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Health Technology Assessment (HTA)

HTA Report

Medicines containing valerian for treating symptoms of insomnia, mental stress and test anxiety

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Title	Medicines containing valerian for treating symptoms of insomnia, mental stress and test anxiety
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Technology	Medicines containing valerian extract, either alone or combined with lemon balm, hops and/or other herbs (Sedonium®, Dormiplant®, Hova®, Redormin®, Relaxane®)
Type of Technology	Phytotherapeutics
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Conflict of Interest:

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Executive Summary

Background: In Switzerland medicines containing valerian extract, either alone or with lemon balm, hops and/or other herbs are reimbursed by the Swiss mandatory health insurance to aid sleep and relief mild symptoms of mental stress and test anxiety. Valerian has gained popularity and the expenditure for valerian-based drugs in Switzerland have tripled since 2014. However, evidence on its clinical effectiveness is inconsistent in the literature. Therefore, there is a need to re-evaluate these medicines to support evidence-based decision making regarding the future reimbursement of these medicines by the Swiss mandatory health insurance.

Objective: This HTA examines the clinical effectiveness, safety, cost-effectiveness, budget impact, ethical, legal, social and organisational aspects of medicines containing valerian extract, either alone or combined with lemon balm, hops and/or other herbal extracts to aid sleep and relief mild symptoms of mental stress and test anxiety.

Research questions: Are medicines containing valerian (alone or in combination) efficacious, effective, safe and cost-effective compared to placebo, other herbal medicines, cognitive behavioural therapy, other medications, or no treatment (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene) in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety? What is the budget impact of Dormiplant®, Hova®, Redormin®, Relaxane®, Sedonium® for the currently reimbursed populations? Are there ethical, legal, social or organisational issues related to the use of medicines containing valerian (alone or in combination) for treating symptoms of insomnia, mental stress or test anxiety?

Methods: A systematic literature search in Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline, PsycInfo and Web of Science databases was conducted. Eligible studies were randomised controlled trials (RCTs), non-randomised controlled trials and controlled observational studies that compared valerian (alone or in combination) with placebo, no treatment or any comparators approved for use in Switzerland. Where possible, meta-analyses were performed to estimate pooled effect estimates. Outcomes which could not be pooled with meta-analyses were summarised narratively by using the Synthesis Without Meta-analysis (SWiM) guideline. The methodological quality of included RCTs were critically appraised according to the Cochrane Risk of Bias tool 2 for randomised trials (RoB 2). The certainty of evidence was assessed for selected outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

A systematic literature search was conducted to identify published cost-effectiveness analyses. A de novo budget impact model was developed for the Swiss setting. The analysis adopted a healthcare payer perspective, focusing on costs covered by Swiss mandatory health insurance over a 5-year time horizon. Furthermore, a targeted search for evidence on the ethical, legal, social and organisational aspects of valerian was conducted and findings were qualitatively summarised and discussed.

Results: In total 36 studies were included (33 RCTs and 3 observational studies), 24 RCTs and 2 observational studies investigated valerian monotherapy in patients with insomnia, 7 RCTs evaluated valerian with lemon balm or hops in patients with insomnia, 3 RCTs and one observational study assessed valerian with lemon balm or hops in patients with mental stress and 2 RCTs examined valerian with lemon balm, passionflower and butterbur in patients with test anxiety/anxiety.

For treatment with valerian monotherapy versus placebo in patients with insomnia, meta-analyses were conducted for sleep latency, sleep duration, sleep quality, night awakenings, sleep efficiency and Pittsburgh Sleep Quality Index (PSQI) total score. No statistically significant difference was observed between valerian and placebo for most outcomes. Two measures showed statistically significant improvements in favour of valerian: sleep quality at post-intervention assessment and PSQI total score. Of note, two of the three RCTs contributing to the post-intervention sleep quality analysis had a follow-up of only one day; when excluded, only one study with a 28-day follow-up remained, resulting in considerable uncertainty around this finding. Subgroup analyses excluding studies with follow-up durations shorter than 7 days and shorter than 14 days confirmed the main results for all other outcomes. When comparing valerian monotherapy versus benzodiazepine in patients with insomnia, meta-analyses could only be computed for sleep quality (for sleep latency, sleep duration and PSQI total score only one study was included) and no statistically significant difference was observed. Regarding treatment with valerian combined with hops or lemon balm versus placebo in patients with insomnia meta-analyses were conducted for sleep latency, sleep duration and sleep efficiency and no statistically significant differences were detected. For studies examining valerian combined with hops or lemon balm versus placebo in patients with mental stress, as well as those investigating valerian combined with lemon balm, passionflower and butterbur versus placebo in patients with test anxiety/anxiety, meta-analyses could not be computed as only one study per outcome was included.

Regarding safety, a meta-analysis could only be computed for valerian combined with lemon balm, passionflower and butterbur versus placebo in patients with test anxiety/anxiety. No statistically significant difference was observed. For other comparisons, meta-analyses could not be computed due to fewer than two eligible studies being available.

The certainty of evidence for the critical outcomes was judged as very low to moderate.

No cost-effectiveness studies were identified in the literature. The budget impact analysis demonstrated substantial potential savings across 3 indication areas over a 5-year time horizon when removing valerian-containing medicines from reimbursement. The combined budget impact of all 5 valerian-containing medicines currently listed on the specialities list resulted in total savings of CHF 202.47 million, including medication costs, healthcare provider consultations and dependence-related healthcare costs associated with substitute treatments. For insomnia symptoms, the model projected savings of CHF 174.05 million. Mental stress symptoms showed estimated savings of CHF 6.14 million. Test anxiety symptoms yielded projected savings of CHF

22.28 million. Sensitivity analyses indicated an uncertainty of CHF -14.8 million to +10.9 million for insomnia symptoms, CHF -3.1 million to +2.3 million for mental stress symptoms, and CHF ± 3.8 million for test anxiety symptoms. Scenario analyses assuming continued prevalence growth projected higher savings of total CHF 244 million, comprising CHF 210 million for insomnia, CHF 7 million for mental stress and CHF 27 million for test anxiety. In a scenario where consumption volumes were aligned to real world claims data, total savings of CHF 222 million were projected, comprising CHF 173 million for insomnia, CHF 10 million for mental stress and CHF 39 million for test anxiety.

The ethical, legal, social and organisational (ELSO) analysis identified key implications of delisting valerian preparations. Ethical considerations underscore that evidence-based resource allocation represents a fundamental principle in solidarity-based healthcare systems when making reimbursement decisions for collective resources. Legally, removal from reimbursement is justified when effectiveness criteria are unmet. Socially, vulnerable populations may face financial barriers requiring transition support. Organisationally, mental health services may experience increased demand and consultation times.

Conclusion: This systematic review found no statistically significant differences between valerian preparations and placebo for most insomnia outcomes, except for sleep quality at post-intervention assessment and PSQI scores, which favoured valerian. Evidence certainty ranged from very low to moderate. For mental stress and test anxiety/anxiety meta-analyses could not be computed. The budget impact analysis projected CHF 202 million savings over 5 years associated with delisting of valerian-containing medicines: CHF 174 million for insomnia symptoms, CHF 22 million for test anxiety symptoms and CHF 6 million for mental stress symptoms. ELSO analysis identified no insurmountable barriers to delisting given the insufficient evidence to demonstrate consistent effectiveness over placebo across outcomes, though transition planning for vulnerable populations is recommended to mitigate potential access issues.

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Abbreviations and acronyms

BZRA	Benzodiazepine receptor agonists
CBT	Cognitive behavioural therapy
CBTI	Cognitive behavioural therapy for insomnia
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	Swiss Franc
CI	Confidence interval
CPM	Complementary and phytomedicinal products
DALYs	Disability-Adjusted Life Years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
EAE	Effectiveness, appropriateness, economic effectiveness
ECG	Electrocardiograms
EEG	Electroencephalogram
e.g.	Exempli gratia (meaning “for example”)
ELSO	Ethical, legal, social and organisational
EMA	European Medicines Agency
ESCOPE	European Scientific Cooperative on Phytotherapy
EUnetHTA	European network for Health Technology Assessment
FC	Federal Constitution
HMPC	Herbal Medicinal Products Committee
ICER	Incremental Cost-Effectiveness Ratio
i.e.	Id est (meaning “in other words”)
FOPH	Federal Office of Public Health
GABA	Gamma-amino butyric acid
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HIA	Health Insurance Act
HIO	Health Insurance Ordinance
HMP	Herbal medicinal products
HTA	Health Technology Assessment
LYs	Life Years
LVC	Low value care
MedReg	Register of medical professions
n.a.	Not applicable
OHB	Ordinance on Healthcare Benefits
OTC	Over the counter
OR	Odds ratio

PICO	Population, Intervention, Comparator and Outcome
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
QALYs	Quality-Adjusted Life Years
RCT	Randomised controlled trial
RoB	Risk of Bias
RR	Risk ratio
SL	Specialities list
SSRI	Selective serotonin reuptake inhibitor
SSSSC	Swiss Society for Sleep Research, Sleep Medicine and Chronobiology
STAI	State-Trait-Anxiety-Inventory
SWiM	Synthesis Without Meta-analysis
TD	Treatment duration
WASO	Wake After Sleep Onset
5HT	5-hydroxytryptophan

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy question and context

The health technology assessment (HTA) topic entails a policy question which will be informed by addressing HTA research questions (see **Chapter 5**).

In healthcare, a policy question is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses uncertainty around a technology. This HTA report addresses the following policy question:

Should the Swiss mandatory health insurance continue to reimburse medicines containing valerian extract or medicines in which valerian is combined with lemon balm, hops and/or other herbal extracts?

Valerian is a herbal remedy that has gained popularity as a sedative and hypnotic alternative to prescription drugs.¹ Proving to be a widespread option due to its favourable safety profile.^{2,3} However, evidence on its clinical effectiveness is inconsistent in the literature.^{1,4–7}

In Switzerland, it is among the most recommended treatments for insomnia by pharmacies, along with relaxation therapy and other phytotherapies, despite this approach being inconsistent with Swiss and European clinical guidelines.^{2,8,9} Medicines containing valerian extract, either alone or with lemon balm, hops and/or other herbs are reimbursed by the Swiss mandatory health insurance to aid sleep and relief mild symptoms of mental stress and test anxiety.^{10,11}

The expenditure^a for valerian-based drugs in Switzerland has tripled, rising from CHF 7 million in 2014 to CHF 21 million in 2023.¹² The increasing expenditures and the uncertain clinical effectiveness of medicines containing valerian for treating symptoms related to insomnia, mental stress and test anxiety, have brought forward the need to re-evaluate these medicines.⁹ The findings of this assessment will support evidence-based decision making regarding the future reimbursement of these medicines by the Swiss mandatory health insurance.

2. Medical background

2.1 Insomnia

Insomnia is the most common sleep problem affecting both the quality and quantity of sleep.^{13,14} Its symptoms include difficulty in falling or staying asleep, waking up too early with problems returning to sleep, or feeling unrefreshed upon waking. These symptoms can manifest as acute, intermittent, or chronic and are often caused by stressors, medications, or underlying physical and

^a These figures reflect only the costs covered by mandatory health insurance for medicines included in the list of pharmaceutical specialties ("Spezialitätenliste"), excluding out-of-pocket expenses and valerian tinctures reimbursed by the mandatory health insurance.

mental health conditions like obesity, pain, anxiety and depression.^{14–17} Additionally, demographic and behavioural factors have been shown to influence the likelihood of experiencing insomnia symptoms.^{15,18} According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), insomnia becomes a disorder when the sleep difficulties occur at least 3 times per week and persist for at least 3 months.¹⁴ Similarly, ICD-11 characterizes insomnia disorders by the persistent difficulty with sleep initiation, duration, consolidation or quality despite adequate opportunity and circumstances for sleep resulting in some form of daytime impairment.¹⁹

The diagnosis of insomnia in Switzerland involves a thorough medical history, covering aspects such as sleep habits, sleep environment, triggers and chronobiological factors, as well as an external assessment of nocturnal abnormalities. A physical examination and laboratory tests are also performed. Additionally, psychiatric and somatic comorbidities, neurological symptoms and internal medicine-related complaints are assessed, along with a detailed review of the patient's medication and substance history. To support the diagnosis, various diagnostic tools are employed, including sleep questionnaires, sleep diaries, actigraphy, sleep electroencephalogram (EEG) and polysomnography (PSG).^{2,9}

In Switzerland, the prevalence of insomnia is reported to be between 30% and 38% in the general population and among primary care patients, with 11% meeting the DSM-5 criteria for insomnia disorder.^{17,18,20,21} Women and older adults are particularly prone to experiencing insomnia disorder, while there has been a significant increase in insomnia among individuals aged 15 to 39 since 1997.^{2,17,20}

When insomnia becomes chronic (i.e., lasting more than 3 months), it can result in impaired daytime functioning and emotional distress, significantly reducing quality of life.^{18,22} It also increases the risk of various other health conditions, contributing to substantial economic costs due to decreased work productivity, higher healthcare utilisation and a greater likelihood of accidents.^{23–25} Chronic insomnia alone is estimated to cause an economic loss of approximately CHF 10 billion per year in Switzerland, which corresponds to 1.3% of the country's gross domestic product.²⁶ Despite this considerable impact, only 1% of the affected patients receive the recommended treatment.²⁰

According to current guidelines from the Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC), the first-line treatment for insomnia and insomnia disorder involves adjusting sleep hygiene practices based on self-reported sleep habits. However, the recommended treatment approach is cognitive behavioural therapy for insomnia (CBTI).² This therapy typically involves 4–8 structured sessions and can be conducted individually or in groups. There are also internet-based, self-help and brief versions, though internet-based programs have not yet been approved in Switzerland.² Randomised controlled trials (RCTs) show that CBTI is efficacious for insomnia, with or without comorbidities and can also alleviate psychiatric symptoms.²⁷ If CBTI does not provide sufficient relief or is unavailable, pharmacotherapy can be considered.^{2,9,15} For short-term use benzodiazepines and benzodiazepine receptor agonists (BZRA), also known as Z-drugs,

are recommended. For longer-term treatment, sedative antidepressants are preferred, although they are not officially approved for insomnia in Switzerland.² The orexin receptor antagonist Daridorexant, approved in Switzerland since 2022 for chronic insomnia with considerable impairment of daytime activity, is also a preferred option. Antipsychotics are not recommended for treating insomnia symptoms due to insufficient evidence, possible side effects and lack of approval in Switzerland. Antihistamines and melatonin are not recommended for the general population, although melatonin may be effective in children and adolescents. In Switzerland, melatonin is only approved for primary insomnia^b in individuals aged 55 and older.

While CBTI has short-term efficacy comparable to hypnotics (e.g., benzodiazepines and BZRA), its long-term benefits are more sustainable, making it the preferred treatment for chronic insomnia, particularly given the risk of tolerance and dependence associated with benzodiazepines and BZRA.² Pharmacotherapy also carries risks such as confusion, falls and daytime sleepiness, especially in elderly patients.¹⁵ Phytotherapeutic treatments, such as medicines containing valerian extract, are widely accepted in Switzerland and serve as a low-threshold option due to their mild positive effects on sleep quality and favourable side effect profile.^{2,3}

2.2 Mental stress and test anxiety

Mental stress is a natural response to life challenges and pressures. However, high levels of stress can negatively impact both physical and mental health and are associated, amongst others, with migraine, obesity, cardio vascular diseases and depression.^{28–30}

Test anxiety, also known as exam anxiety, exam stress, or test stress, is a specific type of anxiety characterised by worry or fear in evaluative situations, such as exams.^{31,32} Anxiety is characterised by symptoms that can manifest physically (e.g., increased heart rate, sweating, trembling), cognitively (e.g., excessive worrying, difficulty concentrating, feeling of fear or nervousness) and behaviourally (e.g., avoidance of situations) and that can vary in severity.³³ Representative surveys suggest that 16% to 22% of students experience high levels of test anxiety.^{32,34} The consequences of test anxiety can extend beyond the classroom and are correlated with poor health behaviours, including dysregulated sleep patterns and poor sleep quality.³⁵

Anxiety disorders are among the most common mental health issues worldwide, affecting approximately 4% of the global population.³⁶ Prevalence rates vary by region, with higher rates observed in high-income countries and have been rising significantly over the past decades.³⁶ In Switzerland, as of 2022, about 7.5% of men and 11.9% of women reported experiencing anxiety disorders within the previous year.³⁷ Anxiety symptoms are more common among women and younger individuals.^{37,38}

According to Global Burden of Disease Study 2010 mental disorders were responsible for 18.9% of all years lived with a disability. Conditions like depression and anxiety contribute substantially to

^b Primary insomnia is defined as not occurring in the context of another mental illness.²

the world's disease burden and therefore place significant strain on the healthcare system.³⁹ A major portion of the costs associated with mental health issues, including anxiety, arise from lost productivity and informal care.⁴⁰

Exercise, meditation and mindfulness have been proposed to help alleviate mental stress and in students, interventions such as cognitive behavioural therapy and meditation have been shown to reduce stress, anxiety and depression.^{28,29,41,42} According to current Swiss guidelines on anxiety disorders, which are based on the German S3 guidelines developed by several psychiatric societies, both pharmacotherapy and psychotherapy can be used as first- or second-line treatments of different symptoms, either individually or in combination.^{43,44} The choice of approach depends on the symptoms, its severity, the required time commitment, the availability of therapies, any costs incurred by the patient, individual preferences and the presence of comorbid mental conditions.⁴³ Pharmacological and psychotherapeutic measures are viewed as complementary and mutually reinforcing methods that can be combined and tailored to the specific needs. A reassessment should take place if there is no response to therapy within 4 to 6 weeks. In cases where patients do not respond to prescribed medication, factors such as correct diagnosis, adherence and sufficient dosage must be reassessed.⁴³ Pharmacotherapy should generally continue for 6-12 months after remission and medications should be tapered off gradually to avoid withdrawal symptoms. Newer antidepressants are preferred for mid- and long-term management due to their lower risk of side effects, while benzodiazepines may be used briefly (max. 3-4 weeks) for acute symptoms. The Swiss Society for Psychiatry and Psychotherapy generally recognises the following evidence-based psychotherapeutic methods: cognitive behavioural therapy (CBT), psychoanalytical oriented therapy and systemic therapy.⁴³ Pharmacotherapy and psychotherapy may be complemented by additional interventions, such as occupational therapy, relaxation techniques, physical activity, psychoeducation, self-help groups and family involvement. However, there is limited evidence from RCTs to confirm their efficacy.⁴³

3. Technology

3.1 Technology description

Valerian is a herbal remedy used as a sedative and hypnotic for treating symptoms related to insomnia, mental stress and test anxiety.¹ In Switzerland, valerian-containing medicines are typically authorised by Swissmedic based on well-established use and compliance with recognised herbal monographs (particularly Herbal Medicinal Products Committee (HMPC) of the European Medicines Agency (EMA) monographs and European Scientific Cooperative on Phytotherapy (ESCOP) monographs) rather than through the conventional clinical trial pathway required for synthetic medicinal products (see also **Chapter 3.3** describing regulatory status). According to the patient information for approved valerian-containing medicines in Switzerland, the indications include

symptoms such as difficulty falling asleep, staying asleep, poor sleep quality, as well as nervousness, tension, agitation and test anxiety (**Table 1**).⁴⁵

Table 1: Indications of reimbursed drugs in Switzerland

Reimbursed drug	Indication	Ingredients	Extraction solvent	Herb extract ratio (DER)
Dormiplant®	Restlessness, nervousness and difficulty falling asleep	Valerian root (160mg) and lemon balm (80mg)	Ethanol	3-6:1
Hova®	Nervous sleep disorders, nervousness, agitation/ restlessness	Valerian root (200mg) and hop cone (45.5mg)	Ethanol	4-7:1
Redormin®	Difficulty falling asleep, sleep disorders and restless sleep	Valerian root (250/500mg) and hop cone (60/120mg)	Methanol	4-6:1
Relaxane®	Nervousness, states of tension and restlessness, test anxiety. These complaints can manifest themselves in the following symptoms, among others: cramp-like gastrointestinal complaints, increased irritability, occasional difficulty falling asleep and staying asleep.	Valerian root (90mg), butterbur root (90mg), passionflower (90mg) and lemon balm leaf (mg)	Methanol	4-6:1
Sedonium®	Difficulty falling asleep and staying asleep as well as restless sleep	Valerian root (300mg)	Ethanol	3-6:1

Source: Compendium⁴⁵⁻⁴⁸

Abbreviation: DER: drug extract ratio

Valerian's mode of action is not fully understood but may involve interactions with gamma-aminobutyric acid (GABA) and 5-hydroxytryptophan (5HT) receptors.⁴⁹ In addition interactions with Adenosine receptors through A1 receptor activation and inhibition could explain the anxiolytic and sleep-inducing effects of valerian, while at the same time expound some of the contradictory findings regarding the efficacy of valerian extracts.⁵⁰ Extracted from the roots of the *Valeriana officinalis* plant, valerian-containing medicines are available in various forms, including capsules, tablets, teas and extracts.^{3,4}

The specific dosage of valerian varies depending on the form and the specific product used.¹¹ Valerian products may contain varying concentrations of the active ingredient and may be combined with other herbal remedies, such as lemon balm, hops, butterbur, or passionflower.⁴⁵⁻⁴⁸ While valerian is generally considered to have a low risk of harm, some side effects have been reported. The most common effects observed in clinical trials include headaches, dizziness, pruritus, and gastrointestinal disturbances; however, similar effects were also reported for placebo groups, suggesting these may not be directly attributable to valerian.⁵¹ Multiple systematic reviews and meta-analyses confirm that valerian is generally well-tolerated, with only mild neurological symptoms (e.g., dizziness, headache, drowsiness) and mild gastrointestinal symptoms (e.g., nausea, diarrhoea) reported, and no serious adverse events.^{3,4} Additionally, individuals should be aware of rare but possible side effects, such as allergic reactions and gastrointestinal discomfort. Liver disorders might also occur, though these are primarily associated with the use of butterbur extract.⁴⁵⁻⁴⁸

3.2 Alternative technologies

Several evidence-based alternatives to valerian exist for treating insomnia, based on the Swiss Sleep Medicine Guidelines from the SSSSC.²

Benzodiazepines are approved for short-term insomnia treatment in Switzerland. The Swiss guidelines specify that these should be used "only on short-term use ≤ 4 weeks, high dependency potential". Available agents include diazepam, flurazepam, nitrazepam, oxazepam, temazepam and triazolam. The evidence quality is rated as "good evidence", with several meta-analyses demonstrating the positive sleep effects of this drug class, but use is strictly limited due to high addiction potential. Studies indicate that 15-44% of chronic benzodiazepine users experienced physical dependency with moderate to severe withdrawal symptoms.⁵² Tolerance development occurs within 3-14 days of continuous use.⁹

Z-drugs including zolpidem and zopiclone (so-called Z-substances) demonstrate "good evidence" for insomnia treatment, with various meta-analyses suggesting a positive effect on sleep. The Swiss guidelines recommend these for "only short-term use ≤ 4 weeks, more favourable than benzodiazepines for longer use". However, the ≤ 4 -week limitation remains identical to benzodiazepines.⁹

For both Benzodiazepines and Z-drugs drugs possible adverse events have to be taken into consideration, such as headaches, nausea, falls and dizziness, as their safety profile might limit their usefulness.^{9,49}

Sleep Hygiene and Lifestyle Modifications are also possible alternatives, with guidelines detailing specific behavioural recommendations including:

- Avoiding stimulating substances from midday onwards
- Avoiding alcohol for at least 2 hours before bedtime
- Not eating or drinking large amounts before bedtime
- Creating a pleasant sleep atmosphere
- Regular physical activity during the day (at least 3 × 50 minutes per week), but not in the evening
- Avoiding bright light (attention: screen exposure) during nighttime awakening
- Avoiding looking at the clock/watch
- Regular bedtime and wake-up times
- Establishing a sleep ritual
- Rest phase before bedtime

According to current guidelines, **CBTI** is the preferred psychotherapeutic treatment for insomnia in adults of all ages. The Swiss guidelines note it consists of 4-8 structured sessions with components

including psychoeducation and recommendations for healthy sleep, relaxation exercises, sleep time restriction, stimulus control and cognitive therapy. The treatment shows comparable short-term effectiveness to hypnotics but demonstrates superior long-term effects. CBTI is delivered individually or in groups, with various versions including internet-based and self-help-based approaches, though these show lower effectiveness than traditional CBTI.

