability… These symptoms are known as withdraw symptoms and can be avoided if the medication is left in a **gradual way**.
- Tolerance: Is when you have to increase the dose of the med to maintain the same effect.
  - Other risks: A long-term use of sleep medicines has been related to **daytime somnolence** (reducing your day performance and your reflexes), **increased risk of falling and bone fractures** (especially in the elderly), **memory disturbances**…

SESSION 2 SUMMARISING SHEET

>HOW GETTING RELAXED?

·We recommend you **the progressive muscle relaxation (PMR)**. However, you can look for those relaxation techniques you feel more useful.

·*Why is important getting relaxed*? The relaxation techniques aim is to reduce the hyperactivity of those brain systems in charge of promoting being awake, in order to facilitate sleep.

·*When should I do the relaxation techniques*? At least **once a day**, especially before going to sleep.

→**PMR exercise** (58)

-This document will present a short version (5 minutes length), but, if you prefer, you can do the version trained in the session.

-Before starting → a) Look for a quiet place and sit down comfortably.

b) The exercise is usually performed with closed eyes.

c) If during the exercise intrusive thought comes up, just acknowledge you have them and continue with the exercise.

-Exercise steps → 1) Screw up your **face** while you inhale, hold on during 5 seconds (keeping a constant breathing) and, with next exhale, relax your face.

2) Tense up your **arms** (lifted arms and closed fists) while you inhale, hold on for 5 seconds (keeping a constant breathing) and, with next exhale, relax them.

3) Repeat the same process with **shoulders and chest** (lifted shoulders and tensed chest) and with your **legs** (lifted legs with toes facing towards you).

>HOW DO I RECONCILE WITH MY BED?

·You may have associated stimulating activities that difficult getting sleep, with the bed (the place to sleep). So, the **stimulus control therapy** looks for reinforcing the relation between sleeping and bed.

·The recommendations you should follow are:

1. Only going to bed when you **feel sleepy**
2. Bed and bedroom are exclusively for **sleeping** and **having sex**
3. If you cannot fall sleep after 15-20 minutes, leave the bedroom and only return when you feel sleepy again (could be a good moment to do PMR)
4. Always **wake up** at the **same time** in the morning.

>SLEEP HYGIENE RULES

TRY TO…	AVOID…
✓ Going to sleep and getting out of the bed **always** at the **same time** (including weekends).	× **Alcohol**, **smoking** and **caffeine** after lunch
✓ Keeping the bedroom **dark**, **quiet** and at a **comfortable temperature**.	× **Napping**
✓ Having **dinner** at least **2 hours** before going to sleep	× **Abundant meals** for dinner
✓ Practice **sport** in the afternoon	× Watching **TV**, using **PC**/ **mobile phone** or playing **videogames** 1 hour before sleep
✓ Doing **relaxing activities** before sleep	× **Worrying** about not being able to sleep (if you cannot sleep, try doing something relaxing until you are sleepy)

ANNEX 7: AN EXAMPLE OF THE WRITTEN EDUCATIVE INTERVENTION

WHY SHOULD I STOP TAKING THE SLEEP MEDICATION?

The aim of this written is to expound some reasons why you should consider letting up taking sleep medicines:

⇒Is normal to notice changes in my sleep pattern?

· Sleep is a life-necessity and well-sleeping is needed for being healthy. However, if you are going through a period of sleep difficulties, do not alarm yourself.

· What is the cause of my sleep disturbance? We shouldn't think that a single cause is responsible of our sleep alterations because, usually, there are multiple factors involved, as for example:

- **AGE**: As we grow old, sleep tends to be more superficial, so night awakenings could be more common.
- **EMOTIONAL STATUS**: During periods of stress (due to work problems, family worries…), anxiety or depression, we use to sleep worse.
- **ABUSING OF CERTAIN SUBSTANCES**: Crossing the line of a reasonable consumption of alcohol or caffeine can have an impact over our sleep quality.

⇒Which are the benefits and risks of the sleep medication?

·The sleep medication are **not** a **curative treatment**.

·Sleep meds can be useful, for a **short** period of time (approx. 1 month), to help you to get to sleep.

·However, a **long-term use is not beneficial** and could imply risks.

·Which are the risks?

- Dependence: Is based on getting used to the sleep pills and needing them to sleep. Also, when these meds are suddenly left, you can experience unpleasant symptoms such as anxiety, more insomnia, sweating, irritability… These symptoms are known as withdraw symptoms and can be avoided if the medication is left in a **gradual way**.
- Tolerance: Is when you have to increase the dose of the med to maintain the same effect.

- Other risks: A long-term use of sleep medicines has been related to **daytime somnolence** (reducing your day performance and your reflexes), **increased risk of falling and bone fractures** (especially in the elderly), **memory disturbances**…

⇒What can I do for improving my sleep quality?