The SSSSC guidelines recommend **sedative antidepressants** to be used as follows: "bei längerfristiger Notwendigkeit einer Pharmakotherapie einsetzen sowie bei Insomnie und depressiver Symptomatik" (for longer-term need for pharmacotherapy as well as for insomnia and depressive symptoms, with consideration of adverse effects).² These include agomelatin, amitriptylin, doxepin, mirtazapin, trazodon and trimipramin, with "mittelgradige Evidenz bei primärer Insomnie" (moderate evidence for primary insomnia). The guidelines recommend weighing adverse effects carefully. Evidence exists for low-dose sedative antidepressants in primary insomnia, though these are not approved for insomnia indication in Switzerland.^{2,53} Trazodon showed moderate effects on subjective sleep quality and nighttime awakening rates in a meta-analysis.⁵⁴ Low dose mirtazapin could extend total sleep time, improve sleep efficiency and enhance subjective sleep quality in several studies.

Based on the German Guidelines for the Treatment of Anxiety Disorders (2021 revision), which represents the most comprehensive European evidence-based guideline for anxiety treatment, **selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants** are recommended for anxiety in addition to benzodiazepines.⁵³

SSRIs are recommended as first-line pharmacological treatment for anxiety disorders including panic disorder, generalised anxiety disorder and social anxiety disorder.⁵³ The German guidelines recommend SSRIs due to their favourable risk-benefit profile compared to other antidepressants. Patients starting SSRI treatment should be advised that these drugs generally take effect after a latency period of about 2 weeks (range 1-6 weeks).⁵³ Regular monitoring is required, particularly in the initial weeks of treatment. SSRIs demonstrate high-level evidence across all major anxiety disorders, with efficacy comparable to tricyclic antidepressants but with better tolerability and safety profiles.⁵³

Tricyclic antidepressants are positioned as second-line treatment options for anxiety disorders due to their adverse effect profile, despite being as effective as SSRIs and SNRIs. Tricyclic antidepressants carry risks including anticholinergic effects, cardiac conduction abnormalities and overdose toxicity. They require careful patient selection and enhanced monitoring, particularly in elderly patients and those with cardiovascular conditions.⁵³

3.3 Regulatory status / provider

In Switzerland, valerian-containing medicines are widely used as hypnotics or sedatives and are available through pharmacies.^{8,45} These medicines are available without a prescription. However, a prescription is required for reimbursement under the mandatory health insurance.

These medicines are reimbursed by Switzerland's mandatory health insurance for the treatment of symptoms related to insomnia, mental stress or test anxiety. Notably, a formal diagnosis of any of the conditions is not required for prescribing these medicines and it can also be prescribed for mild symptoms. The reimbursed products are Dormiplant®, Hova®, Redormin®, Relaxane® and Sedonium®. All but Sedonium® contain valerian combined with another herb, such as lemon balm, hops, butterbur or passionflower.¹¹

Based on the EMA HMPC monographs, valerian-containing medicines are approved through 2 regulatory pathways.^{55,56} Well-established medicinal use supported by controlled clinical studies demonstrating efficacy for mild nervous tension and sleep disorders and traditional use based on long-standing historical application for mild mental stress symptoms and sleep aid.⁵⁷ They demonstrate acceptable safety profiles with known, manageable gastrointestinal side effects. The monographs establish standardised dosing regimens and quality specifications for various valerian preparations, including single-ingredient and combination products with hops, providing regulatory framework for marketing authorisation. Furthermore, they facilitate the harmonisation of the processes of approval and registration for herbal medicinal products in the EU, with the corresponding national competent authority taking the monographs into account when examining an application.

In the United States, United Kingdom and other major countries of the world, valerian is sold as a dietary supplement and in the case of the US, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the Food and Drug Administration are not required unless claims are made for specific disease prevention or treatment. Because dietary supplements are not always tested for manufacturing consistency, the composition may vary considerably between manufacturing lots.⁵¹

4. Population, Intervention, Comparator, Outcome (PICO)

PICO provides a structured framework for evidence-based medicine by defining the main components of an HTA research question. PICO 1 (**Table 2**) and PICO 2 (**Table 3**) present the PICOs regarding insomnia, PICO 3 (**Table 4**) regarding mental stress and PICO 4 (**Table 5**) regarding test anxiety. PICO 1 represents medicines containing valerian extract alone, while PICO 2 and 3 valerian combined with lemon balm or hops and PICO 4 valerian combined with lemon balm, passionflower and butterbur. The PICOs were defined in consultation with Swiss clinical experts in psychiatry and neurology, as well as a phytotherapy expert, which is a member of the “Schweizerische Medizinische Gesellschaft für Phytotherapie”.

Table 2: PICO 1 Patients with symptoms of insomnia treated with medicines containing valerian extract alone

P:	Patients (≥ 6 years) with symptoms ^c of insomnia
I:	Medicines containing valerian extract alone
C:	C-1 Placebo C-2 Lifestyle adaptation C-3 Improvement of sleep hygiene C-4 Other herbal medicines C-5 Cognitive behaviour therapy C-6 Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), or sedative antidepressants) C-7 No treatment
O:	Efficacy/effectiveness: – latency time in minutes until getting to sleep – number of night awakenings – wakefulness after sleep onset (WASO) – wake duration – sleep duration – objective sleep quality/efficiency (as per PSG or wrist actigraphy) – subjective sleep quality – feeling of waking up refreshed – daytime sleepiness – quality of life Safety: – adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) – serious adverse events – discontinuation due to intervention Economic: – total and incremental costs, total and incremental Quality-Adjusted Life Years (QALYs) and effects and Incremental Cost-Effectiveness Ratio (ICER) – budget impact

^c Insomnia symptoms such as difficulty falling or staying asleep and unsatisfying sleep.

Table 3: PICO 2 Patients with symptoms of insomnia treated with medicines containing valerian extract combined with lemon balm or hops

P:	Patients (≥ 6 years) with symptoms ^d of insomnia
I:	Medicines containing valerian extract in combination with lemon balm or hops
C:	C-1 Placebo C-2 Lifestyle adaptation C-3 Improvement of sleep hygiene C-4 Other herbal medicines C-5 Cognitive behaviour therapy C-6 Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), or sedative antidepressants) C-7 No treatment
O:	Efficacy/effectiveness: – latency time in minutes until getting to sleep – number of night awakenings – wakefulness after sleep onset (WASO) – wake duration – sleep duration – objective sleep quality/efficiency (as per PSG or wrist actigraphy) – subjective sleep quality – feeling of waking up refreshed – daytime sleepiness – quality of life Safety: – adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) – serious adverse events – discontinuation due to intervention Economic: – total and incremental costs, total and incremental QALYs and effects and ICER. – budget impact

^d Insomnia symptoms such as difficulty falling or staying asleep and unsatisfying sleep.

Table 4: PICO 3 Patients with symptoms of mental stress treated with medicines containing valerian extract combined with lemon balm or hops

P:	Patients (≥ 6 years) with symptoms of mental stress
I:	Medicines containing valerian extract in combination with lemon balm or hops
C:	C-1 Placebo C-2 Other herbal medicines C-3 Cognitive behaviour therapy C-4 Medication (e.g., selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, or benzodiazepines) C-5 No treatment
O:	Efficacy/effectiveness: – change in anxiety symptoms (e.g., Hamilton Anxiety Scale (HAM-A) and other anxiety symptom scales) – quality of life Safety: – adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) – serious adverse events – discontinuation due to intervention Economic: – total and incremental costs, total and incremental QALYs and effects and ICER. – budget impact

Table 5: PICO 4 Patients with symptoms of test anxiety treated with medicines containing valerian extract combined with lemon balm, passionflower and butterbur

P:	Patients (≥ 6 years) with symptoms of test anxiety
I:	Medicines containing valerian extract in combination with lemon balm, passionflower and butterbur
C:	C-1 Placebo C-2 Other herbal medicines C-3 Cognitive behaviour therapy C-4 Medication (e.g., selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, or benzodiazepines) C-5 No treatment
O:	Efficacy/effectiveness: – change in test anxiety symptoms (e.g., STAI-State and other anxiety symptom scales) – quality of life Safety: – adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) – serious adverse events – discontinuation due to intervention Economic: – total and incremental costs, total and incremental QALYs and effects and ICER. – budget impact

5. HTA research questions

The evaluated technology are medicines containing valerian extract, either alone or combined with lemon balm, hops and/or other herbal extracts. For the evaluation of this health technology the following research questions, covering central HTA domains, as designated by the European network for HTA (EUnetHTA) Core Model (clinical effectiveness, safety, cost-effectiveness, budget impact, ethical, legal, social and organisational (ELSO) aspects), are addressed. Research questions 1 and 2 evaluate the efficacy, effectiveness and safety of these medicines and research questions 3 and 4 evaluate the cost-effectiveness and budget impact. Research question 5 examines the ethical, legal, social and organisational issues related to the use of medicines containing valerian.

1. Are medicines containing valerian (alone or in combination) efficacious or effective compared to placebo, other herbal medicines, CBT, other medications or no treatment (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene) in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety?
2. Are medicines containing valerian (alone or in combination) safe compared to placebo, other herbal medicines, CBT, other medications, or no treatment (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene) in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety?
3. What is the cost-effectiveness of medicines containing valerian (alone or in combination)?
4. What is the budget impact of Dormiplant®, Hova®, Redormin®, Relaxane®, Sedonium® for the currently reimbursed populations?
5. Are there ethical, legal, social or organisational issues related to the use of medicines containing valerian (alone or in combination) for treating symptoms of insomnia, mental stress or test anxiety?

6. Effectiveness, efficacy and safety

Summary statement efficacy, effectiveness and safety

A systematic review of 36 studies (33 RCTs and 3 observational studies) examined valerian-containing preparations for insomnia (31 RCTs and 2 observational studies), mental stress (3 RCTs and one observational study) and anxiety/test anxiety (2 RCTs). Meta-analyses of valerian monotherapy versus placebo for most insomnia outcomes showed no statistically significant benefits: sleep latency (mean difference (MD): -0.99 minutes, 95% confidence interval (CI) -5.41 to 3.44, moderate certainty), sleep duration (MD: 3.16 minutes, 95% CI -7.07 to 13.39, moderate certainty), sleep quality reported as change from baseline (standardised MD (SMD) : -0.03, 95% CI -0.21 to 0.15, moderate certainty), night awakenings (SMD for outcomes reported as post-intervention: -0.20, 95% CI -0.65 to 0.25, moderate certainty, SMD for outcomes reported as change from baseline: -0.06, 95% CI -0.42 to 0.30, low certainty), and sleep efficiency (MD: 1.36, 95% CI -2.58 to 5.30, low certainty). In contrast, two outcomes showed statistically significant differences in favour of valerian: sleep quality at post-intervention assessment (SMD: -1.51, 95% CI -2.84 to -0.17, low certainty) and the PSQI total score (MD: -3.67, 95% CI -5.22 to -2.13, moderate certainty). Of note, two of the three RCTs contributing to the post-intervention sleep quality analysis had a follow-up of only one day. When excluded, only one study with a 28-day follow-up remained, resulting in considerable uncertainty around this finding. Subgroup analyses excluding studies with follow-up durations shorter than 7 days and shorter than 14 days confirmed the main results for all other outcomes. Valerian combinations with hops or lemon balm for symptoms of insomnia demonstrated no significant differences versus placebo (very low certainty). Comparisons with benzodiazepines were limited but showed no significant differences (very low to moderate certainty). For symptoms of mental stress and test anxiety or anxiety, meta-analysis was not possible as only one study per outcome was included. Regarding safety, a meta-analysis was only feasible for the combination of valerian, lemon balm, passionflower and butterbur versus placebo in patients with test anxiety or anxiety, which showed no statistically significant difference. Observational studies compared valerian-containing medicines against different other complementary medicines and did not include placebo or benzodiazepine comparators. Meta-analysis was not possible due to heterogeneity in comparators.

6.1 Methodology effectiveness, efficacy and safety

6.1.1 Databases and search strategy

A systematic literature review of RCTs, non-randomised controlled trials and controlled observational studies has been conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions⁵⁸ and follows the reporting guidelines outlined in the Preferred Reporting

Items for Systematic Review and Meta-Analysis (PRISMA).⁵⁹ The search strategy has been developed based on the PICO framework (**Chapter 4**) in collaboration with a medical librarian, following current best practice guidelines and taking the European Union herbal monographs on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos and on *Valeriana officinalis* L., radix into account.^{55,56,58} Both, the PICO framework and the search strategy were developed with the consultation of 3 clinical experts specialising in sleep medicine, psychiatry and phytotherapy. Several relevant systematic reviews, meta-analyses and network meta-analyses studies were also considered when building the search strategy and were also used to validate its quality.^{1,4–7,60–69} The systematic literature search was conducted using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE, PsycInfo and Web of Science. The search strategy focused only on the intervention component of PICO, while population, comparators and outcomes were not specified to avoid undue narrowing of the search results. Search limits were applied to capture only controlled clinical studies conducted in humans. Eligible study designs included RCTs, non-randomised controlled studies, observational studies with a control group (including longitudinal and retrospective designs and post marketing surveillance studies). Studies on infants and conference abstracts were excluded. The detailed search strategy in each database is outlined in **Appendix A**. All studies were imported to CADIMA for study selection.

The inclusion and exclusion criteria have been defined according to the PICO framework and are presented in **Table 6**. All relevant outcomes defined in the PICOs were considered. Although valerian-containing medicines in Switzerland are specifically indicated for symptoms related to mental stress or test anxiety (PICO 3 and 4), the literature search included a broader population (anxiety in general) to optimise the pool of evidence, in case little evidence for the subpopulation was available. There were no restrictions on the country, setting, sample size or publication period. The study design for the systematic literature review was restricted to RCT, non-randomised controlled trials and controlled observational studies. The publication language had to be English, French, German, or Italian. Studies were eligible if they provided results for at least one outcome of interest.

Table 6: Inclusion and exclusion criteria for clinical evidence

	Inclusion	Exclusion
Population	Human patients (≥ 6 years) with symptoms of insomnia, mental stress or test anxiety/anxiety	Any other population
Intervention	Medicines containing valerian extract alone and medicines in which valerian is combined with either: 1) Lemon balm 2) Hops 3) Lemon balm, butterbur and passionflower	Any other intervention
Comparator	• Placebo • Lifestyle adaptation • Improvement of sleep hygiene • Other herbal medicines • Cognitive behaviour therapy • Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), sedative antidepressants, selective serotonin reuptake inhibitors or tricyclic antidepressants)) • No treatment Only medications approved for use in Switzerland will be considered as comparators.	Any other comparator
Outcomes	Efficacy, effectiveness and safety outcomes mentioned in Chapter 4	No efficacy, effectiveness or safety outcomes Outcomes only on pharmacokinetics or pharmacodynamics
Study design	RCT, non-randomised controlled trials or controlled observational studies	Any other study design
Language	English, French, German or Italian	Any other language—
Country	No restrictions	—
Setting	No restrictions	—
Publication period	No restrictions	—
Publication status	Published in a peer-reviewed journal with full-text or essential content available	Published as a book, conference abstract, or journal article without full-text or essential content available

Abbreviation: RCT, Randomised Controlled Trial

In the first step, references were screened by title and abstract by 2 reviewers independently using the inclusion/exclusion criteria. In the second step, full texts of retained studies were reviewed independently by 2 reviewers. Disagreements were resolved by consensus or by consulting a third reviewer. Prior training sessions were held to increase consistency between reviewers. A PRISMA flow diagram was created to illustrate study selection results, including the primary reasons for exclusion.

6.1.2 Other sources

Systematic searches were conducted in clinicaltrials.gov and the WHO International Clinical Trials Registry to gain insights into planned or ongoing RCTs. References were screened as described above. Search terms are outlined in **Appendix A**. Inclusion and exclusion criteria were defined as presented in **Table 6**, except that publication status was unrestricted.

6.1.3 Assessment of quality of evidence

The methodological quality of RCTs reporting outcomes presented in the **Chapter 6.2.5 Findings** efficacy and effectiveness were critically appraised according to the Cochrane Risk of Bias 2 tool for randomised trials (RoB 2).^{70,71} RoB assessment was conducted at the outcome level, covering all outcomes included in the meta-analyses. RoB Figures were generated. If a study adequately

addressed the specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it was judged as “low risk of bias” in this domain. Description of an inadequate method was judged as “high risk of bias” and, if minor concerns appeared or when insufficient information was reported to assess the domain adequately, as “some concerns in risk of bias”. The judgement of the most severe individual domain was assigned to the overall risk of bias. Outcomes judged as some concerns for multiple domains could lead to an overall high risk of bias if the concerns substantially lowered the confidence in the results. The assessment was performed independently in duplicate and inconsistencies were solved by consensus. Where consensus was not reached, a third reviewer was consulted. Funnel plots were not performed to assess publication bias or the effects of small sample sizes, as fewer than 10 studies per outcome and comparison were available, which could compromise the reliability of these methods.^{72–75}

Observational studies eligible for meta-analysis would have been assessed for quality using the Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.⁷⁶ However, none of the included observational studies were eligible for meta-analysis, as none used placebo or benzodiazepines as comparators. Therefore, their quality was not appraised.

To obtain an overall rating of confidence in the estimated effects, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied and the confidence in evidence was rated in duplicate.⁷⁷ For PICO 1 and 2 the outcomes sleep latency (time to fall asleep), quality, duration, efficacy (percentage of total time in bed actually spent in sleep), night awakenings, Pittsburgh Sleep Quality Index (PSQI) total score and adverse events were assessed. For PICO 3 and 4 State-Trait-Anxiety-Inventory (STAI), anxiety and adverse events were examined. The GRADE evidence tables were derived using the online tool.⁷⁸ Disagreements between raters were solved by consensus. Where consensus was not found, a third reviewer was consulted. As some outcomes are presented in the form of composite scores, a brief explanation of these measures is provided here.