·Our recommendation is that you try to **change your sleep habits**

TRY TO…	AVOID…
✓ Going to sleep and getting out of the bed **always** at the **same time** (including weekends).	× **Alcohol**, **smoking** and **caffeine** after lunch
✓ Keeping the bedroom **dark**, **quiet** and at a **comfortable temperature**.	× **Napping**
✓ Having **dinner** at least **2 hours** before going to sleep	× **Abundant meals** for dinner
✓ Practice **sport** in the afternoon	× Watching **TV**, using **PC/ mobile phone** or playing **videogames** 1 hour before sleep
✓ Doing **relaxing activities** before sleep	× Using the bed for activities other than sleeping.
	× **Worrying** about not being able to sleep (if you cannot sleep, try doing something relaxing until you are sleepy)

·Try new activities that you think can help you to be more relax (e.g. yoga, meditation…)

·Consult your doctor, he/she can help you dealing with you sleep problems and will solve any question you have about it.

·**Don't leave the sleep medication without medical supervision**.

ANNEX 8: EXAMPLE OF A BENZODIAZEPINE REDUCTION DOSE SCHEDULE

This schedule is a BZD tapering plan example that starts at 5 mg of diazepam (which, for example, could be suitable for a participant with a hypnotic dose of 1mg of lormetazepam). It is inspired on an example from TerapICS (37).

	Monday	*Tuesday*	*Wednesday*	*Thursday*	*Friday*	*Saturday*	*Sunday*
Week 1	5 mg	5 mg	5 mg	5 mg	5 mg	2 mg	5 mg
Week 2	5 mg	2 mg	5 mg	5 mg	2 mg	5 mg	5 mg
Week 3	2,5 mg	5 mg	2 mg	5 mg	2 mg	5 mg	2,5 mg
Week 4	5 mg	2,5 mg	2,5 mg	-	2,5 mg	2,5 mg	2,5 mg
Week 5	2,5 mg	2,5 mg	-	2,5 mg	2,5 mg	2 mg	2,5 mg
Week 6	2 mg	2 mg	-	2 mg	2 mg	-	-
Week 7	2 mg	-	-	-	-	-	-
Week 8	-	-	-	-	-	-	-

*If after initiating the new week program you don't feel good (e.g. appetite loss, irritability, headache, insomnia gets worse or feeling anxious) keep previous week plan and retry it the next week.

**Doses indicated are of diazepam

ANNEX 9: INFORMATION SHEET FOR PARTICIPANTS

FULL D'INFORMACIÓ AL PARTICIPANT

TÍTOL DE L'ESTUDI: Estudi comparatiu sobre l'eficàcia d'una intervenció educativa i conductual per a la retirada d'hipnòtics d'ús perllongat
INVESTIGADOR PRINCIPAL:
CENTRE:

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació, en el qual el seu CAP participa, i convidar-lo a participar-hi. L'estudi ha estat aprovat pel Comitè Ètic d'Investigació (CEI) de l'IDIAP Jordi Gol, d'acord amb la legislació vigent, la Llei 14/2007 del 3 de juliol d'Investigació biomèdica, que regula la recerca biomèdica amb intervencions mèdiques en humans.

La nostra intenció és proporcionar-li la informació suficient perquè pugui comprendre perquè és necessari l'estudi, quines implicacions té la seva participació, quin ús se'n farà de les seves dades i quins seran els possibles beneficis, riscs i molèsties; per tal que pugui decidir si desitja o no participar en aquest estudi. Li preguem que llegeixi atentament aquest full informatiu i ens consulti qualsevol dubte que li pugui sorgir al respecte.

Participació voluntària

El convidem a participar en l'estudi perquè vostè està realitzant un tractament farmacològic per l'insomni des de fa 6 setmanes o més. Ha de saber que la seva participació en l'estudi és voluntària i pot decidir NO participar-hi. En cas que decideixi participar, en qualsevol moment podrà canviar decisió i retirar el seu consentiment, sense que s'alteri la relació amb el seu metge ni es produeixi cap perjudici en la seva atenció sanitària.

Objectiu de l'estudi

Aquest estudi té com a principal objectiu comparar dues intervencions no farmacològiques per determinar quina és la millor per aconseguir retirar la medicació de l'insomni, quan aquesta s'ha usat de forma perllongada.

Descripció de l'estudi

L'estudi va dirigit a aquelles persones entre 18 i 85 anys, que fan un ús diari de medicaments per l'insomni des de fa 6 setmanes o més i resideixen a la ciutat de Girona.

Es preveu que participin 400 persones a l'estudi, procedents de les 4 àrees bàsiques de salut (CAP Santa Clara, CAP de Can Gibert del Pla, CAP de Montilivi i Vila-Roja i CAP de Taialà) de la ciutat de Girona. Els participants de l'estudi es dividiran en 2 grups, un grup rebrà la intervenció d'estudi i l'altre, rebrà una intervenció de comparació, de la qual se n'espera una menor eficàcia. Les intervencions seran assignades a l'atzar a cada àrea bàsica de salut, per tant, vostè rebrà aquella intervenció que s'hagi assignat al seu CAP. Ha de ser conscient que no se li dirà quina intervenció realitzarà, de la mateixa manera que tampoc ho sabrà el seu metge de família ni l'equip encarregat de recollir els resultats. En canvi, l'equip investigador principal, encarrega de coordinar les activitats de l'estudi, sí que ho coneixerà.

Activitats de l'estudi

La seva participació en l'estudi tindrà una durada aproximada d'1 any i 2 mesos. No obstant això, podem distingir entre la fase d'intervenció (2 mesos) i la fase de seguiment (1 any).

Durant la setmana prèvia a la fase d'intervenció, serà citat al seu CAP per fer una avaluació inicial, a la qual haurà de portar un diari del son del mes previ a l'entrevista, el qual se li proporcionarà i se li explicarà el funcionament. A l'entrevista, realitzarà 2 qüestionaris (sobre la severitat de l'insomni i la qualitat del son) i haurà de respondre a unes preguntes relatives a vostè.

La fase d'intervenció es realitzarà en un període de 9 setmanes, presentant dues etapes diferenciades, separades per 1 setmana. Durant les 3 primeres setmanes, realitzarà l'etapa d'intervenció específica, on vostè realitzarà únicament aquella intervenció a la qual hagi estat assignat. De la 5a a la 9a setmana, es farà l'etapa comuna, la qual serà igual per a tots els participants. Aquesta consistirà en una entrevista individual, entre la 5a i 6a setmana, on es valorarà si està prou motivat per iniciar la retirada de la medicació per l'insomni, donant-se 2 possibles situacions: si l'avaluador considera que està prou motivat, li donarà unes instruccions per deixar la medicació; però si considera que no està preparat, es repetirà el procés a la 9a setmana. Tota la fase d'intervenció serà realitzada pel seu metge de família i tindrà lloc al seu CAP.

La fase de seguiment consistirà en 2 visites al seu CAP, una als 6 i l'altre als 12 mesos, realitzades per infermeres independents de l'estudi. Per cadascuna de les visites haurà

de portar un diari del son, que nosaltres li proporcionarem, del mes previ. A les visites, es valorarà si encara fa ús de les pastilles per dormir i haurà de respondre un qüestionari sobre qualitat del son.

	Intervenció									Seguiment	
	Novembre 2022 a Desembre 2024										
Setmana	0	1	2	3	4	5	6	7	8	9	6 mesos	12 mesos
Entrevista inicial	x											
Intervenció												
-Etapa d'intervenció específica		x	x	x								
-Etapa comuna						x	x			x		
Visita seguiment 1											x	
Visita seguiment 2												x

Table 9. Participants' chronogram

Riscs i molèsties derivats de la seva participació a l'estudi

Existeixen alguns estudis amb intervencions de base educativa i psicològica, que han demostrat que aquestes intervencions són més eficaces en la retirada de fàrmacs per l'insomni respecte als mètodes habitualment usats en la pràctica clínica. A més a més, pel tractament de l'insomni crònic, la teràpia cognitiva-conductual és considerada el tractament d'elecció.

No s'espera efectes adversos derivat de les intervencions realitzades a l'estudi. Els únics possibles riscs són l'aparició d'insomni de rebot o símptomes d'abstinència secundaris a la retirada de les benzodiazepines. Per tal de minimitzar-ho, se li proposarà una retirada gradual.

Com a participant, les seves responsabilitats seran:

- Assistir a totes les visites programades, tant de la intervenció com del seguiment.
- Completar els 3 diaris del son, respecte al mes previ, necessaris abans de l'avaluació inicial i les dues visites de seguiment.
- Intentar aplicar els coneixements apresos a la intervenció.
- Notificar qualsevol esdeveniment advers o canvi en la seva situació clínica.

Possibles beneficis

Els beneficis esperats de la seva participació són l'abandonament de la medicació per l'insomni, evitant així experimentar els seus possibles efectes indesitjats, i una millora

de la qualitat del son. A més a més, la seva participació contribuirà a determinar l'eficàcia d'un nou abordatge, del qual se'n podran beneficiar futurs pacients.

Ha de saber que és possible que no obtingui cap benefici de la seva participació en l'estudi.