The Pittsburgh Sleep Quality Index (PSQI) is a widely used self-report questionnaire that assesses sleep quality over a one-month period. The instrument comprises seven components, each scored from 0 to 3, with higher scores indicating greater dysfunction. These component scores are summed to yield a global PSQI score ranging from 0 to 21. Scores above 5 suggest significant sleep difficulties, with higher values reflecting poorer sleep quality. The validity of the PSQI has been rigorously established.⁷⁹

The State-Trait Anxiety Inventory (STAI), developed by Spielberger, Gorsuch, Lushene, Vagg and Jacobs (1983), is a widely utilised instrument for measuring both state and trait anxiety. The most widely used version, Form Y, comprises 40 items total: 20 dedicated to evaluating trait anxiety and 20 for state anxiety. Examples of state anxiety questions include: "I am tense; I am worried" and "I feel calm; I feel secure," while trait anxiety questions feature items such as: "I worry too much over something that really doesn't matter" and "I am content; I am a steady person." Respondents rate

each item using a 4-point scale (ranging, for instance, from "Almost Never" to "Almost Always"), with elevated scores reflecting increased anxiety levels.⁸⁰

6.1.4 Methodology data extraction, analysis and synthesis of the domain's efficacy, effectiveness and safety

6.1.4.1 Data extraction

Relevant data from included studies were extracted by a single reviewer using REDCap, which was pilot-tested with selected studies retained after full-text screening. A second reviewer checked the data against the original publication. Disagreements were resolved by consensus, with a third reviewer consulted if needed. To ensure consistency, prior training sessions were conducted. The REDCap data extraction form included the following information (for outcomes on study arm level):

- Study characteristics: first author, title, country, publication year, setting, study period, length of follow-up and source of funding.
- Population: age and sex, diagnosis, symptoms, sample size, number of randomised persons per study arm, comorbidities.
- Intervention: valerian drug, administration regimen, dosage, herbal preparation, timing after symptom onset and timing in relation to CBT, frequency, treatment duration.
- Comparator: exact comparator, administration regimen, dosage, timing after symptom onset, frequency, treatment duration.
- Outcomes: effect sizes and summary measures of clinical efficacy, effectiveness and safety outcomes mentioned in **Chapter 4** (incl. method of assessment of adverse events).
- Quality Assessment: Information relevant to assess the quality of studies (i.e., information to perform the Risk of Bias (RoB) and Grading of Recommendations Assessment, Development and Evaluation (GRADE)).
- Additional Comments: Study limitations or issues not identifiable from other extracted data.

Details of ongoing or stopped RCTs identified in clinical trial registries were extracted and summarised in a table. This table includes information on trial status, country, study period, population, intervention, comparator, outcomes and estimated completion date.

6.1.4.2 Data analysis and synthesis

The included studies were presented separately for insomnia, mental stress and test anxiety/anxiety in a table with information on study characteristics and relevant outcomes. RoB Figures and a GRADE summary table were provided (See **Chapter 6.1.3**).

Before conducting pairwise meta-analyses, clinical and methodological heterogeneity among included studies were assessed by evaluating whether participants, interventions, comparisons and outcomes are judged to be sufficient similar to ensure that pooling estimates is methodologically

appropriate (i.e., similar instruments). Separate pairwise meta-analyses were conducted for each outcome and each comparator to pool the estimated effects from the included studies with sufficient data for outcomes reported by at least 2 studies. When a study reported outcomes at multiple follow-up time points, the longest available follow-up period was included in the analysis. When a study measured the outcome using both subjective (e.g. sleep diary or questionnaire) and objective (e.g. polysomnography or wrist actigraphy) instruments, the objectively measured outcome was prioritized for inclusion in the meta-analysis. When both polysomnography and wrist actigraphy were available, polysomnography was prioritized as it represents the gold standard for objective sleep measurement. Including only one measurement per outcome per study ensures the independence of observations required for valid meta-analytic pooling. When meta-analysis was possible, forest plots were presented. Cumulative meta-analysis was not feasible due to the insufficient number of studies included. Pairwise meta-analyses were conducted using the *metafor* package in R.⁸¹ Heterogeneity was addressed by employing a random-effects model with the restricted maximum likelihood method following the guidance of the Cochrane Handbook.⁵⁸ Continuous data were pooled using weighted mean differences (MD) or standardised mean differences (SMD). MD were calculated when all studies measured outcomes using the same scale, while SMD were calculated when studies assessed the same outcome using different measurement scales. Post-intervention values and change from baseline values were pooled in MD meta-analyses. However, in SMD meta-analyses, these two types of metrics were analysed separately (i.e., one meta-analysis was conducted for change from baseline values and one for post-intervention values). Where means were not available, medians were transformed to means^{82–84} and 95% confidence intervals (CI) or p-values were converted to standard deviations.^{83,84} Binary outcomes were analysed using relative risks as the effect measure.⁵⁸ For studies with no events in one or both arms, computation error may arise due to division by zero, which occurs when the calculations involve a zero count. To address this issue, studies with no events in both arms were excluded from the meta-analysis. They were also excluded because studies with no events in both arms do not provide any indication of either the direction or magnitude of the relative treatment effect. For studies with no events in one arm, a fixed value of 0.5 was added to all cells of the 2×2 table.⁸⁵ Uncertainty was expressed with 95% confidence intervals. When the number of studies is limited, heterogeneity measures such as I square and Tau square are subject to considerable uncertainty. Therefore, simple thresholds for identifying heterogeneity were not applied and prediction intervals were not calculated. Where pairwise meta-analyses were not possible, the evidence was described narratively using the Synthesis Without Meta-analysis (SWiM) guideline.⁸⁶

Meta-regression analyses were not feasible due to the limited number of included studies, which also precluded extensive subgroup analyses. Subgroup meta-analyses were conducted excluding studies with follow-up durations shorter than 7 days and shorter than 14 days. Furthermore, subgroup meta-analyses were conducted excluding studies involving specific comorbidities. According to a clinical expert consulted, none of the comorbidities included in this analysis represented contraindications for valerian therapy. However, certain conditions such as restless leg syndrome,

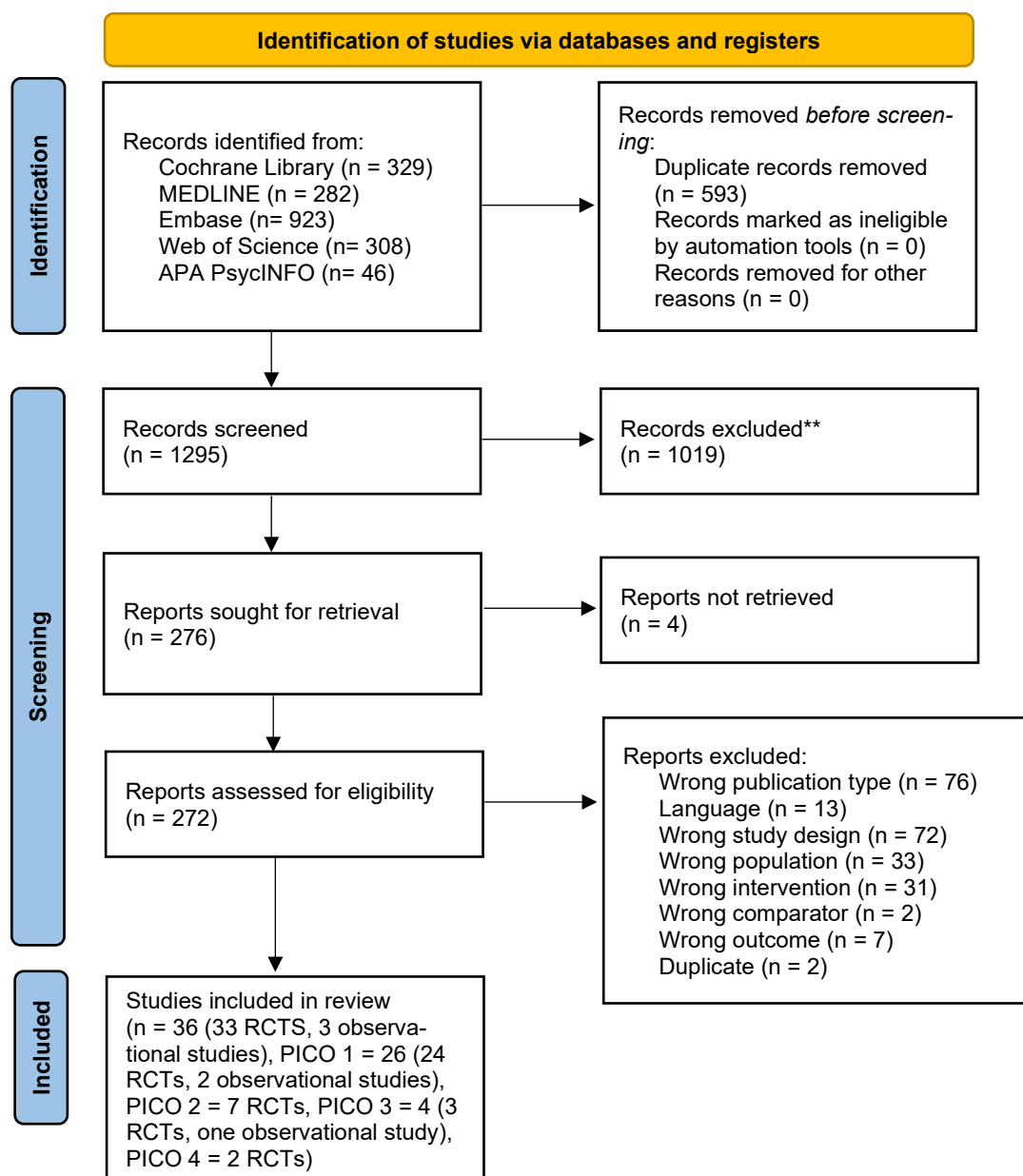
menopausal/postmenopausal conditions, or inflammatory complaints may have caused sleep disturbances that did not substantially respond to valerian therapy, potentially biasing results. Sub-group meta-analyses excluding studies involving these conditions were therefore conducted. Other conditions such as somatoform disorder or haemodialysis patients were retained in the main analyses, as they were not expected to substantially interfere with the treatment response to valerian.

6.2 Results effectiveness, efficacy and safety

6.2.1 PRISMA flow diagram

In total, 1'295 unique records were identified through the literature searches (*Figure 1*) Of these, 1'019 were excluded based on their titles and abstracts and 4 due to missing full texts. The full texts of the remaining 272 records were screened, resulting in the exclusion of 236 records. The most common reasons for exclusion were that the studies had either a wrong publication type (not published in a peer-reviewed journal), wrong study design or a wrong population or intervention. Ultimately 36 records were included for the assessment of clinical efficacy, 33 RCTs and 3 observational studies with control.

Figure 1: PRISMA flow diagram



6.2.2 Study characteristics and quality assessment of included studies

6.2.2.1 PICO 1, 26 studies (**Table 7**)

Interventions and Comparators: 19 RCTs compared valerian with placebo^{87–105}, 3 RCTs compared valerian with benzodiazepines^{106–108} and one RCT compared valerian with Gabapentin¹⁰⁹. 2 observational studies compared valerian with other treatments (Lavender¹¹⁰ and Neurexan¹¹¹). One study did not report the study design but compared valerian with relaxation therapy (Benson method) and placebo.¹¹²

Dosage: Dosages ranged from 200mg to 3600mg of valerian, with the most frequently used dosage being 600mg.^{92–94,103,105–107} Other commonly used dosages included 450mg^{88,90,98} and

530mg.^{87,104,109} The minimum⁸⁹ and maximum⁹⁹ dosages were each used in only one study. Two studies analysed multiple dosages within the same trial.^{92,98} One study did not report the dosage administered.¹⁰⁸

Population: 15 RCTs and one observational study focused on adults without specific medical conditions^{89,90,92–100,103,105–107,111}, 7 RCTs investigated patients with specific health conditions (HIV⁸⁷, cancer⁸⁸, chronic heart failure¹⁰⁸, haemodialysis patients^{104,109}, arthritis¹⁰², or restless leg syndrome⁹¹) and 3 studies focused on women-specific populations (menopause (study design not reported)¹¹², postmenopause (RCT)¹⁰¹ and pregnancy (observational study)¹¹⁰). Twenty RCTs recruited both women and men, while 3 RCTs recruited only women.^{100,101,103} The mean age of participants ranged from 33 to 60 years across all studies. Sample sizes ranged from 8 to 405 participants, with a total of 2.52 participants across all 26 studies.

Follow-up: The follow-up duration varied considerably across studies. Four RCTs investigated acute effects over 1-3 days^{92,93,97,98}, 5 RCTs examined short-term effects over 1-2 weeks^{94,99,100,102,103} and 16 studies (14 RCTs^{87–91,95,96,101,104–109}, one observational study¹¹¹, one study design not reported¹¹²) investigated medium-term effects over 1-2 months. One observational study did not report follow-up duration.¹¹⁰

Funding: Three RCTs^{89,94,97} were industry-funded, 8 RCTs^{87,88,99,101,102,104,108,109} and one observational study¹¹⁰ were publicly funded and 11 RCTs^{91–93,95,96,98,100,103,105–107}, one observational study¹¹¹ and one study without reported study design¹¹² did not report their funding source. One RCT⁹⁰ received mixed funding from both industry and public institutions.

Geographic Distribution: The studies were conducted across multiple countries: Iran^{87,101,104,108,109,112}, Germany^{94,96,105,106}, USA^{88,91,95,103}, Switzerland^{97,110} and one study each in India⁸⁹, Australia⁹⁰, Norway⁹⁹ and UK⁹². Five RCTs did not report the country, where it took place.^{93,98,100,102,107}

6.2.2.2 PICO 2, 7 studies (**Table 8**)

Interventions and Comparators: Seven RCTs compared valerian combinations (valerian-lemon balm^{113,114}, valerian-hops^{96,97,115–117}) with placebo and 2 RCTs additionally compared valerian-hops combinations with other treatments (chlorpheniramine¹¹⁵ and diphenhydramine¹¹⁶).

Dosage: All RCTs employed fixed-dose combinations of valerian with other herbal ingredients. Valerian dosages ranged from 320 mg to 640 mg. Five RCTs combined valerian with hops (80-200 mg) and 2 RCTs combined valerian with lemon balm (160-320 mg).

Population: 5 RCTs focused on adults without specific medical conditions^{96,97,113,116,117}, one RCT investigated war refugees¹¹⁵ and one RCT focused on menopausal women¹¹⁴. Five RCTs recruited both women and men, with the proportion of women varying between 40% and 73.5%. One RCT recruited only women¹¹⁴, while another RCT did not report the share of females¹¹⁷. The mean age of participants ranged from 35.8 to 59.7 years. Sample sizes ranged from 15 to 262 participants per RCT, with a total of 813 participants across all 7 RCTs.

Follow-up: The follow-up duration varied considerably. 2 RCTs investigated acute effects over one day^{97,115}, one RCT examined short-term effects over 14 days¹¹³ and 4 RCTs investigated medium-term effects ranging from 28 to 42 days^{96,114,116,117}.

Funding: Three RCTs were industry-funded^{97,116,117}, one RCT was funded by an academic institution¹¹⁵ and 3 RCTs did not report their funding source^{96,113,114}.

Geographic Distribution: Three RCTs have been conducted in Germany^{96,113,117} and 1 study each in Jordan¹¹⁵, Switzerland⁹⁷, United States¹¹⁶ and Iran¹¹⁴.

6.2.2.3 PICO 3, 4 studies (**Table 9**)

Interventions and Comparators: Three RCTs compared valerian combinations (valerian-hops^{115,118}, valerian-lemon balm¹¹⁹ with placebo, one RCT additionally compared valerian-hops combination with Chlorpheniramine¹¹⁵ and one observational study compared valerian with melissa and/or passionflower and other herbal remedies¹²⁰.

Dosage: All RCTs employed fixed-dose combinations of valerian with various herbal ingredients. Valerian dosages ranged from 320 mg to 1080 mg. Two RCTs combined valerian with hops (80mg¹¹⁵/120 mg¹¹⁸) and one study combined valerian with lemon balm in multiple dosages (240-720 mg)¹¹⁹.

Population: One RCT¹¹⁹ and the observational study¹²⁰ focused on adults without specific medical conditions, one RCT focused on patients after molar tooth removal¹¹⁸ and one RCT investigated war refugees¹¹⁵. The RCTs and the observational study recruited both women and men, with share of females ranging from 50% to 66.9%. The mean age ranged between 23.3 and 46 years and the sample sizes from 24 to 374 with a total of 703 participants across all 4 studies.

Follow-up: The follow-up duration varied across studies, ranging from an acute single-dose RCT¹¹⁹ with 0 days of follow up to a short-term observational study of 15 days¹²⁰. Two RCTs had a follow-up period of 1 day.^{115,118}

Funding: 1 RCT received funding of an academic institution¹¹⁵ and the observational study was industry-funded¹²⁰. The 2 other RCTs did not report their funding source.^{118,119}

Geographic Distribution: Two RCTs have been conducted in Jordan¹¹⁵ and Brazil¹¹⁸. The observational study was conducted in Italy¹²⁰ and one RCT did not report the country, where the RCT took place¹¹⁹.

6.2.2.4 PICO 4, 2 studies (**Table 10**)

Interventions and Comparators: Both RCTs compared valerian multi-herb combinations with placebo^{121,122}. Additionally one RCT¹²¹ included a no-treatment control group and one RCT¹²² used as a 3rd arm almost the same combination, leaving out only the butterbur.

Dosage: Both RCTs^{121,122} employed identical fixed-dose combinations containing 4 herbal ingredients: valerian 270 mg, lemon balm 180 mg, passion flower 270 mg and butterbur 270 mg. The 3rd arm of an RCT¹²² used the same dosages of valerian, lemon balm and passion flower, but without the butterbur.

Population: One RCT¹²¹ focused on healthy men without specific medical conditions who were exposed to an experimental acute stress setting (n=72, mean age 24.7 (intervention) and 26.74

(control). The second RCT¹²² investigated patients with somatoform disorders (physical discomfort without a recognizable organic cause) (n=182, mean age 39 (intervention) and 43.6 (control); 65-72% female). Total sample size across both RCTs was 254 participants.

Follow-up: Both RCTs investigated short-term effects only, with follow-up periods of 5 and 14 days respectively.

Funding: Both RCTs were industry-funded.

Geographic Distribution: The studies were conducted in Switzerland¹²¹ and Germany¹²².

6.2.3 Evidence table

Table 7: Study characteristics of included studies for PICO 1

First author year	Study design	Country Funding	Study arms	Length of follow-up	Mean age Share of females	Total sam- ple size	Comorbidities/ Characteristics	Dosage (mg)
Ahmadi 2017 ⁸⁷	RCT	Iran grant from the Office of Vice- Chancellor for Research of Tehran University of Medical Sciences	Valerian + Placebo	28 Days	I: 36.4 (7.73) C: 34.1 (7.09) I: 36% C: 30.7%	51	HIV	Valerian: 530
Aliakbari 2018 ¹⁰⁸	RCT	Iran Research and Technology Dep- uty of Sharekord University of Medical Sciences	Valerian + Benzodi- azepines	1 Month	58.1 (10) 62.5%	80	Chronic heart failure	NR
Barton 2011 ⁸⁸	RCT	USA Public Health Service grants	Valerian + Placebo	2 Months	I: 59.5 (11.95) C: 58.3 (12.71) I: 80% C: 85%	119	Cancer	Valerian: 450
Chandra Shekhar 2024 ⁸⁹	RCT	India OmniActive Health Technolo- gies Limited	Valerian + Placebo	56 Days	I: 35.35 (0.92) C: 33.57 (1.06) I: 59.46% C: 54.29%	80	none	Valerian: 200
Coxeter 2003 ⁹⁰	RCT	Australia General Practice Evaluation Program and Mediherb	Valerian + Placebo	42 Days	I: 54 (15) I: 54%	42	none	Valerian: 450
Cuellar 2009 ⁹¹	RCT	USA NR	Valerian + Placebo	56 Days	I: 50.3 (13.5) C: 48.7 (13.1) I: 70.6% C: 78.9%	37	Restless leg syndrome	Valerian: 800
Diaper 2004 ⁹²	RCT	UK NR	Valerian + Placebo	1 Day	55.9 (4.68) 69%	16	none	Valerian: 300
Diaper 2004 ⁹²	RCT	UK NR	Valerian + Placebo	1 Day	55.9 (4.68) 69%	16	none	Valerian: 600
Dimpfel 2007 ⁹³	RCT	NR NR	Valerian + Placebo	3 Days	I: 54.9 (8.3) C: 47.6 (6.7) 44%	36	none	Valerian: 600
Donath 2000 ⁹⁴	RCT	Germany Lichtwer Pharma GmbH	Valerian + Placebo	14 Days	49 75%	16	none	Valerian: 600
Dorn 2000 ¹⁰⁷	RCT	NR NR	Valerian + Benzodi- azepines	28 Days	I: 50.6 (12.4) C: 53.9 (12) I: 77% C: 61%	75	none	Valerian: 600

Gantner 2021 ¹¹⁰	Observational study with control	Switzerland One author contributed to this project while being financially supported by the Swiss National Science Foundation (SNF; Sinergia) grant	Valerian + Lavender	NR	NR NR	26	Pregnancy	none
Hajizadeh 2023 ¹⁰⁹	RCT	Iran Rafsanjan University of Medical Sciences	Valerian + Gabapentin	1 Month	I: 59.37 (15.14) C: 60.26 (14.9) I: 56% C: 53%	40	Haemodialysis patients	Valerian: 530
Jacobs 2005 ⁹⁵	RCT	USA NR	Valerian + Placebo	28 Days	I: 42.7 (10) C: 40.5 (10) I: 79% C: 78%	391	none	Valerian: 640
Jokar 2016 ¹¹²	RCT	Iran NR	Valerian + Relaxation therapy (Benson method) + Placebo	1 Month	I: 54.68 (6.95) C: 55.23 (4.88) I: 100% C: 100%	129	Menopause	Valerian: 1060
Koetter 2007 ⁹⁶	RCT	Germany NR	Valerian + Placebo	28 Days	I: 36.1 (12.7) C: 41.4 (17.2) I: 60% C: 40%	30	none	Valerian: 500
Leathwood 1982 ⁹⁶	RCT	Switzerland Nestlé Research Laboratories	Valerian + Placebo	1 Day	NR 44%	128	none	Valerian: 400
Leathwood 1985 ⁹⁸	RCT	NR NR	Valerian + Placebo	1 Day	45 37.5%	8	none	Valerian: 450
Leathwood 1985 ⁹⁸	RCT	NR NR	Valerian + Placebo	1 Day	45 37.5%	8	none	Valerian: 900
Oxman 2007 ⁹⁹	RCT	Norway Norwegian Knowledge Centre for the Health Services	Valerian + Placebo	14 Days	I: 45.7 (13.8) C: 41.8 (12.9) I: 62% C: 60%	405	none	Valerian: 3600
Schulz 1994 ¹⁰⁰	RCT	NR NR	Valerian + Placebo	7 Days	I: 62 (6.8) C: 61.3 (6.7) I: 100% C: 100%	14	none	Valerian: 405
Taavoni 2011 ¹⁰¹	RCT	Iran Tehran University Medical Sciences	Valerian + Placebo	1 Month	I: 52.6 (3.3) C: 53.1 (3.5) I: 100% C: 100%	100	Postmenopausal	Valerian: 1060
Taibi 2009 ¹⁰²	RCT	NR NR	Valerian + Placebo	7 Days	I: 39.29 (18.67) C: 53.13 (10.73) I: 71% C: 87.5%	15	Arthritis: Osteoarthritis, Rheumatoid arthritis, Inflammatory polyarthritis, Ankylosing spondylitis or Psoriatic arthritis	Valerian: 300
Taibi 2009 ¹⁰³	RCT	USA NIH grants	Valerian + Placebo	14 Days	69.4 (8.1) I: 100% C: 100%	16	none	Valerian: 600

Tammadon 2021 ¹⁰⁴	RCT	Iran Semnan University of Medical Sciences	Valerian + Placebo	1 Month	66.4 48.7%	39	Haemodialysis patients	Valerian: 530
Vorbach 1996 ¹⁰⁵	RCT	Germany NR	Valerian + Placebo	28 Days	I: 47.2 (11.1) C: 47.6 (11.1) I: 62.3% C: 55%	121	none	Valerian: 600
Waldschütz 2008 ¹¹¹	Observational study with control	Germany NR	Valerian + Neurexan	28 Days	I: 50.1 (14.7) C: 50.5 (14.1) I: 68% C: 77%	320	none	Valerian: 250
Ziegler 2002 ¹⁰⁶	RCT	Germany NR	Valerian + Benzodiazepines	42 Days	I: 54.2 (12.3) C: 50.6 (12.6) I: 73.1% C: 61.3%	186	none	Valerian: 600

Abbreviations: SD, standard deviation; NR, not reported; RCT, randomized controlled trial; I, intervention group; C, control group

Table 8: Study characteristics of included studies for PICO 2

First author year	Study design	Country Funding	Study arms	Length of follow-up	Mean age and share of females	Total sample size	Comorbidities	Dosage (mg)
Dreßing 1996 ¹²³	RCT	Germany NR	Valerian combination + Placebo	14 Days	I: 59.7 C: 54.2 I: 73.5% C: 70.6%	68	none	Valerian: 640 Lemon balm: 320
Gammoh 2017 ¹¹⁵	RCT	Jordan American University of Madaba	Valerian combination + Placebo + Chlorpheniramine	1 Days	54 (13.61) 59.7%	262	none	Valerian: 320 Hops: 80
Koetter 2007 ⁹⁶	RCT	Germany NR	Valerian combination + Placebo	28 Days	I: 35.8 (13.2) C: 41.4 (17.2) I: 60% C: 40%	30	none	Valerian: 500 Hops: 120
Leathwood 1982 ⁹⁶	RCT	Switzerland Nestlé Research Laboratories	Valerian combination + Placebo	1 Days	NR 44%	128	none	Valerian: 400 Hops: 200
Morin 2005 ¹¹⁶	RCT	United States SmithKline Beecham	Valerian combination + Placebo + Diphenhydramine	42 Days	I: 43.9 (10.5) C: 45.2 (10.2) I: 59.3% C: 60%	210	none	Valerian: 374 Hops: 84
Rodenbeck 1998 ¹¹⁷	RCT	Germany Firma Knoll Deutschland GmbH	Valerian combination + Placebo	28 Days	I: 45.4 (11.6) C: 47.6 (12.5)	15	none	Valerian: 500 Hops: 120
Taavoni 2013 ¹¹⁴	RCT	Iran NR	Valerian combination + Placebo	1 Months	I: 52.5 (7.8) C: 53.7 (3.5) I: 100% C: 100%	100	Menopause	Valerian: 320 Lemon balm: 160

Abbreviations: SD, standard deviation; NR, not reported; RCT, randomized controlled trial; I, intervention group; C, control group

Table 9: Study characteristics of included studies for PICO 3

First author year	Study design	Country Funding	Study arms	Length of follow-up	Mean age and share of females	Total sample size	Comorbidities	Dosage (mg)
Gammoh 2017 ¹¹⁵	RCT	Jordan American University of Madaba	Valerian combination + Placebo + Chlorpheniramine	1 Days	45 (13.61) 59.7%	262	none	Valerian: 320 Hops: 80
Gasparini 2016 ¹²⁰	Observational study with control	Italy MediPragma Srl	Valerian combination+ Melissa and/or passion flower (C1) + other herbal remedies (C2)	15 Days	46 I: 66.9% C1: 52.4% C2: 69.1%	374	none	NR
Kennedy 2006 ¹¹⁹	RCT	NR NR	Valerian combination + Placebo	0 Days	23.48 (5.3) 50%	24	none	Valerian: 360 Lemon balm: 240
Kennedy 2006 ¹¹⁹	RCT	NR NR	Valerian combination + Placebo	0 Days	23.48 (5.3) 50%	24	none	Valerian: 720 Lemon balm: 480
Kennedy 2006 ¹¹⁹	RCT	NR NR	Valerian combination + Placebo	0 Days	23.48 (5.3) 50%	24	none	Valerian: 1080 Lemon balm: 720
Silva dos Santos 2023 ¹¹⁸	RCT	Brasil NR	Valerian combination + Placebo	1 Days	23.3 (3.1) 62.8%	43	Molar tooth removal	Valerian: 500 Hops: 120

Abbreviations: SD, standard deviation; NR, not reported; RCT, randomized controlled trial; I, intervention group; C, control group

Table 10 Study characteristics of included studies for PICO 4

First author year	Study design	Country Funding	Study arms	Length of follow-up	Mean age and share of females	Total sample size	Comorbidities/ Characteristics	Dosage (mg)
Meier 2018 ¹²¹	RCT	Switzerland Max Zeller Söhne AG	Valerian combination + Placebo + No treatment	5 Days	I: 24.7 (3.28) C: 26.74 (5.55) NR	72	none	Valerian: 270 Lemon balm: 180 Passion flower: 270 Butterbur: 270
Melzer 2009 ¹²²	RCT	Germany Zeller AG	Valerian combination + Placebo + Combination without butterbur	14 Days	I: 39 (14.3) C: 43.6 (15.3) I: 65% C: 72%	182	Somatoform disorders	Valerian: 270 Lemon balm: 180 Passion flower: 270 Butterbur: 270

Abbreviations: SD, standard deviation; NR, not reported; RCT, randomized controlled trial; I, intervention group; C, control group

Information regarding extraction solvent, drug extraction rate, composition and commercial preparation name of the included studies can be found in the **Appendix C**.

6.2.4 Risk of bias assessment

Figure 2 shows the risk of bias across all included RCTs and outcomes. The item "selection of the reported result" was judged as having some concerns in the vast majority of studies (93% across all outcomes), with only a small minority showing low risk, because no pre-specified analysis plan was available for most of the included studies. The risk of bias concerning the item "measurement of the outcome" was assessed as low in nearly all studies (95% of outcomes), with only a very small proportion showing high risk (5%) in which outcome assessors were not blinded to interventions status. For the item "missing outcome data", approximately 65% of outcomes showed low risk of bias, while about 7% had some concerns and 28% showed high risk because data were not available for all or nearly all participants randomised. The "deviations from intended interventions" showed low risk of bias for the vast majority of studies (91%), with some concerns in a smaller proportion (9%) because participants were not blinded. For "randomisation process", approximately 47% of outcomes resulted in low risk of bias, about 45% showed some concerns and roughly 8% had high risk of bias because baseline differences between intervention groups suggested a problem with the randomisation process.

The detailed risk of bias assessments for each outcome of interest of the included RCTs are presented in the **Appendix D**.

Regarding PICO 1 (insomnia), based on 21 unique studies with 60 outcomes, the overall bias for efficacy outcomes was predominantly judged as "some concerns" (75%) with 18% showing "high risk" and only 7% showing "low risk". The selection of the reported results resulted in "some concerns" for 93% of outcomes, with only 7% showing "low risk", as no pre-specified analysis was available for most of the included RCTs. The randomisation process showed mixed results, with 45% of outcomes having "low risk", 53% showing "some concerns" and 2% "high risk". Missing outcome data was generally well-handled with 78% "low risk", but 13% of outcomes showed "high risk". Measurement of the outcome performed well with 95% low risk outcomes. Safety outcomes followed similar patterns, with the majority being judged as "some concerns" due to the consistent issues with selection of reported results and occasional concerns about randomisation and missing data.

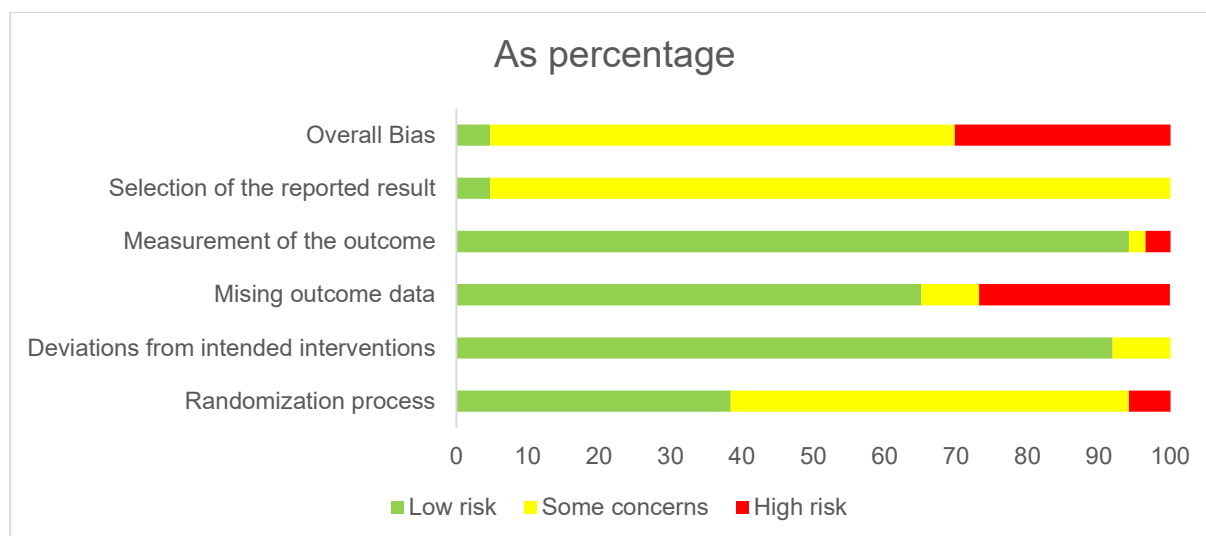
For PICO 2 (insomnia) based on 7 unique studies with 18 outcomes, the overall risk of bias was judged as predominantly "high risk" (67%) with 33% showing "some concerns" and no studies achieving low risk. All outcomes (100%) resulted in having "some concerns" regarding the selection of the reported results due to absent pre-specified analyses. The randomisation process was particularly problematic with only 11% showing "low risk", 67% having "some concerns" and 22% "high risk". Missing outcome data was a major concern with 67% of outcomes showing "high risk" and

only 33% “low risk”. However, deviations from intended interventions and measurement of outcomes performed well with 100% “low risk” outcomes.

For PICO 3 (mental stress) based on 3 unique studies with 4 outcomes, the overall bias was rated as predominantly “high risk” (75%) for most outcomes with only 25% showing “some concerns” and no studies achieving “low risk”. All outcomes (100%) had “some concerns” regarding the selection of the reported results due to the same issues as described for other PICOs. The randomisation process was reported as “some concerns” for all outcomes. Missing outcome data was particularly problematic with 75% of outcomes showing “high risk” and only 25% “low risk”. The measurement of outcomes and deviations from intended interventions performed better with 100% “low risk” outcomes.

For PICO 4 (test anxiety/anxiety) based on 2 unique studies with 4 outcomes, the overall bias was consistently rated as “some concerns” (100%) with no studies showing “high or low risk”. The randomisation process performed well with 100% “low risk” outcomes. Selection of reported results showed “some concerns” for all outcomes due to them missing pre-specified analyses. Missing outcome data and measurement of outcomes each showed 50% “low risk” and 50% “some concerns”. Deviations from intended interventions performed excellently with 100% of the outcomes reported as being “low risk” of bias.

Figure 2: Risk of bias across all studies and outcomes as percentage



6.2.5 Findings efficacy and effectiveness

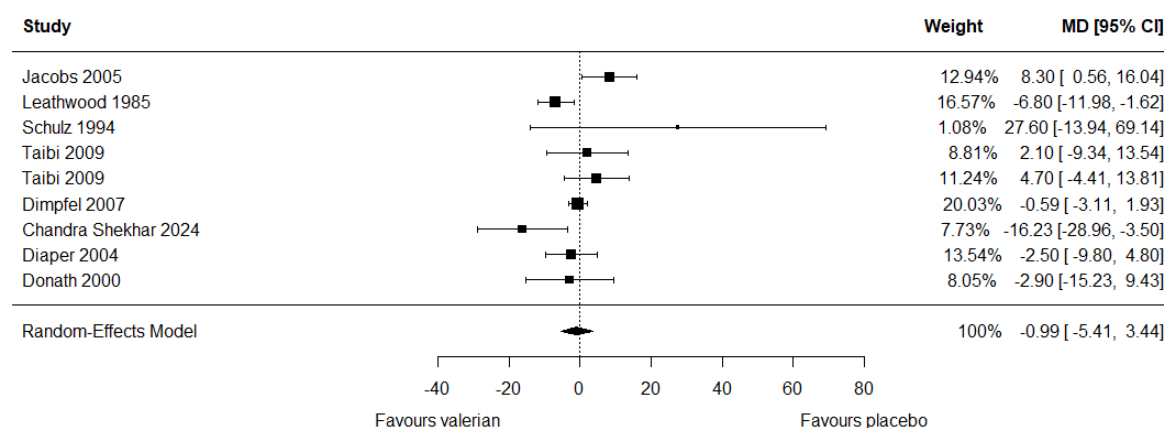
6.2.5.1 PICO 1: Placebo

6.2.5.1.1 Sleep latency

Nine RCTs that assessed sleep latency (time to fall asleep) for valerian compared to placebo were included in the meta-analysis. Sleep latency was not statistically significantly different between valerian and placebo. The pooled estimated MD was -0.99 minutes (95% CI -5.41 to 3.44, **Figure 3**), with substantial heterogeneity ($I^2 = 89.75\%$). An MD smaller than zero would favour valerian and

an MD greater than zero would favour placebo. Subgroup meta-analysis restricted to studies with follow-up ≥ 7 days, follow-up ≥ 14 days and no comorbidities also showed no statistically significant difference in sleep latency between valerian and placebo (**Figure A 1**, **Figure A 2** and **Figure A 3** in **Appendix E**).

Figure 3: Forest-plot of meta-analysis on sleep latency comparing valerian versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

Table 11 summarises the results of the RCTs that were not included in the meta-analysis. Koetter et al. 2007⁹⁶ did not report uncertainty measures and was therefore excluded from meta-analysis. Leathwood et al. 1985⁹⁸ assessed sleep latency using both an objective method (wrist actigraphy), which was included in the meta-analysis and a subjective method (questionnaire), which is presented in the **Table 11**. Similarly, Taibi et al. 2009¹⁰² used wrist actigraphy (included in the meta-analysis) and a questionnaire (shown in the **Table 11**). Chandra Shekhar et al. 2024⁸⁹ used 2 objective methods (polysomnography and wrist actigraphy). The polysomnography data was included in the meta-analysis, as it represents the gold standard for objective sleep measurement, and the actigraphy data is presented in the **Table 11**. Oxman et al. 2007⁹⁹, Coxeter et al. 2003⁹⁰ and Cuellar et al 2009⁹¹ did not report sleep latency in minutes but rather as proportion of treatment success or PSQI score. To calculate MD (rather than SMD) these studies were excluded from the meta-analysis and are presented in the **Table 11** only. Donath et al. 2000⁹⁴ measured sleep latency using both a polysomnography (included in the meta-analysis) and a questionnaire (shown in the **Table 11**).

Regarding treatment effects, Koetter et al. 2007⁹⁶, Leathwood et al. 1985⁹⁸, Chandra Shekhar et al. 2024⁸⁹ and Donath et al. 2000⁹⁴ favoured valerian, while Taibi et al. 2009¹⁰², Coxeter et al. 2003⁹⁰ and Cuellar et al 2009⁹¹ favoured placebo. Results from Oxman et al. 2007⁹⁹ were comparable between groups. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 11: Synthesis without meta-analysis on sleep latency comparing valerian versus placebo

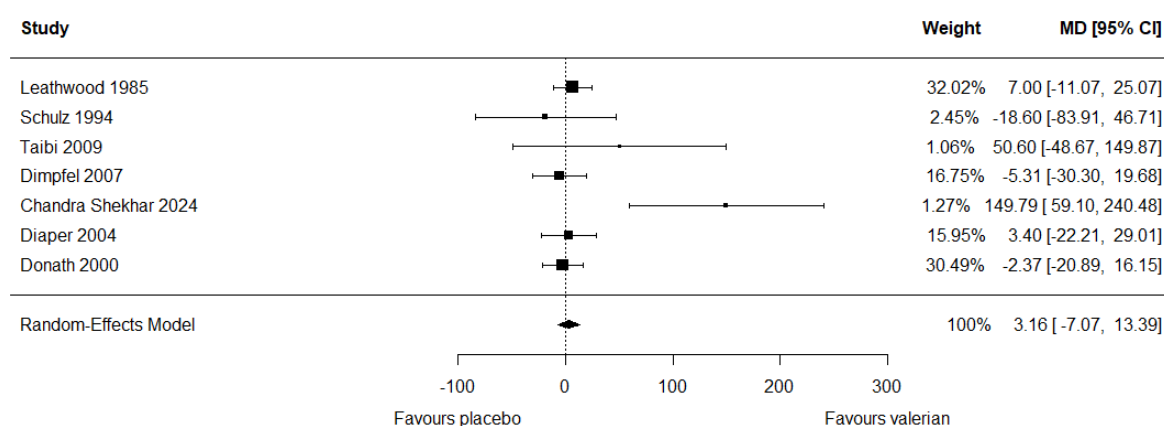
Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Koetter 2007 ⁹⁶	objective	change from baseline	minutes	-22.1	10	5.5	8
Leathwood 1985 ⁹⁸	subjective	change from baseline	9-point score (higher score = longer sleep latency)	4.3	7	4.9	7
Oxman 2007 ⁹⁹	subjective	change from baseline	score 1 to 7 (1 = < 5 minutes, 7 = ≥ 3 hours)	0.15	202	0.14	203
Taibi 2009 ¹⁰²	subjective	post-interv.	minutes	24.8	7	11.3	8
Chandra Shekhar 2024 ⁸⁹	objective	change from baseline	minutes	-48.03	37	-11.73	35
Coxeter 2003 ⁹⁰	subjective	change from baseline	proportion of treatment success	0.43	24	0.57	24
Cuellar 2009 ⁹¹	subjective	change from baseline	score 0 to 3 (higher score = longer sleep latency)	-0.4	17	-0.6	20
Donath 2000 ⁹⁴	subjective	post-interv.	minutes	45.83	16	60	16

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.1.2 Sleep duration

Seven RCTs that assessed sleep duration (time asleep) for valerian compared to placebo were included in the meta-analysis. Sleep duration was not statistically significantly different between valerian and placebo. The pooled estimated MD was 3.16 minutes (95% CI -7.07 to 13.39, **Figure 4**), with low heterogeneity ($I^2 = 0.00\%$). An MD smaller than zero would favour placebo and an MD greater than zero would favour valerian. Subgroup meta-analysis restricted to studies with follow-up ≥ 7 days, follow-up ≥ 14 days and no comorbidities also showed no statistically significant difference in sleep duration between valerian and placebo (**Figure A 4**, **Figure A 5** and **Figure A 6** in **Appendix E**).