Contacte en cas de dubtes

Si durant la seva participació li sorgeix algun dubte o necessita més informació, posis en contacte amb el seu metge de família o CAP de referència.

En cas d'urgència o emergència acudeixi al seu centre habitual.

Si requereix atenció mèdica per un equip diferent del que li ha ofert participar aquest estudi, ha d'informar-los de la seva participació en aquest assaig i facilitar-los tota la informació possible.

Advertència relativa a l'embaràs

En cas de produir-se un embaràs durant la seva participació en l'estudi, haurà d'informar immediatament al seu metge.

Tractaments alternatius

Actualment, la retirada dels fàrmacs per l'insomni sol realitzar-se a proposta del metge de família i es basa a anar reduint progressivament la dosi, mitjançant visites de control, fins a aconseguir l'abandonament.

Si desitja més informació, consulti al seu metge de família.

Costos i compensació econòmica

El promotor de l'estudi és l'encarregat de gestionar-ne el finançament i per a realitzar-lo, ha signat un contracte amb els metges de l'estudi i centres on es realitzarà.

La seva participació en l'estudi no li suposarà cap cost addicional.

Quin tractament rebré quan finalitzi l'assaig clínic?

Un cop finalitzada la seva participació, rebrà el millor tractament disponible i que el seu metge consideri més adequat, però existeix la possibilitat que no se li pugui realitzar la intervenció de l'estudi.

Protecció de dades personals

El promotor de l'estudi es compromet al compliment de la Llei Orgànica 3/2018, de 5 de desembre, de protecció de dades personals i garantia dels drets digitals (BOE núm. 294). Les dades recollides per a l'estudi estaran associades a un codi d'identificació, evitant així informació que permeti identificar-lo; per tant, només els investigadors de l'estudi podran relacionar les dades amb vostè i la seva història clínica. La seva identitat no serà revelada excepte en situacions d'urgència mèdica o requeriment legal.

L'accés a la seva informació personal quedarà restringit als investigadors de l'estudi, a les autoritats sanitàries, al Comitè Ètic d'Investigació i al personal autoritzat pel promotor, quan es requereixi per comprovar dades i procediments de l'estudi, però mantenint sempre la confidencialitat d'aquests d'acord amb la legislació vigent.

En compliment de la legislació de protecció de dades, vostre podrà exercir els seus drets d'accés, modificació, oposició i cancel·lació de dades, dirigint-se al seu metge/essa de l'estudi.

Si durant l'estudi decideix retirar el seu consentiment, no es recollirà cap dada nova, però sí que s'utilitzaran les dades ja recollides.

Les dades codificades poden ser transmeses a tercers i a altres països, però en cap cas presentaran informació que permeti identificar-los directament, com noms i cognoms, adreça, núm. seguretat social...

Altra informació rellevant

Qualsevol informació, descoberta durant la seva participació en l'estudi, referent a la intervenció usada a l'estudi que pugui modificar la seva disposició per a participar-hi, li serà comunicada pel metge/essa responsable tan aviat com sigui possible.

Ha de saber que si el promotor o els investigadors de l'estudi ho consideren necessari, podrà ser exclòs de l'estudi, sigui per raons de seguretat o perquè considerin que no està complint amb els procediments establerts. En qualsevol cas, rebrà una explicació adequada del motiu que ha provocat la seva retirada de l'estudi.

En signar el full de consentiment informat adjunt, es compromet a complir amb els procediments de l'estudi que se li han exposat.

Girona,_____ de _____de 20___.

ANNEX 10: INFORMED CONSENT FORM

FULL DE CONSENTIMENT INFORMAT

TÍTOL DE L'ESTUDI: Estudi comparatiu sobre l'eficàcia d'una intervenció educativa i conductual per a la retirada d'hipnòtics d'ús perllongat

Jo,_____(nom i cognoms), declaro:

- Haver llegit el full d'informació que se m'ha entregat sobre l'estudi.
- Haver pogut fer preguntes relatives a l'estudi i que aquestes han estat resoltes.
- Haver rebut suficient informació sobre l'estudi.
- Haver parlat amb l'investigador responsable.
- Comprendre que la meva participació és voluntària.
- Entendre que puc retirar-me de l'estudi:
    - Quan ho desitgi
    - Sense haver de donar explicacions
    - Sense que això repercuteixi en les meves cures mèdiques

Rebré una copia signada i datada d'aquesta full d'informació i consentiment informat.

Presto lliurament la meva conformitat per a participar en l'estudi.

Signatura del participant: Signatura de l'investigador:

Girona,_____ de _____de 20___.

Desitjo rebre els resultats obtinguts en l'estudi: ☐ SÍ ☐ NO

Signatura del participant: Signatura de l'investigador:

Girona,_____ de _____de 20___.