Figure 4: Forest-plot of meta-analysis on sleep duration comparing valerian versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

Table 12 summarises the results of the RCTs that were not included in the meta-analysis. Oxman et al. 2007⁹⁹, Coxeter et al. 2003⁹⁰ and Cuellar et al. 2009⁹¹ did not report sleep duration in minutes but rather as score or as proportion of treatment success. To calculate MD (rather than SMD) these studies were excluded from the meta-analysis and are presented in the **Table 12** only. Taibi et al. 2009¹⁰² used wrist actigraphy (included in the meta-analysis) and a sleep diary (shown in the **Table 12**). Chandra Shekhar et al. 2024⁸⁹ used 2 objective methods (polysomnography and wrist actigraphy) and the polysomnography data was included in the meta-analysis and the actigraphy data is presented in the **Table 12**. Donath et al. 2000⁹⁴ measured sleep duration using both a polysomnography (included in the meta-analysis) and a questionnaire (shown in the **Table 12**).

Regarding treatment effects, Oxman et al. 2007⁹⁹ and Chandra Shekhar et al. 2024⁹⁰ favoured valerian, while Taibi et al. 2009¹⁰², Coxeter et al. 2003⁹⁰ and Donath et al. 2000⁹⁴ favoured placebo. Cuellar et al. 2009⁹¹ found no difference between treatments. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 12: Synthesis without meta-analysis on sleep duration comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value in- terv.	N interv.	Value comp.	N comp.
Oxman 2007 ⁹⁹	subjective	change from baseline	score 1 to 7 (1 = < 4 h bis 7 = ≥ 8 h)	0.28	202	0.17	203
Taibi 2009 ¹⁰²	subjective	post-interv.	minutes	406.9	7	419.3	8
Chandra Shekhar 2024 ⁹⁰	objective	change from baseline	minutes	56.31	37	2.33	35
Coxeter 2003 ⁹⁰	subjective	change from baseline	proportion of treatment success	0.35	24		24
Cuellar 2009 ⁹¹	subjective	change from baseline	score	-0.6	17	-0.6	20
Donath 2000 ⁹⁴	subjective	post-interv.	minutes	325	16	335	16

Abbreviations: comp, comparator; interv, intervention; N, sample size

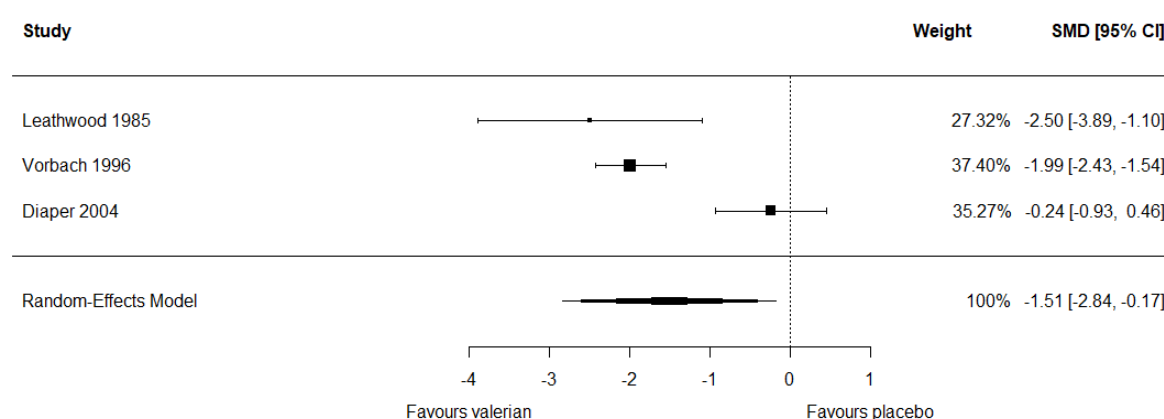
6.2.5.1.3 Sleep quality

Six RCTs that assessed sleep quality for valerian compared to placebo were included in the meta-analyses. The studies used different instruments to assess sleep quality, necessitating the calculation of standardised mean differences (SMD) for meta-analysis. Consequently, 2 separate meta-analyses were conducted: one analysing post-intervention scores (3 studies) and another examining change from baseline scores (3 studies). Sleep quality showed statistically significant improvement with valerian compared to placebo for post-intervention scores, but no statistically significant difference was observed for change from baseline scores. The pooled estimated SMD for outcomes reported as post-intervention was -1.51 (95% CI -2.84 to -0.17, **Figure 5**) and for outcomes reported as change from baseline was -0.03 (95% CI -0.21 to 0.15, **Figure 6**). An SMD smaller than zero would favour valerian and an SMD greater than zero would favour placebo. Subgroup change

from baseline meta-analysis restricted to studies with no comorbidities also showed no statistically significant difference in sleep quality between valerian and placebo (**Figure A 7** in **Appendix E**).

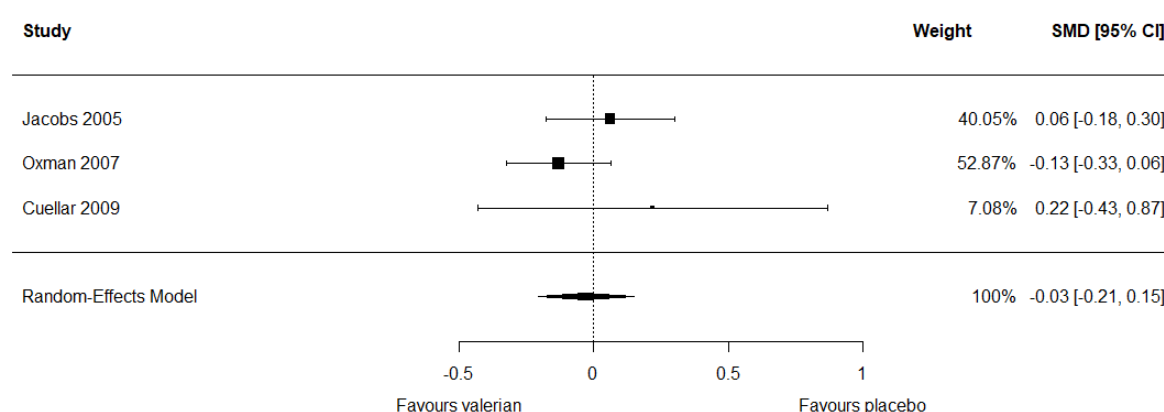
Of note, two of the three RCTs included in the post-intervention meta-analysis had a follow-up period of only one day (Leathwood et al. 1985⁹⁸ and Diaper et al. 2004⁹²). When these two studies are excluded, only one study remains (follow-up 28 days), resulting in high uncertainty around this finding. The three RCTs included in the change from baseline meta-analysis had follow up ≥ 14 days.

Figure 5: Forest-plot of meta-analysis on sleep quality comparing valerian versus placebo post-intervention scores



Abbreviations: CI, confidence interval; SMD, standardised mean difference

Figure 6: Forest-plot of meta-analysis on sleep quality comparing valerian versus placebo change from baseline scores



Abbreviations: CI, confidence interval; SMD, standardised mean difference

Table 13 summarises the results of the RCTs that were not included in the meta-analysis. Leathwood et al. 1982⁹⁷ reported sleep quality as proportion of people in categories (worse than usual/better than usual) rather than as a continuous score. Taibi et al. 2009¹⁰² did not specify the direction of the score (i.e., whether higher scores indicated better or worse sleep quality) and Coxeter et al.

2003⁹⁰ did not report sleep quality as score but rather as proportion of treatment success. Donath et al. 2000⁹⁴ reported sleep quality as a percentage, but the reference value was not specified.

Regarding treatment effects, Leathwood et al. 1982⁹⁷ favoured valerian based on the percentage of respondents who reported sleeping better than usual, while Coxeter et al. 2003⁹⁰ favoured placebo. The direction of treatment effects in Taibi et al. 2009¹⁰² and Donath et al. 2000⁹⁴ could not be determined. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 13: Synthesis without meta-analysis on sleep quality comparing valerian versus placebo

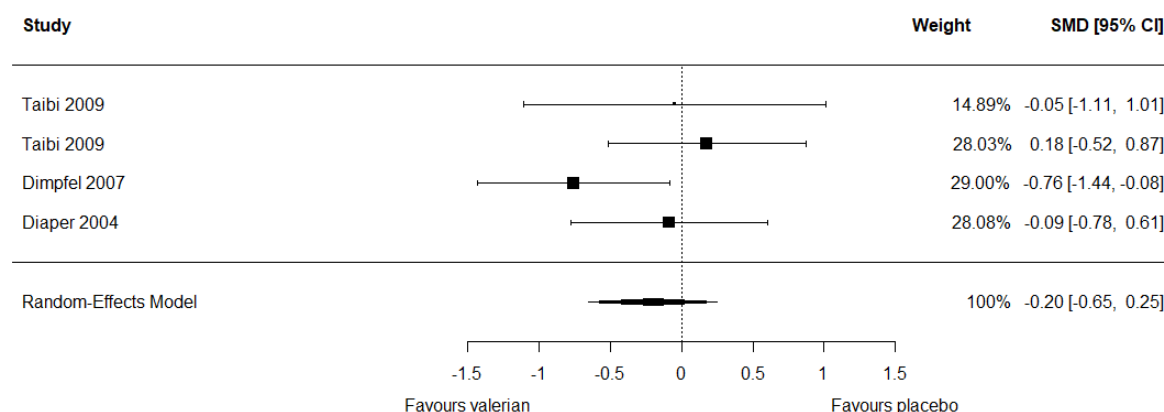
Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Leathwood 1982 ⁹⁷	subjective	post-interv.	percent of responses	worse than usual: 28.14, better than usual: 52.24	61	worse than usual: 24.04, better than usual: 27.76	61
Taibi 2009 ¹⁰²	subjective	post-interv.	score 0 to 10 (direction unknown)	6.10	7	5.8	8
Coxeter 2003 ⁹⁰	subjective	post-interv.	proportion of treatment success	0.49	24		24
Donath 2000 ⁹⁴	subjective	post-interv.	percent	47.53	16	52.267	16

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.1.4 Night awakenings

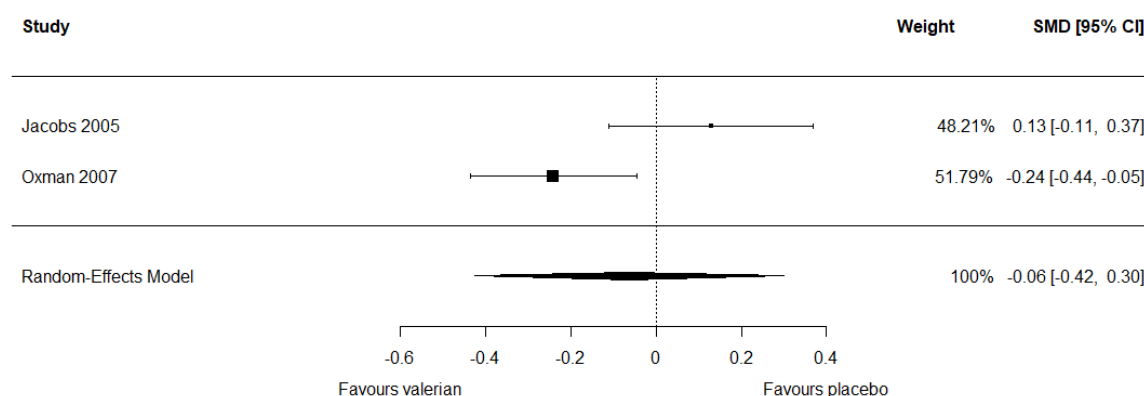
Six RCTs that assessed night awakenings for valerian compared to placebo were included in the meta-analyses. The studies used different instruments to assess night awakenings, necessitating the calculation of standardised mean differences (SMD) for meta-analysis. Consequently, 2 separate meta-analyses were conducted: one analysing post-intervention scores (4 studies) and another examining change from baseline scores (2 studies). No statistically significant difference in night awakenings was observed between valerian and placebo for either the post-intervention or the change from baseline analysis. The pooled estimated SMD for outcomes reported as post-intervention was -0.2 (95% CI -0.65 to 0.25, **Figure 7**) and for outcomes reported as change from baseline was -0.06 (95% CI -0.42 to 0.30, **Figure 8**). An SMD smaller than zero would favour valerian and an SMD greater than zero would favour placebo. Subgroup meta-analysis restricted to studies with follow-up ≥ 7 days and no comorbidities also showed no statistically significant difference in night awakenings reported as post-intervention between valerian and placebo (**Figure A 8** and **Figure A 9** in **Appendix E**). Subgroup post-intervention meta-analysis restricted to studies with follow-up ≥ 14 days was not possible as only one study had a follow-up of ≥ 14 days. Of note, both studies included in the change from baseline meta-analysis had follow-up ≥ 17 days.

Figure 7: Forest-plot of meta-analysis on night awakenings comparing valerian versus placebo post-intervention



Abbreviations: CI, confidence interval; SMD, standardised mean difference

Figure 8: Forest-plot of meta-analysis on night awakenings comparing valerian versus placebo change from baseline



Abbreviations: CI, confidence interval; SMD, standardised mean difference

Table 14 summarises the results of the RCTs that were not included in the meta-analysis. Taibi et al. 2009¹⁰² used wrist actigraphy (included in the meta-analysis) and a sleep diary (shown in the **Table 14**). Coxeter et al. 2003⁹⁰ did not report number of night awakenings but rather proportion of treatment success. Diaper et al. 2004⁹² assessed night awakenings using sleep electroencephalography (EEG) (included in the meta-analysis) and a questionnaire (shown in the **Table 14**). Additionally, Diaper et al. 2004⁹² reported number of awakenings measured by EEG using two thresholds: awakenings lasting less than 1 minute (shown in the **Table 14**) and awakenings lasting more than 1 minute (included in the meta-analysis).

Regarding treatment effects, Taibi et al. 2009¹⁰², Coxeter et al. 2003⁹⁰ and Diaper et al. 2004⁹² favoured placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

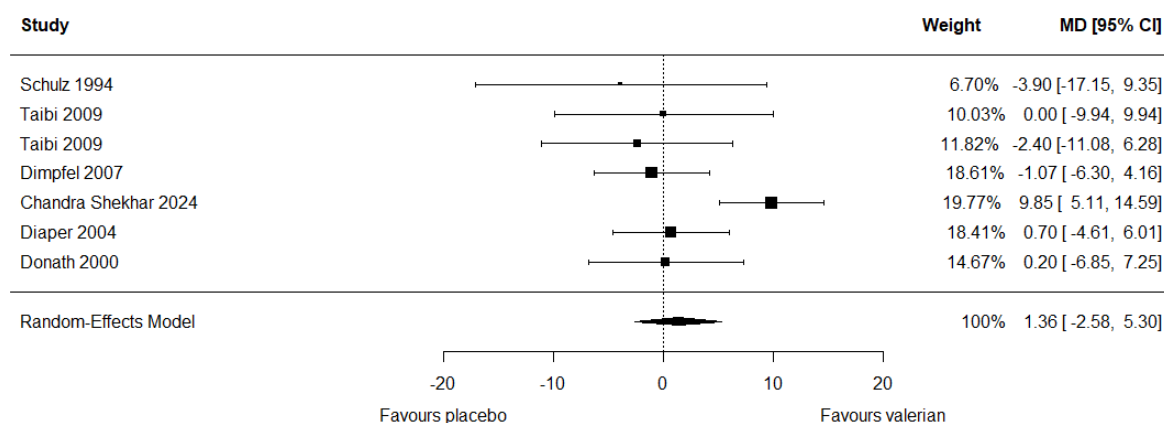
Table 14: Synthesis without meta-analysis on night awakenings comparing valerian versus placebo.

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Taibi 2009 ¹⁰²	subjective	post-interv.	percent	4.6	7	2.8	8
Coxeter 2003 ⁹⁰	subjective	post-interv.	proportion of treatment success	0.35	24		24
Diaper 2004 ⁹²	subjective	post-interv.	score 1 to 100 (higher = easier and quicker than usual)	49.8	16	52.5	16
Diaper 2004 ⁹²	objective	post-interv.	number of awakenings < 1min	27.3	16	22.7	16

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.1.5 Sleep efficiency

Seven RCTs that assessed sleep efficiency for valerian compared to placebo were included in the meta-analysis. Sleep efficiency was not statistically significantly different between valerian and placebo. The pooled estimated MD was 1.36 (95% CI -2.58 to 5.30, **Figure 9**), with moderate heterogeneity ($I^2 = 55.59\%$). An MD smaller than zero would favour placebo and an MD greater than zero would favour valerian. Subgroup meta-analysis restricted to studies with follow-up ≥ 7 days, follow-up ≥ 14 days and no comorbidities also showed no statistically significant difference in sleep efficiency between valerian and placebo (**Figure A 10**, **Figure A 11**, and **Figure A 12** in **Appendix E**).

Figure 9: Forest-plot of meta-analysis on sleep efficiency comparing valerian versus placebo.

Abbreviations: CI, confidence interval; MD, mean difference

Table 15 summarises the results of the RCTs that were not included in the meta-analysis. Taibi et al. 2009¹⁰² used wrist actigraphy (included in the meta-analysis) and a sleep diary (shown in the **Table 15**). Chandra Shekhar et al. 2024⁸⁹ used 2 objective methods (polysomnography and wrist actigraphy) and the polysomnography data was included in the meta-analysis and the actigraphy data is presented in the **Table 15**. Cuellar et al 2009⁹¹ did not report sleep efficiency as percentage

of time in bed but rather as PSQI score. To calculate MD (rather than SMD) the study of Cuellar et al 2009⁹¹ was excluded from the meta-analysis and is presented in the **Table 15** only.

Regarding treatment effects, Chandra Shekhar et al. 2024⁸⁹ and Cuellar et al 2009⁹¹ favoured valerian while Taibi et al. 2009¹⁰² favoured placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 15: Synthesis without meta-analysis on sleep efficiency comparing valerian versus placebo

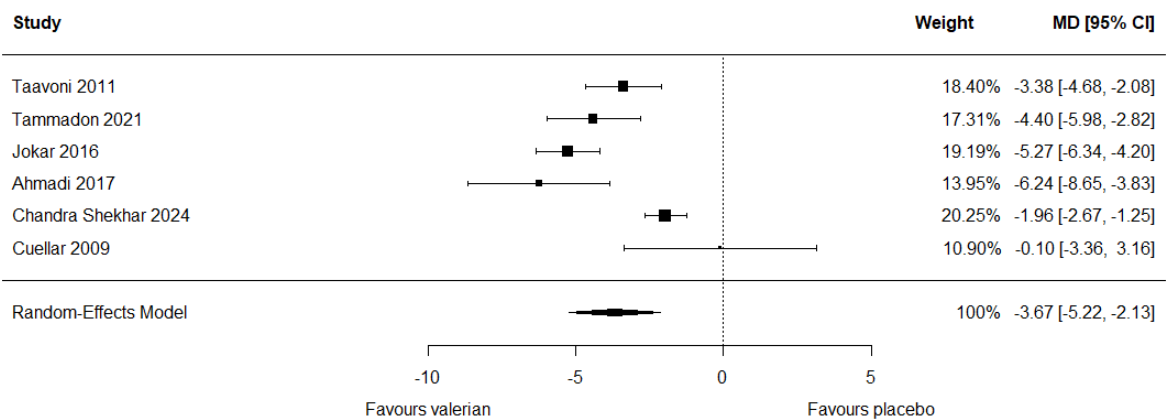
Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Taibi 2009 ¹⁰²	subjective	post-interv.	percent	83.2	7	90.2	8
Chandra Shekhar 2024 ⁸⁹	objective	change from baseline	percent	11.33	37	0.61	35
Cuellar 2009 ⁹¹	subjective	change from baseline	score 0 to 3 (higher = lower -0.6 efficiency)		17	-0.5	20

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.1.6 PSQI total score

Six RCTs that assessed PSQI total score for valerian compared to placebo were included in the meta-analysis. PSQI total score was statistically significantly lower (better) with valerian compared to placebo. The pooled estimated MD was -3.67 (95% CI -5.22 to -2.13, **Figure 10**), with substantial heterogeneity ($I^2 = 84.15\%$). An MD smaller than zero would favour valerian and an MD greater than zero would favour placebo. Of note, all studies included in the meta-analysis had follow-up ≥ 28 days. Subgroup meta-analysis restricted to studies with no comorbidities also showed statistically significant lower (better) PSQI total score with valerian compared to placebo (**Figure A 13 in Appendix E**). Of note, the study by Tammadon et al. 2021¹⁰⁴ included haemodialysis patients but was, after consultation with a clinical expert, not excluded in subgroup meta-analysis, as this comorbidity was not deemed to be a contraindication or a reason to forego treatment.

Figure 10: Forest-plot of meta-analysis on PSQI total score comparing valerian versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

6.2.5.1.7 Feeling of waking up refreshed

Four RCT that assessed the feeling of waking up refreshed for valerian compared to placebo were included in the present analysis. **Table 16** summarises the results of these RCTs. Meta-analysis was not possible for the following reasons: Leathwood et al. 1985⁹⁸ did not report uncertainty measures and Coxeter et al. 2003⁹⁰ did not report values for the placebo group. Among the two remaining studies, different outcome measurement scales were employed, necessitating the calculation of SMD. However, one study reported change from baseline values while the other reported post-intervention values. Since these two types of effect measures cannot be pooled when calculating SMD, meta-analysis was not feasible.

Regarding treatment effects, Leathwood et al. 1985⁹⁸, Vorbach et al. 1996¹⁰⁵ and Chandra Shekhar et al. 2024⁸⁹ favoured valerian whereas for Coxeter et al. 2003⁹⁰ it is unclear whether it favoured valerian or placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 16: Synthesis without meta-analysis on feeling of waking up refreshed comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Leathwood 1985 ⁹⁸	subjective	post-interv.	9 point scale (higher = better form (less sleepiness))	5.4	7	5.2	7
Vorbach 1996 ¹⁰⁵	subjective	post-interv.	score 0 to 4 (higher = better feeling of waking up refreshed)	3	59	2.7	58
Chandra Shekhar 2024 ⁸⁹	subjective	change from baseline	Visual analogue scale of 10cm, (higher = worse feeling of waking up refreshed)	-1.04	37	-0.27	35
Coxeter 2003 ⁹⁰	subjective	post-interv.	Likert scale: 0 = very tired or fatigued, 5 = average, 10 = very refreshed	0.40	24		24

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.1.8 Daytime sleepiness

One RCT that assessed daytime sleepiness for valerian compared to placebo was included in the present analysis. The results of this study are presented in **Table 17**. Regarding daytime sleepiness Chandra Shekhar 2024⁸⁹ favoured valerian. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 17: Synthesis without meta-analysis on daytime sleepiness comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Chandra Shekhar 2024 ⁸⁹	subjective	change from baseline	score from 0 to 24 (higher score = higher daytime sleepiness)	-0.76	37	-0.03	35

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.2 PICO 1: Benzodiazepines

6.2.5.2.1 Sleep latency

One RCT that assessed sleep latency for valerian compared to benzodiazepine was included in the present analysis. The results of this study are presented in **Table 18**. Aliakbari et al. 2018¹⁰⁸ did not report the value for sleep latency in the control group but stated that sleep latency was shorter in the intervention group compared to the control group.

Table 18: Synthesis without meta-analysis on sleep latency comparing valerian versus benzodiazepine

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Aliakbari 2018 ¹⁰⁸	subjective	post-interv.	hours	0.74	40		40

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.2.2 Sleep duration

One RCT that assessed sleep duration for valerian compared to benzodiazepine was included in the present analysis. The results of this study are presented in **Table 19**. Aliakbari et al. 2018¹⁰⁸ did not report the value for sleep duration in the control group but stated that sleep duration was longer in the intervention group compared to the control group.

Table 19: Synthesis without meta-analysis on sleep duration comparing valerian versus benzodiazepine

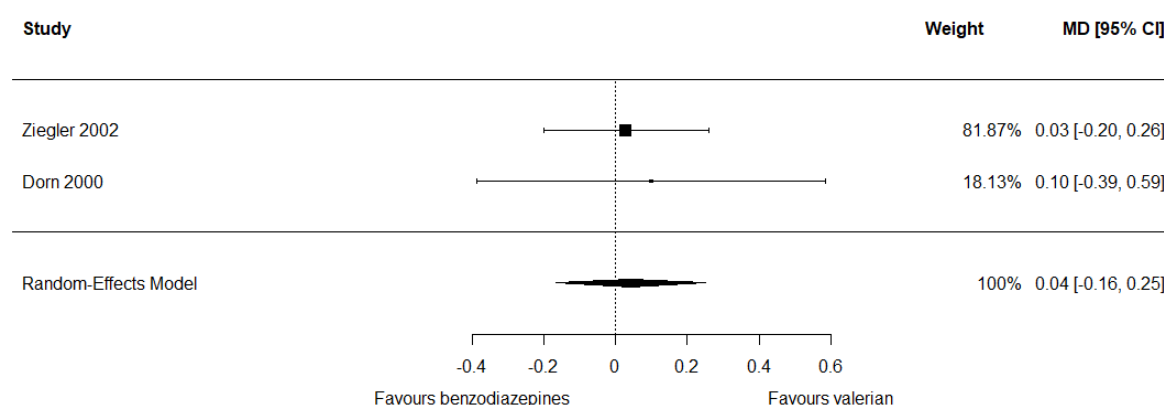
Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Aliakbari 2018 ¹⁰⁸	subjective	post-interv.	score	5.38	40		40

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.2.3 Sleep quality

Two RCTs that assessed sleep quality for valerian compared to benzodiazepine were included in the meta-analysis. Sleep quality was not statistically significantly different between valerian and benzodiazepine. The pooled estimated MD was 0.04 (95% CI -0.16 to 0.25, **Figure 11**). An MD smaller than zero would favour benzodiazepines and an MD greater than zero would favour valerian. Of note, both studies included in the meta-analysis had follow-up ≥ 28 days.

Figure 11: Forest-plot of meta-analysis on sleep quality comparing valerian versus benzodiazepines



Abbreviations: CI, confidence interval; MD, mean difference

6.2.5.2.4 PSQI total score

One RCT that assessed PSQI total score for valerian compared to benzodiazepine was included in the present analysis. The results of this study are presented in **Table 20**. Aliakbari et al. 2018¹⁰⁸ did not report PSQI total scores for intervention and control group but stated that the intervention group had lower PSQI total scores than the control group, indicating better sleep quality.

Table 20: Synthesis without meta-analysis on PSQI total score comparing valerian versus benzodiazepine

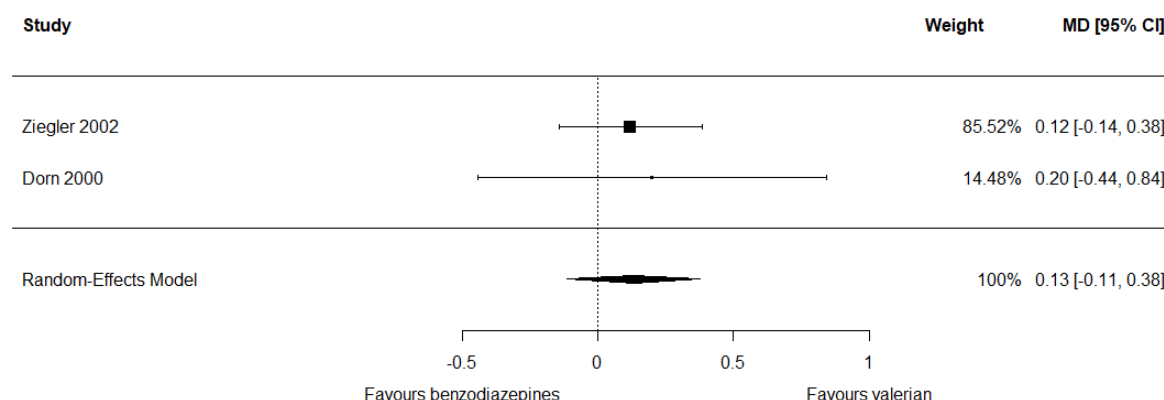
Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Aliakbari 2018 ¹⁰⁸	subjective	Unknown	score 0 to 21 (higher = worse sleep quality)		40		40

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.2.5 Feeling of waking up refreshed

Two RCTs that assessed feeling of waking up refreshed for valerian compared to benzodiazepine were included in the meta-analysis. The feeling of waking up refreshed was not statistically significantly different between valerian and benzodiazepine. The pooled estimated MD was 0.13 (95% CI -0.11 to 0.38, **Figure 12**). An MD smaller than zero would favour benzodiazepines and an MD greater than zero would favour valerian. Of note, both studies included in the meta-analysis had follow-up ≥ 28 days.

Figure 12: Forest-plot of meta-analysis on feeling of waking up refreshed comparing valerian versus benzodiazepines



Abbreviations: CI, confidence interval; MD, mean difference

6.2.5.3 PICO 1: Others

6.2.5.3.1 Sleep latency

One RCT that assessed sleep latency for valerian compared to neurexan was included in the present analysis. The results of this study are presented in **Table 21**. Regarding sleep latency Waldschütz 2008¹¹¹ favoured valerian. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 21: Synthesis without meta-analysis on sleep latency comparing valerian versus neurexan

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Waldschütz 2008 ¹¹¹	subjective	change from baseline	minutes	-38.2	164	-37.3	156

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.3.2 Sleep duration

One RCT that assessed sleep duration for valerian compared to neurexan was included in the present analysis. The results of this study are presented in **Table 22**. Regarding sleep duration Waldschütz 2008¹¹¹ favoured neurexan. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 22: Synthesis without meta-analysis on sleep duration comparing valerian versus neurexan

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Waldschütz 2008 ¹¹¹	subjective	change from baseline	hours	2	164	2.2	156

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.3.3 Sleep quality

Three RCTs that assessed the sleep quality for valerian compared to gabapentin¹⁰⁹, neurexin¹¹¹ or relaxation therapy¹¹² were included in the present analysis. **Table 23** summarises the results of these RCTs. Meta-analysis was not possible because the three RCTs used different comparators. Regarding sleep quality Hajizadeh 2023¹⁰⁹ and Jokar 2016¹¹² favoured valerian and Waldschütz 2008¹¹¹ favoured neurexin. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 23: Synthesis without meta-analysis on sleep quality comparing valerian versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Hajizadeh 2023 ¹⁰⁹	subjective	change from baseline	score 0 to 21 (higher = worse sleep quality)	-3.15	15	-1.86	16
Waldschütz 2008 ¹¹¹	subjective	change from baseline	score 0 to 21 (higher = worse sleep quality)	-7.3	164	-7.5	156
Jokar 2016 ¹¹²	subjective	change from baseline	score 0 to 21 (higher = worse sleep quality)	-5.31	43	-5.19	43

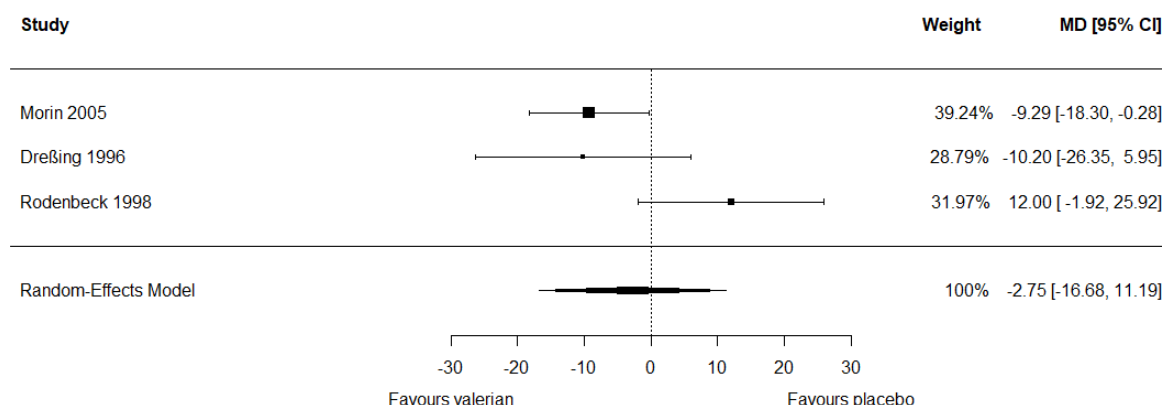
Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4 PICO 2: Placebo

6.2.5.4.1 Sleep latency

Three RCTs that assessed sleep latency (time to fall asleep) for valerian with lemon balm or hops compared to placebo were included in the meta-analysis. Morin et al. 2005¹¹⁶ and Rodenbeck et al. 1998¹¹⁷ evaluated valerian-hops combination versus placebo while Dreßing et al. 1996¹²³ evaluated a valerian-lemon balm combination versus placebo. Sleep latency was not statistically significantly different between valerian with lemon balm or hops and placebo. The pooled estimated MD was -2.75 (95% CI -16.68 to 11.19, **Figure 13**). An MD smaller than zero would favour valerian and an MD greater than zero would favour placebo. Of note, all studies included in the meta-analysis had follow-up ≥ 14 days.

Figure 13: Forest-plot of meta-analysis on sleep latency comparing valerian with lemon balm or hops versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

Table 24 summarizes the results of the studies that were not included in the meta-analysis. All of these compared a combination of valerian with hops versus placebo. Koetter et al. 2007⁹⁶ and Gammoh et al. 2017¹¹⁵ did not report uncertainty measures and were therefore excluded from meta-analysis. Morin et al. 2005¹¹⁶ assessed sleep latency using both an objective method (polysomnography), which was included in the meta-analysis and a subjective method (sleep diary), which is presented in the **Table 24**.

Regarding treatment effects, Koetter et al. 2007⁹⁶ and Gammoh et al. 2017¹¹⁵ favoured valerian with hops while Morin et al. 2005¹¹⁶ favoured placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 24: Synthesis without meta-analysis on sleep latency comparing valerian with lemon balm or hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Koetter 2007 ⁹⁶	objective	change from baseline	minutes	-44.5	9	5.5	8
Morin 2005 ¹¹⁶	subjective	post-interv.	minutes	25.89	59	23.71	65
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score 0 to 100 (higher = better getting to sleep)	5.02	65	4.82	76
Gammoh 2017 ¹¹⁵	subjective	post-interv.	minutes	64.11	65	71.83	76

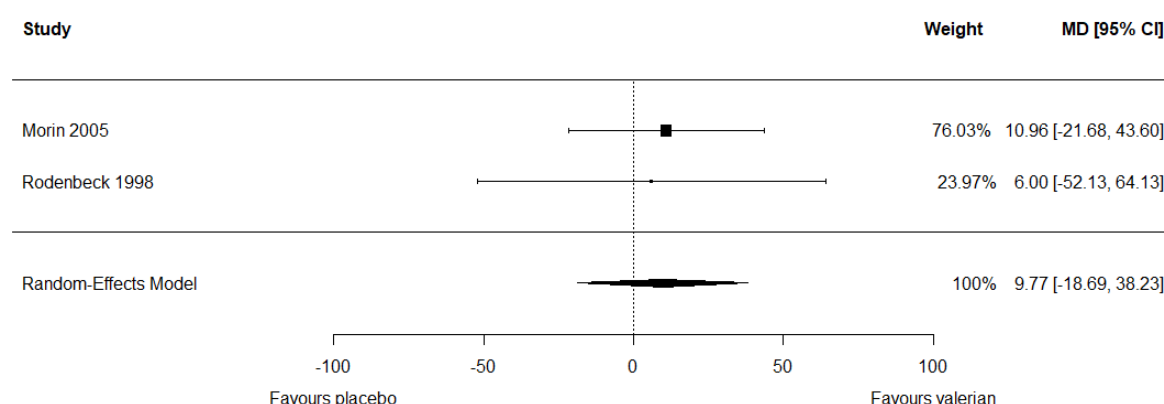
Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.2 Sleep duration

Two RCTs that assessed sleep duration for valerian with hops compared to placebo were included in the meta-analysis. Sleep duration was not statistically significantly different between valerian with hops and placebo. The pooled estimated MD was 9.77 (95% CI -18.69 to 38.23, **Figure 14**).

An MD smaller than zero would favour placebo and an MD greater than zero would favour valerian. Of note, both studies included in the meta-analysis had follow-up ≥ 14 days.

Figure 14: Forest-plot of meta-analysis on sleep duration comparing valerian with hops versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

Table 25 summarises the results of the RCTs that were not included in the meta-analysis. Morin et al. 2005¹¹⁶ and Gammoh et al. 2017¹¹⁵ evaluated valerian-hops combination versus placebo. Gammoh et al. 2017¹¹⁵ did not report uncertainty measures and was therefore excluded from meta-analysis. Morin et al. 2005¹¹⁶ assessed sleep duration using both an objective method (polysomnography), which was included in the meta-analysis and a subjective method (sleep diary), which is presented in the **Table 25**.

Regarding treatment effects, Gammoh et al. 2017¹¹⁵ and Morin et al. 2005¹¹⁶ favoured valerian with hops. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 25: Synthesis without meta-analysis on sleep duration comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	subjective	post-interv.	minutes	418.82	58	405.75	65
Gammoh 2017 ¹¹⁵	subjective	post-interv.	minutes	413.4	65	408	76

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.3 Sleep quality

Three RCT that assessed sleep quality for valerian with lemon balm or hops compared to placebo were included in the present analysis. As only the study of Dreßing et al. 1996¹²³ reported uncertainty measures meta-analysis was not possible. **Table 26** summarizes the results of these studies. Leathwood et al. 1982⁹⁷ and Gammoh et al. 2017¹¹⁵ evaluated valerian-hops combination versus placebo while Dreßing et al. 1996¹²³ evaluated a valerian-lemon balm combination versus placebo.

Regarding treatment effects, Leathwood et al. 1982⁹⁷ favoured valerian with hops based on the percentage of respondents who reported sleeping better than usual, Dreßing et al. 1996¹²³ favoured valerian with lemon balm, while Gammoh et al. 2017¹¹⁵ favoured placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 26: Synthesis without meta-analysis on sleep quality comparing valerian with lemon balm or hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Leathwood 1982 ⁹⁷	subjective	post-interv.	percent of participants	worse than usual: 30.12, better than usual: 54	61	worse than usual: 24.04, better than usual: 27.76	61
Dreßing 1996 ¹²³	subjective	post-interv.	score unknown range	2.64	32	2.32	34
Dreßing 1996 ¹²³	subjective	post-interv.	score 0 to 10 (higher = better sleep quality)	5.5	32	4.8	34
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score (higher = worse sleep quality)	5.33	65	4.85	76

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.4 Night awakenings

Two RCT that assessed night awakenings for valerian with hops compared to placebo were included in the present analysis. As only the study of Rodenbeck et al. 1998¹¹⁷ reported uncertainty measures meta-analysis was not possible. **Table 27** summarizes the results of these studies. Regarding treatment effects, Gammoh et al. 2017¹¹⁵ favoured valerian with hops while Rodenbeck et al. 1998¹¹⁷ favoured placebo. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 27: Synthesis without meta-analysis on night awakenings comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score (higher = better)	5.26	65	4.79	76
Rodenbeck 1998 ¹¹⁷	objective	post-interv.	number	34	8	23	7

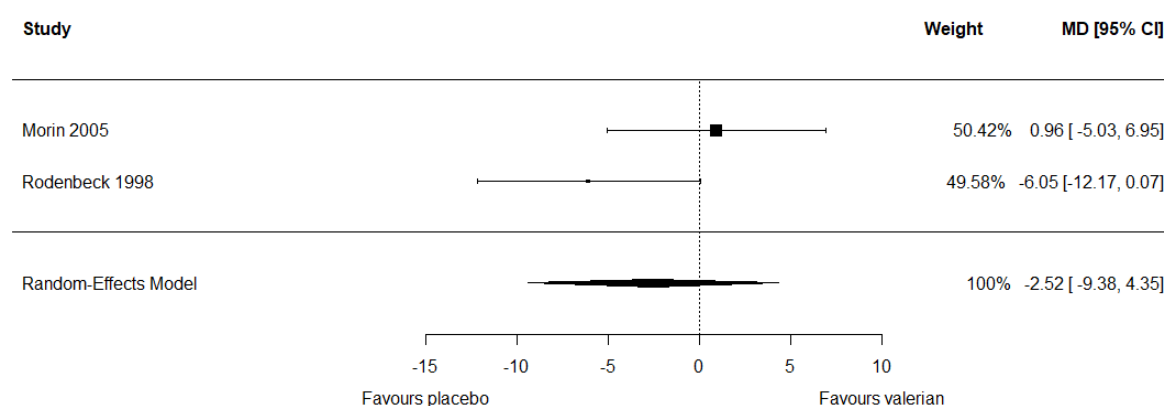
Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.5 Sleep efficiency

Two RCTs that assessed sleep efficiency for valerian with hops compared to placebo were included in the meta-analysis. Sleep efficiency was not statistically significantly different between valerian with hops and placebo. The pooled estimated MD was -2.52 (95% CI -9.38 to 4.35, **Figure 15**). An

MD smaller than zero would favour placebo and an MD greater than zero would favour valerian. Of note, both studies included in the meta-analysis had follow-up ≥ 14 days.

Figure 15: Forest-plot of meta-analysis on sleep efficiency comparing valerian with hops versus placebo



Abbreviations: CI, confidence interval; MD, mean difference

Table 28 presents the results of the outcome that was not included in the meta-analysis. Morin et al. 2005¹¹⁶ assessed sleep efficiency using both an objective method (polysomnography), which was included in the meta-analysis and a subjective method (sleep diary), which is presented in the **Table 28**. Regarding treatment effects, Morin et al. 2005¹¹⁶ favoured valerian with hops. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 28: Synthesis without meta-analysis on sleep efficiency comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	subjective	post-interv.	percent total sleep time of time spent in bed	86.37	58	83.38	65

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.6 PSQI total score

One RCT that assessed PSQI total score for valerian with lemon balm compared to placebo was included in the present analysis. The results of this study are presented in **Table 29**. Regarding treatment effects, Taavoni et al. 2013¹¹⁴ favoured valerian with lemon balm. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 29: Synthesis without meta-analysis on PSQI total score comparing valerian with lemon balm versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Taavoni 2013 ¹¹⁴	subjective	post-interv.	score 0 to 21 (higher = worse sleep quality)	6.5	50	10.5	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.7 Feeling of waking up refreshed

One RCT that assessed feeling of waking up refreshed for valerian with hops compared to placebo was included in the present analysis. The results of this study are presented in **Table 30**. Regarding feeling of waking up refreshed Gammoh et al. 2017¹¹⁵ favoured valerian with hops. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 30: Synthesis without meta-analysis on feeling of waking up refreshed comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score 0 to 100 (higher = better behaviour following wakefulness)	5.37	65	4.8	76

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.4.8 Daytime sleepiness

One RCT that assessed daytime sleepiness for valerian with lemon balm compared to placebo was included in the present analysis. The results of this study are presented in **Table 31**. Regarding daytime sleepiness Dreßing 1996¹²³ favoured valerian with lemon balm. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 31: Synthesis without meta-analysis on daytime sleepiness comparing valerian with lemon balm versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Dreßing 1996 ¹²³	subjective	post-interv.	Visual analogue scale 0 to 4.8 10 (higher = more tiredness)		32	5.8	34

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5 PICO 2: Others

6.2.5.5.1 Sleep latency

Two RCTs that assessed the sleep latency for valerian compared to diphenhydramine¹¹⁶, or chlorpheniramine¹¹⁵ were included in the present analysis. **Table 32** summarises the results of these RCTs. Meta-analysis was not possible because the two RCTs used different comparators. Regarding sleep latency Morin 2005¹¹⁶ favoured valerian with hops when objectively measured and diphenhydramine when subjectively measured, while Gammoh 2017¹¹⁵ favoured chlorpheniramine. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 32: Synthesis without meta-analysis on sleep latency comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	objective	post-interv.	minutes	9.06	22	10.46	26
Morin 2005 ¹¹⁶	subjective	post-interv.	minutes	25.89	59	22.11	60
Gammoh 2017 ¹¹⁵	subjective	post-interv.	minutes	64.11	65	36.08	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5.2 Sleep duration

Two RCTs that assessed the sleep duration for valerian with hops compared to diphenhydramine¹¹⁶, or chlorpheniramine¹¹⁵ were included in the present analysis. **Table 33** summarises the results of these RCTs. Meta-analysis was not possible because the two RCTs used different comparators. Regarding sleep duration Morin 2005¹¹⁶ favoured diphenhydramine when objectively measured and valerian with hops when subjectively measured, while Gammoh 2017¹¹⁵ favoured valerian with hops. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 33: Synthesis without meta-analysis on sleep duration comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	objective	post-interv.	minutes	381.36	22	382.77	26
Morin 2005 ¹¹⁶	subjective	post-interv.	minutes	418.82	58	399.96	58
Gammoh 2017 ¹¹⁵	subjective	post-interv.	minutes	413.4	65	394.8	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5.3 Sleep quality

One RCT that assessed sleep quality for valerian with hops compared to chlorpheniramine was included in the present analysis. The results of this study are presented in **Table 34**. Regarding sleep quality Gammoh 2017¹¹⁵ favoured valerian with hops. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 34: Synthesis without meta-analysis on sleep quality comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score (higher = worse sleep quality)	5.33	65	6.82	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5.4 Night awakenings

One RCT that assessed night awakenings for valerian with hops compared to chlorpheniramine was included in the present analysis. The results of this study are presented in **Table 35**. Regarding night awakenings Gammoh 2017¹¹⁵ favoured chlorpheniramine. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 35: Synthesis without meta-analysis on night awakenings comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score (higher = better)	5.26	65	6.32	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5.5 Sleep efficiency

One RCT that assessed sleep efficiency for valerian with hops compared to diphenhydramine was included in the present analysis. The results of this study are presented in **Table 36**. Regarding sleep efficiency Morin 2005¹¹⁶ favoured diphenhydramine when objectively measured and valerian with hops when subjectively measured. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 36: Synthesis without meta-analysis on sleep efficiency comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	objective	post-interv.	percent	84.68	22	86.31	26
Morin 2005 ¹¹⁶	subjective	post-interv.	percent	86.37	58	85.62	58

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.5.6 Feeling of waking up refreshed

One RCT that assessed feeling of waking up refreshed for valerian with hops compared to chlorpheniramine was included in the present analysis. The results of this study are presented in **Table 37**. Regarding feeling of waking up refreshed Gammoh 2017¹¹⁵ favoured chlorpheniramine. However, statistical significance cannot be determined for these outcomes as MD and confidence intervals were not calculated.

Table 37: Synthesis without meta-analysis on feeling of waking up refreshed comparing valerian with hops versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score 0 to 100 (higher = better behaviour following wakefulness)	5.37	65	6.64	50

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.6 PICO 3: Placebo

6.2.5.6.1 Anxiety measured by State STAI

One RCT that assessed anxiety by State (STAI) for valerian with lemon balm compared to placebo was included in the present analysis. The results of this study are presented in **Table 38**. Regarding treatment effects, Kennedy et al. 2006¹¹⁹ favoured valerian with lemon balm. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 38: Synthesis without meta-analysis on State (STAI) comparing valerian with lemon balm versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Kennedy 2006 ¹¹⁹	subjective	change from baseline	score 20 to 80 (higher = greater anxiety)	-3.29		-0.71	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.6.2 Anxiety measured by Trait STAI

One RCT that assessed anxiety by Trait (STAI) for valerian with lemon balm compared to placebo was included in the present analysis. The results of this study are presented in **Table 39**. Regarding treatment effects, Kennedy et al. 2006¹¹⁹ favoured valerian with lemon balm. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 39: Synthesis without meta-analysis on Trait (STAI) comparing valerian with lemon balm versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Kennedy 2006 ¹¹⁹	subjective	change from baseline	score 20 to 80 (higher = greater anxiety)	-0.96		0.33	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.6.3 Anxiety measured by a visual analogue scale

One RCT that assessed anxiety for valerian with hops compared to placebo was included in the present analysis. The results of this study are presented in **Table 40**. Regarding treatment effects, Gammoh et al. 2017¹¹⁵ favoured valerian with hops. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 40: Synthesis without meta-analysis on anxiety comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Gammoh 2017 ¹¹⁵	subjective	post-interv.	score 0 to 10 (higher = greater anxiety)	4.9	65	5.15	76

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.7 PICO 4: Placebo

6.2.5.7.1 Anxiety measured by STAI

One RCT that assessed STAI-state for valerian with lemon balm, passionflower and butterbur compared to placebo was included in the present analysis. The results of this study are presented in **Table 41**. Regarding treatment effects, Meier et al. 2018¹²¹ showed similar values between the valerian-containing combination product and placebo. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 41: Synthesis without meta-analysis on STAI-state comparing valerian with lemon balm, passionflower and butterbur versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Meier 2018 ¹²¹	subjective	post-interv.	score 20 to 80 (higher = greater anxiety)	31.9	23	31.2	23

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.7.2 Anxiety measured by a visual analogue scale

One RCT that assessed anxiety for valerian with lemon balm, passionflower and butterbur compared to placebo was included in the present analysis. The results of this study are presented in **Table 42**. Regarding treatment effects, Melzer et al. 2009¹²² favoured valerian with lemon balm,

passionflower and butterbur. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 42: Synthesis without meta-analysis on anxiety comparing valerian with lemon balm, passionflower and butterbur versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	subjective	post-interv.	visual analogue scale in millimetre (higher = greater anxiety)	13.5	59	28.6	54

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.5.8 PICO 4: Others

6.2.5.8.1 Anxiety measured by a visual analogue scale

One RCT that assessed anxiety for valerian with lemon balm, passionflower and butterbur compared to valerian with passionflower and lemon balm was included in the present analysis. The results of this study are presented in **Table 43**. Regarding treatment effects, Melzer et al. 2009¹²² favoured valerian with lemon balm, passionflower and butterbur. However, statistical significance cannot be determined for this outcome as MD and confidence intervals were not calculated.

Table 43: Synthesis without meta-analysis on anxiety comparing valerian with lemon balm, passionflower and butterbur versus valerian with passionflower and lemon balm

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	subjective	post-interv.	visual analogue scale in millimetre (higher = greater anxiety)	13.5	59	19.7	49

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6 Findings safety

6.2.6.1 PICO 1: Placebo

6.2.6.1.1 Adverse events

Four RCTs that assessed adverse events for valerian compared to placebo were included in the present analysis. Koetter et al. 2007⁹⁶ reported zero events in both treatment groups and therefore needed to be excluded from meta-analysis. Coxeter et al. 2003⁹⁰ and Donath et al. 2000⁹⁴ reported number of events and not number of participants and the number of events were higher than the sample size therefore they had to be excluded from meta-analyses. Finally, meta-analysis was not possible. **Table 44** summarises the results of these studies.

Regarding adverse events, Chandra Shekhar 2024⁸⁹ and Donath et al. 2000⁹⁴ favoured valerian while Coxeter et al. 2003⁹⁰ favoured placebo. Koetter et al. 2007⁹⁶ found no difference between treatments. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 44: Synthesis without meta-analysis on adverse events comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Koetter 2007 ⁹⁶	Unknown	post-interv.	number of events	0	10	0	8
Chandra Shekhar 2024 ⁸⁹	Unknown	post-interv.	number of events	5	40	7	40
Coxeter 2003 ⁹⁰	subjective	post-interv.	number of events	99	24	74	24
Donath 2000 ⁹⁴	Unknown	post-interv.	number of events	3	16	18	16

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.1.2 Specific adverse events

Seven RCTs that assessed specific adverse events for valerian compared to placebo were included in the present analysis. **Table 45** summarises the results of these RCTs. Meta-analysis was not possible because the RCTs reported different specific adverse events.

Table 45: Synthesis without meta-analysis on specific adverse events comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Jacobs 2005 ⁹⁵	Unknown	post-interv.	number of events	headache: 39, drymouth: 29, dizziness: 13, abdominal pain: 14, diarrhea: 22, drowsiness: 25, morning hangover: 22, restlessness: 12, fatigue: 25, backpain: 21	135	headache: 28, drymouth: 24, dizziness: 8, abdominalpain: 11, diarrhea: 9, drowsiness: 28, morning hangover: 16, restlessness: 14, Fatigue: 29, backpain: 12	135
Vorbach 1996 ¹⁰⁵	Unknown	post-interv.	number of participants	headache: 2, morning drowsiness: 1	59	fatigue: 1, nausea and vomiting associated with gastric ulcer: 1	58
Chandra Shekhar 2024 ⁸⁹	subjective	post-interv.	number of events	upper respiratory tract infection: 1, sore throat: 1, headache: 1, viral fever: 1, loose motion: 1	40	fever: 2, upper respiratory tract infection: 1, sorethroat: 1, headache: 1, gastritis: 1, common cold: 1	40
Coxeter 2003 ⁹⁰	subjective	post-interv.	number of events	headache: 29, over-stimulation: 4, restlessness: 13, Palpitations: 3, nervousness: 11, nausea: 6, stomach pain: 11, agitation: 12, diarrhoea: 8, stomach cramps: 2, tiredness: 1, increased snoring: 1, indigestion: 1, gastric reflux : 1, vomiting: 1,		headache: 2, over-stimulation: 6, restlessness: 15, nervousness: 9, nausea: 5, stomach pain: 7, agitation: 9, diarrhoea: 6, constipation: 2	

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
				strange dreams: 2, dry mouth: 3, constipation: 3			
Diaper 2004 ⁹²	Unknown	post-interv.	number of events	drowsiness: 4, headache: 1, exaggerated feelings of well-being: 1, mental dullness: 1	16	drowsiness: 1, headache: 2, sleep difficult: 5, depression: 1, irritability: 1, confusion: 1, dehydration: 1, tiredness: 1	16
Diaper 2004 ⁹²	Unknown	post-interv.	number of parti- pants	drowsiness: 4, headache: 1, exaggerated feelings of well-being: 1, mental dullness: 1	16	drowsiness: 1, headache: 2, sleep difficult: 4, depression: 1, irritability: 1, confusion: 1, dehydration: 1, tiredness: 1	16
Donath 2000 ⁹⁴	Unknown	post-interv.	number of events	urticaria accidents: 1, migraine attack: 1, gastrointestinal com- plaints: 1	16	urticaria_accidents: 4, 16 exacerbation of chronic diseases epi- zoonosis: 5, headaches: 4, migraine attack: 2, gastrointestinal com- plaints: 1, left-side thoracic pain: 1, flu and common colds pharyngeal com- plaints: 1	
Donath 2000 ⁹⁴	Unknown	post-interv.	number of parti- pants	urticaria accidents: 1, migraine attack: 1, gastrointestinal com- plaints: 1	16	urticaria accidents: 3, 16 exacerbation of chronic diseases epi- zoonosis: 3, headaches: 4, migraine attack: 1, gastrointestinal com- plaints: 1, left-side thoracic pain: 1, flu and common colds pharyngeal com- plaints: 1	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.1.3 Serious adverse events

One RCT that assessed serious adverse events for valerian compared to placebo was included in the present analysis. The results of this study are presented in **Table 46**. Regarding serious adverse events Coxeter 2003⁹⁰ favoured placebo. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

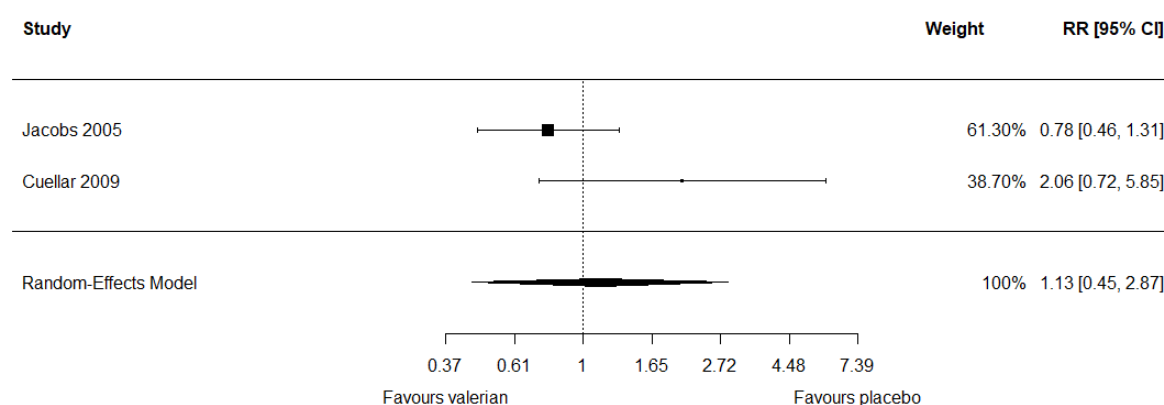
Table 46: Synthesis without meta-analysis on serious adverse events comparing valerian versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Coxeter 2003 ⁹⁰	subjective	post-interv.	number of events	13		7	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.1.4 Discontinuation

Two RCTs that assessed discontinuation for valerian compared to placebo were included in the meta-analysis. Discontinuation was not statistically significantly different between valerian and placebo. The pooled estimated RR was 1.13 (95% CI 0.45 to 2.87, **Figure 16**). An RR smaller than one would favour valerian and an RR greater than one would favour placebo. Of note, both studies included in the meta-analysis had follow-up ≥ 28 days.

Figure 16: Forest-plot of meta-analysis on discontinuation comparing valerian versus placebo

Abbreviations: CI, confidence interval; RR, risk ratio

6.2.6.2 PICO 1: Benzodiazepines

6.2.6.2.1 Adverse events

One RCT that assessed adverse events for valerian compared to benzodiazepines was included in the present analysis. The results of this study are presented in **Table 47**. Regarding adverse events Dorn et al. 2000¹⁰⁷ favoured benzodiazepines. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 47: Synthesis without meta-analysis on adverse events comparing valerian versus benzodiazepines

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Dorn 2000 ¹⁰⁷	subjective	post-interv.	number of participants	14	39	11	36

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.2.2 Specific adverse events

One RCT that assessed specific adverse events for valerian compared to benzodiazepines was included in the present analysis. The results of this study are presented in **Table 48**. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 48: Synthesis without meta-analysis on specific adverse events comparing valerian versus benzodiazepines

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Dorn 2000 ¹⁰⁷	Unknown	post-interv.	number of participants	Upper respiratory tract infections: 2, headaches: 2, fatigue: 1, itching: 3, dry mouth: 3, nausea: 3		Upper respiratory tract infections: 4, headaches: 3, fatigue: 3, itching: 1, dry mouth: 1, nausea: 1	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.2.3 Discontinuation

One RCT that assessed discontinuation for valerian compared to benzodiazepines was included in the present analysis. The results of this study are presented in **Table 49**. Regarding discontinuation Dorn et al. 2000¹⁰⁷ showed a marginal numerical trend in favour of valerian, though statistical significance cannot be determined as RR and confidence intervals were not calculated. Two of the discontinuations in the valerian group and 3 in the benzodiazepines group were rated by physicians as probably related to the study medication.

Table 49: Synthesis without meta-analysis on discontinuation comparing valerian versus benzodiazepines

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Dorn 2000 ¹⁰⁷	Unknown	post-interv.	number of participants	5	39	5	36

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.3 PICO 1: Others

6.2.6.3.1 Specific adverse events

One RCT that assessed specific adverse events for valerian compared to gabapentin was included in the present analysis. The results of this study are presented in **Table 50**. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 50: Synthesis without meta-analysis on specific adverse events comparing valerian versus gabapentin

Study	Instrument	Measure	Unit	Value interv.	N interv. Value comp.	N comp.
Hajizadeh 2023 ¹⁰⁹	Unknown	post-interv.	number of participants	nausea: 2, vomiting: 1, diarrhea: 1, stomach ache: 1, halitosis: 1, drowsiness: 0	nausea: 0, vomiting: 0, diarrhea: 0, stomach ache: 0, halitosis: 0, drowsiness: 2	

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.4 PICO 2: Placebo

6.2.6.4.1 Adverse events

Two RCT that assessed adverse events for valerian with hops compared to placebo were included in the present analysis. Meta-analysis was not possible. **Table 51** summarises the results of these studies. Koetter et al. 2007⁹⁶ reported zero events in both treatment groups and therefore needed to be excluded from meta-analysis. Therefore, meta-analysis was not possible. Regarding adverse events Morin et al. 2005¹¹⁶ favoured valerian. Koetter et al. 2007⁹⁶ found no difference between treatments. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 51: Synthesis without meta-analysis on adverse events comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Koetter 2007 ⁹⁶	Unknown	post-interv.	number of events	0	9	0	8
Morin 2005 ¹¹⁶	Unknown	post-interv.	number of events	63	59	76	65
Morin 2005 ¹¹⁶	Unknown	post-interv.	number of participants	33	59	34	65

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.4.2 Specific adverse events

One RCT that assessed specific adverse events for valerian with lemon balm compared to placebo was included in the present analysis. The results of this study are presented in **Table 52**, with 8 adverse events in the intervention group (n=32) and 5 in the placebo group (n=34). However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 52: Synthesis without meta-analysis on adverse events comparing valerian with lemon balm versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Dreßing 1996 ¹²³	Unknown	post-interv.	number of events	feeling of coldness before falling asleep: 1, headaches: 1, bronchial catarrh: 1, vomiting: 1, headaches: 1, stomach pain: 1, calf cramps: 1, gastrointestinal complaints: 1	32	headaches: 1, tingling in hands: 1, daytime fatigue: 1, nausea: 1, nausea, restlessness: 1	34

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.5 PICO 2: Others

6.2.6.5.1 Adverse events

One RCT that assessed adverse events for valerian with hops compared to diphenhydramine was included in the present analysis. The results of this study are presented in **Table 53**. Regarding adverse events Morin 2005¹¹⁶ favoured valerian with hops. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 53: Synthesis without meta-analysis on adverse events comparing valerian with hops versus diphenhydramine

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Morin 2005 ¹¹⁶	Unknown	post-interv.	number of participants	33	59	44	60
Morin 2005 ¹¹⁶	Unknown	post-interv.	number of events	63	59	77	60

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.6 PICO 3: Placebo

6.2.6.6.1 Specific adverse events

One RCT that assessed specific adverse events for valerian with hops compared to placebo was included in the present analysis. The results of this study are presented in **Table 54**. Regarding adverse events Silva dos Santos et al. 2023¹¹⁸ favoured placebo. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 54: Synthesis without meta-analysis on specific adverse events comparing valerian with hops versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Silva dos Santos 2023 ¹¹⁸	subjective	post-interv.	number of events	drowsiness: 16, dizziness: 2, muscle relaxation: 19	43	drowsiness: 3	43

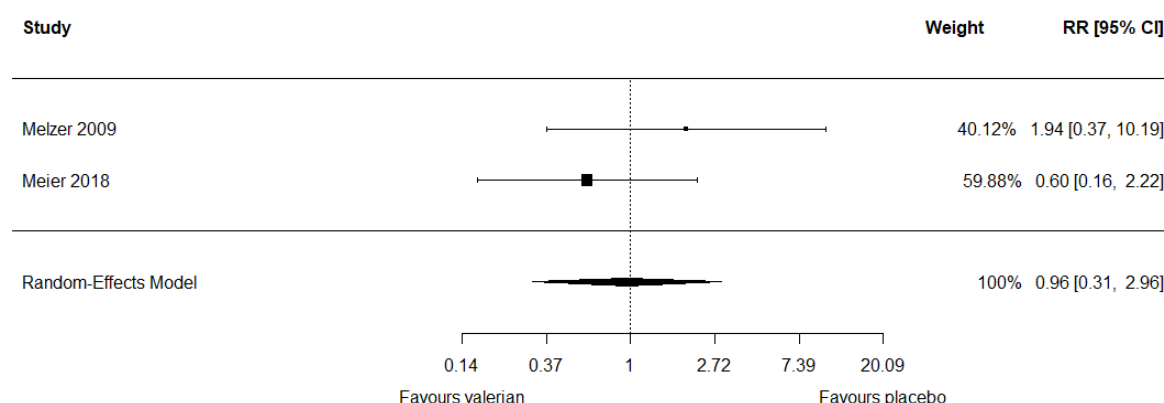
Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.7 PICO 4: Placebo

6.2.6.7.1 Adverse events

Two RCTs that assessed adverse events for valerian with lemon balm, passionflower and butterbur compared to placebo were included in the meta-analysis. Adverse events were not statistically significantly different between valerian with lemon balm, passionflower and butterbur and placebo. The pooled estimated MD was 0.96 (95% CI 0.31 to 2.96, **Figure 17**). An RR smaller than one would favour valerian and an RR greater than one would favour placebo.

Figure 17: Forest-plot of meta-analysis on adverse events comparing valerian with lemon balm, passionflower and butterbur versus placebo



Abbreviations: CI, confidence interval; RR, risk ratio

6.2.6.7.2 Serious adverse events

Two RCT that assessed serious adverse events for valerian with lemon balm, passionflower and butterbur compared to placebo were included in the present analysis. The results of these studies are presented in **Table 55**. Regarding serious adverse events Melzer et al. 2009¹²² and Meier et al. 2018¹²¹ reported zero events in both treatment groups. However, statistical significance cannot be determined for these outcomes, because a meta-analysis could not be computed, as both included studies reported zero events in both the intervention and control groups, rendering effect size calculations technically not feasible.

Table 55: Synthesis without meta-analysis on serious adverse events comparing valerian with lemon balm, passionflower and butterbur versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	Unknown	post-interv.	number of participants	0	63	0	61
Meier 2018 ¹²¹	Unknown	post-interv.	number of participants	0	23	0	23

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.7.3 Discontinuation

One RCT that assessed discontinuation for valerian with lemon balm, passionflower and butterbur compared to placebo was included in the present analysis. The results of this study are presented in **Table 56**. Regarding discontinuation Meier 2018¹²¹ favoured valerian with lemon balm, passionflower and butterbur (one person in the placebo arm was withdrawn from the study due to forbidden medication). However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 56: Synthesis without meta-analysis on discontinuation comparing valerian with lemon balm, passionflower and butterbur versus placebo

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Meier 2018 ¹²¹	Unknown	post-interv.	number of participants	0	23	1	23

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.8 PICO 4: Others

6.2.6.8.1 Adverse events

Two RCTs that assessed adverse events for valerian with lemon balm, passionflower and butterbur compared to valerian with passionflower and lemon balm¹²² or no treatment¹²¹ were included in the present analysis. The results of these studies are presented in **Table 57**. Regarding adverse events Melzer 2009¹²² favoured valerian with butterbur, passionflower and lemon balm while Meier 2018¹²¹ found no difference. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 57: Synthesis without meta-analysis on adverse events comparing valerian with lemon balm, passionflower and butterbur versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	Unknown	post-interv.	number of participants	4	63	3	58
Melzer 2009 ¹²²	Unknown	post-interv.	number of events	5	63	3	58
Meier 2018 ¹²¹	Unknown	post-interv.	number of participants	3	23	3	24

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.8.2 Specific adverse events

One RCT that assessed specific adverse events for valerian with lemon balm, passionflower and butterbur compared to valerian with passionflower and lemon balm was included in the present analysis. The results of this study are presented in **Table 58**, with 5 adverse events in the intervention group (n=63) and 3 in the placebo group (n=58). However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 58: Synthesis without meta-analysis on specific adverse events comparing valerian with lemon balm, passionflower and butterbur versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	Unknown	post-interv.	number of events	nausea: 1, vomiting: 1, flatulence: 1, constipation: 0, disc dislocation: 1, sleep disorder: 1, cold: 0, tightness in the throat: 0	63	nausea: 2, vomiting: 0, flatulence: 0, constipation: 1, disc dislocation: 0, sleep disorder: 0, cold: 0, tightness in the throat: 0	58

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.8.3 Serious adverse events

Two RCT that assessed serious adverse events for valerian with lemon balm, passionflower and butterbur compared to valerian with passionflower and lemon balm¹²² or no treatment¹²¹ were included in the present analysis. The results of these studies are presented in Table 59. Regarding serious adverse events Melzer et al. 2009¹²² and Meier et al. 2018¹²¹ reported zero events in both treatment groups. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 59: Synthesis without meta-analysis on serious adverse events comparing valerian with lemon balm, passionflower and butterbur versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Melzer 2009 ¹²²	Unknown	post-interv.	number of participants	0	63	0	58
Meier 2018 ¹²¹	Unknown	post-interv.	number of participants	0	23	0	24

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.6.8.4 Discontinuation

One RCT that assessed discontinuation for valerian with lemon balm, passionflower and butterbur compared to no treatment was included in the present analysis. The results of this study are presented in **Table 60**. Regarding discontinuation Meier 2018¹²¹ reported zero events in both treatment groups. However, statistical significance cannot be determined for these outcomes as RR and confidence intervals were not calculated.

Table 60: Synthesis without meta-analysis on discontinuation comparing valerian with lemon balm, passionflower and butterbur versus others

Study	Instrument	Measure	Unit	Value interv.	N interv.	Value comp.	N comp.
Meier 2018 ¹²¹	Unknown	post-interv.	number of participants	0	23	0	24

Abbreviations: comp, comparator; interv, intervention; N, sample size

6.2.7 GRADE Summary of Findings Table

The results of the outcomes from the systematic review, meta-analysis and GRADE assessment on the clinical efficacy and safety are summarised in **Table 61** to **Table 65** for the different interventions and comparators for PICO 1, 2, 3 and PICO 4.

PICO 1: Valerian (monotherapy) compared to placebo for insomnia

The certainty of evidence was rated as moderate for sleep duration, sleep latency, night awakenings, sleep quality and PSQI total score and low for sleep efficiency and adverse events (**Table 61**). Inconsistency was downgraded in all the 7 outcomes due to variability in the time to follow-up, the dosage and/or due to unexplained heterogeneity. Furthermore, imprecision was downgraded for sleep efficiency and adverse events due to wide confidence intervals and small sample sizes.

PICO 1: Valerian (monotherapy) compared to benzodiazepine for insomnia

The certainty of evidence was rated as moderate for sleep quality and adverse events and very low for sleep latency and sleep duration (**Table 62**). No studies reported data for night awakenings or sleep efficiency and one study that planned to report the PSQI total score provided no results. Across all assessable studies, evidence was downgraded for imprecision due to wide confidence

intervals, small sample sizes, or inadequate reporting (presenting only intervention group values with p-value for between-group comparison). Risk of bias was downgraded for sleep latency and sleep duration because high risk of bias was detected in the measurement of the outcome. Indirectness was also downgraded for sleep latency and sleep duration because the study population (patients with chronic heart failure) differs from our target population (general population), limiting the generalisability of findings.

PICO 2: Valerian (with hops or lemon balm) compared to placebo for insomnia

The certainty of evidence was rated as low for PSQI total score and very low for the other 6 outcomes assessed (**Table 63**). Evidence was downgraded across all 4 GRADE domains. Risk of bias was high due to concerns regarding missing outcome data and/or randomisation processes. Inconsistency arose from methodological heterogeneity, including variable follow-up periods, differing dosages and/or use of different measurement instruments. Imprecision was evident through wide confidence intervals and/or small sample sizes. Sleep quality, night awakenings and PSQI total score were additionally downgraded for indirectness due to limited generalisability; the former 2 from studies in war refugee populations and the latter from a study in menopausal women.

PICO 3: Valerian (with hops or lemon balm) compared to placebo for mental stress

The certainty of evidence was rated as low for STAI-State, STAI-Trait and specific adverse events and very low for anxiety (**Table 64**). All outcomes were based on single studies with small sample sizes, resulting in imprecision downgrades. Anxiety and adverse events received additional downgrades for indirectness due to limited generalisability from specific populations (war refugees and dental surgery patients). STAI-State, STAI-Trait and Anxiety were downgraded for risk of bias due to concerns regarding missing outcome data.

PICO 4: Valerian (with lemon balm, butterbur and passion flower) compared to placebo for test anxiety

The certainty of evidence was rated as moderate for STAI (combined State and Trait), low for anxiety and very low for adverse events (**Table 65**). None of the included studies specifically measured test anxiety; instead, studies assessed state anxiety, trait anxiety and general anxiety. All 3 outcomes were downgraded for imprecision due to small sample sizes, single studies, or large effect sizes. Anxiety and adverse events received downgrades for indirectness due to analysis of specific population groups limiting generalisability. The outcome adverse events was downgraded for inconsistency due to variability in study populations and follow-up duration.

Table 61: Summary of findings table – PICO 1 – Valerian (monotherapy) vs. placebo for insomnia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Valerian (mon-otherapy)	Placebo	Relative (95% CI)	Absolute (95% CI)		
sleep latency (time to fall asleep) (follow-up: range 1 days to 56 days)												
9	RCT	not serious	serious ^{a,b}	not serious	not serious	2 RCTs industry funded	259	257		MD 0.99 minutes less (5.41 fewer to 3.44 more)	⊕⊕⊕○ Moderate ^{a,b}	Critical
sleep duration (time asleep) (follow-up: range 1 days to 56 days)												
7	RCT	not serious	serious ^{a,b}	not serious	not serious	2 RCTs industry funded	108	106		MD 3.16 minutes more (7.07 fewer to 13.39 more)	⊕⊕⊕○ Moderate ^{a,b}	Critical
sleep quality change from baseline (follow-up: range 14 days to 56 days)												
3	RCT	not serious	serious ^{a,b}	not serious	not serious	No study industry funded	354	358		SMD 0.03 SD lower (0.21 lower to 0.15 higher)	⊕⊕⊕○ Moderate ^{a,b}	Critical
sleep quality post-intervention (follow-up: range 1 day to 28 days)												
3	RCT	not serious	serious ^a	not serious	serious ^{c,d}	No study industry funded	82	81		SMD 1.51 SD lower (2.84 lower to 0.17 lower)	⊕⊕○○ Low ^{a,c,d}	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (monotherapy)	Placebo	Relative (95% CI)	Absolute (95% CI)		

night awakenings post-intervention (follow-up: range 1 days to 14 days)

4	RCT	not serious	serious ^{a,b}	not serious	not serious	No study industry funded	56	58		SMD 0.2 SD lower (0.65 lower to 0.25 higher)	⊕⊕⊕○ Moderate ^{a,b}	Critical
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night awakenings change from baseline (follow-up: range 14 days to 28 days)

2	RCT	not serious	serious ^b	not serious	serious ^d	No study industry funded	337	338		SMD 0.06 SD lower (0.42 lower to 0.30 higher)	⊕⊕○○ Low ^{b,d}	Critical
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sleep efficiency (follow-up: range 1 days to 56 days)

7	RCT	not serious	serious ^{a,b}	not serious	serious ^d	2 RCTs industry funded	117	115		MD 1.36 higher (2.58 lower to 5.3 higher)	⊕⊕○○ Low ^{a,b,d}	Critical
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PSQI total score (follow-up: range 28 days to 56 days)

6	RCT	not serious	serious ^{b,e,f}	not serious	not serious	1 RCT industry funded	194	191		MD 3.67 lower (5.22 lower to 2.13 lower)	⊕⊕⊕○ Moderate ^{b,e,f}	Critical
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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (monotherapy)	Placebo	Relative (95% CI)	Absolute (95% CI)		

adverse events (number of events) (follow-up: range 14 days to 56 days)

4	RCT	not serious	serious ^{a,b}	not serious	serious ^{c,d}	1 RCT industry funded	107/90 (118.9%)	99/88 (112.5%)	Not estimable: studies reported total event counts without specifying the number of participants affected.	⊕⊕○○ Low ^{a,b,c,d}	Important
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Abbreviations: CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; SMD standardised mean difference

Explanations

a. The follow-up time varied.

b. Different dosages were used.

c. The sample size was not sufficiently large, the optimal information size is not met.

d. The 95% CI is wide.

e. The statistical heterogeneity was high with $I^2 = 84.15\%$.

f. Comorbidity profiles differed between study populations.

Table 62: Summary of findings table – PICO 1 – Valerian (monotherapy) vs. benzodiazepine for insomnia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Valerian (mon-otherapy)	Benzodiazepine	Relative (95% CI)	Absolute (95% CI)		
sleep latency (time to fall asleep) (follow-up: 1 month)												
1	RCT	serious ^a	not serious ^b	serious ^c	serious ^d	Not industry funded	40	40		Mean vale-rian: 0.74h ; mean placebo not reported p-value re-ported p=0.001 in fa-vour of vale-rian	⊕○○○ Very low ^{a,b,c,d}	Critical
sleep duration (time asleep) (follow-up: 1 month)												
1	RCT	serious ^a	not serious ^b	serious ^c	serious ^d	Not industry funded	40	40		Mean vale-rian: 5.38h ; mean placebo not reported p-value re-ported p<0.05 in favour of valerian	⊕○○○ Very low ^{a,b,c,d}	Critical
sleep quality (follow-up: range 28 days to 42 days)												
2	RCT	not serious	not serious	not serious	serious ^e	Not industry funded	129	127		MD 0.04 SD higher (0.16 lower to 0.25 higher)	⊕⊕⊕○ Moderate ^e	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (monotherapy)	Benzodiazepine	Relative (95% CI)	Absolute (95% CI)		

night awakenings

0	RCT											Critical
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sleep efficiency

0	RCT											Critical
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PSQI total score (follow-up: 1 month)

1	RCT					Not industry funded	40	40	The mean for PSQI was not reported in the results, even though it was described in the method			Critical
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Adverse events (total adverse events) (follow-up: 28 days)

1	RCT	not serious	not serious ^b	not serious	serious ^f	Not industry funded	14/39 (35.9%)	11/36 (30.6%)	No pooled effect	⊕⊕⊕○ Moderate ^{b,f}		Important
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Abbreviations: CI: confidence interval; MD: mean difference; RCT: randomised controlled trial

Explanations

a. High risk of bias due to measurement of outcome.

b. Only one study.

c. Patients with chronic heart failure only.

d. Only mean of the intervention group reported and direction of the effect and p-value.

e. The 95% CI is wide.

f. The sample size was not sufficiently large, the optimal information size is not met.

Table 63: Summary of findings table – PICO 2 – Valerian (with hops or lemon balm) vs. placebo for insomnia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Valerian (with hops or lemon balm)	Placebo	Relative (95% CI)	Absolute (95% CI)		
sleep latency (time to fall asleep) (follow-up: range 14 days to 42 days)												
3	RCT	serious ^{a,b}	serious ^{c,d}	not serious	serious ^{e,f}	2 RCTs industry funded	62	67		MD 2.75 minutes lower (16.68 lower to 11.19 higher)	⊕○○○ Very low ^{a,b,c,d,e,f}	Critical
sleep duration (time asleep) (follow-up: range 28 days to 42 days)												
2	RCT	serious ^{a,b}	serious ^{c,d}	not serious	serious ^{e,f}	All RCTs industry funded	30	33		MD 9.77 minutes higher (18.69 lower to 38.23 higher)	⊕○○○ Very low ^{a,b,c,d,e,f}	Critical
sleep quality (follow-up: range 1 days to 14 days)												
3	RCT	serious ^a	serious ^{c,d,g}	serious ^h	serious ^{e,f,i}	1 RCT industry funded	158	171	The results reported in the included studies for this outcome were very different, making it impos- sible to calculate an over- all mean		⊕○○○ Very low ^{a,c,d,e,f,g,h,i}	Critical
night awakenings (follow-up: range 1 days to 28 days)												
2	RCT	serious ^a	serious ^{c,d,g}	serious ^h	serious ^{e,f}	1 RCT industry funded	73	83	No overall effect, studies with different units (num- ber, score)		⊕○○○ Very low ^{a,c,d,e,f,g,h}	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (with hops or lemon balm)	Placebo	Relative (95% CI)	Absolute (95% CI)		

sleep efficiency (follow-up: range 28 days to 42 days)

2	RCT	serious ^{a,b}	serious ^{c,d}	not serious	serious ^{e,f}	All RCTs industry funded	30	33		MD 2.52 lower (9.38 lower to 4.35 higher)	⊕○○○ Very low ^{a,b,c,d,e,f}	Critical
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PSQI total score (follow-up: 1 month)

1	RCT	not serious	not serious ^j	serious ^k	serious ^e	Not industry funded	50	50		Mean for Valerian: 6.5 ; Mean for placebo: 10.5	⊕⊕○○ Low ^{e,j,k}	Critical
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Adverse events (total adverse events) (follow-up: range 28 days to 42 days)

2	RCT	serious ^{a,b}	serious ^{c,d}	not serious	serious ^{e,k}	1 RCT industry funded	33/68 (49%)	34/73 (47%)	No overall effect, studies with different units (number of events, number of participants with adverse events)	⊕○○○ Very low ^{a,b,c,d,e,k}	Important
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Abbreviations: CI: confidence interval; MD, mean difference; RCT: randomised controlled trial

Explanations

- a. High risk of bias due to missing outcome data.
- b. High risk of bias due to concerns about randomization process.
- c. The follow-up time varied.
- d. Different dosages were used.
- e. The sample size was not sufficiently large, the optimal information size is not met.
- f. The 95% CI is wide.
- g. Different measurement instruments used.
- h. Study with war refugees.
- i. Different direction of the effects.
- j. Only one study
- k. Study with menopausal women only.
- l. Wide range of results.

Table 64: Summary of findings Table – PICO 3 – Valerian (with hops or lemon balm) vs. placebo for mental stress

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (with hops or lemon balm)	Placebo	Relative (95% CI)	Absolute (95% CI)		

State (STAI) (follow-up: 1 days)

1	RCT	serious ^a	not serious ^b	not serious	serious ^{b,c}	Not industry funded	24	24		Change from baseline for valerian: - 3.29 ; Change from baseline for placebo: - 0.71	⊕⊕○○ Low ^{a,b,c}	Critical
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Trait (STAI) (follow-up: 1 days)

1	RCT	serious ^a	not serious ^b	not serious	serious ^{b,c,d}	Not industry funded	24	24		Change from baseline for valerian: - 0.96 ; Change from baseline for placebo: 0.33	⊕⊕○○ Low ^{a,b,c,d}	Critical
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Anxiety (follow-up: 1 days)

1	RCT	serious ^a	not serious ^b	serious ^e	serious ^b	Not industry funded	65	76		Mean for valerian: 4.9 ; Mean for placebo: 5.15	⊕○○○ Very low ^{a,b,e}	Critical
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valerian (with hops or lemon balm)	Placebo	Relative (95% CI)	Absolute (95% CI)		

Adverse events (specific adverse events) (follow-up: 1 days)

1	RCT	not serious	not serious ^b	serious ^f	serious ^{b,c,g}	Not industry funded	37/43 (86.05%)	3/43 (6.98%)	No pooled effect	⊕⊕○○ Low ^{b,c,f,g}	Important
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Abbreviations: RCT: randomised controlled trial

Explanations

a. High risk of bias due to missing outcome data.

b. Only one study.

c. The sample size was not sufficiently large, the optimal information size is not met.

d. Different direction of the effects.

e. Study with war refugees.

f. Tooth removal, before-after comparison (within participant).

g. Large effect.

Table 65: Summary of findings Table – PICO 4 – Valerian (with lemon balm, butterbur and passion flower) vs. placebo for test anxiety

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Valerian (with lemon balm, butterbur and passion flower)	Placebo	Relative (95% CI)	Absolute (95% CI)		

STAI (follow-up: 5 days)

1	RCT	not serious	not serious ^a	not serious	serious ^{a,b}	RCT industry funded	23	23		Mean for Valerian: 31.9 ; Mean for placebo: 31.2	⊕⊕⊕○ Moderate ^{a,b}	Critical
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Anxiety (follow-up: 14 days)

1	RCT	not serious	not serious ^a	serious ^c	serious ^{b,d}	RCT industry funded	59	54		Mean for Valerian: 13.5 ; Mean for placebo: 28.6	⊕⊕○○ Low ^{a,b,c,d}	Critical
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Adverse events (total adverse events) (follow-up: range 5 days to 14 days)

2	RCT	not serious	serious ^{a,f}	serious ^c	serious ^{g,h}	2 RCTs industry funded	7/86 (8.1%)	7/84 (8.3%)	RR 0.96 (0.31 to 2.96)	3 fewer per 1'000 (from 57 fewer to 163 more)	⊕○○○ Very low ^{c,e,f,g,h}	Important
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Abbreviations: RCT: randomised controlled trial

Explanations

- a. Only one study.
- b. The sample size was not sufficiently large, the optimal information size is not met.
- c. Study with somatoforme disorder.
- d. Large effect.
- e. The follow-up time varied.
- f. Inconsistency in population.
- g. The 95% C is wide.
- h. Different direction of the effects.

7. Cost, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

No review of cost-effectiveness analysis was possible due to the absence of studies meeting inclusion criteria. A de novo budget impact analysis from a Swiss healthcare payer perspective estimated total potential cost savings of CHF 202.47 million over 5 years for the 5 reimbursed valerian-containing medicines across all indications when removing them from reimbursement. For insomnia symptoms, the largest indication, savings were estimated at CHF 174.05 million for approximately 1.7 million patients, with sensitivity analyses revealing an uncertainty of CHF -14.8 million to +10.9 million. For mental stress symptoms, cost savings were CHF 6.14 million for 1.2 million patients with an uncertainty of CHF -3.1 million to +2.3 million. For test anxiety symptoms, savings were CHF 22.28 million for 0.3 million patients with an uncertainty of CHF $\pm$ 3.8 million. Scenario analyses 1) assuming continued prevalence growth at historically observed rates and 2) aligned to real-world claims data from SASIS projected higher savings than the base case. Total cost savings across all indications increased to 1) CHF 244 million (CHF 210 million for insomnia, CHF 7 million for mental stress and CHF 27 million for test anxiety) and 2) CHF 222 million (CHF 173 million for insomnia, CHF 10 million for mental stress and CHF 39 million for test anxiety).

7.1 Methodology costs, cost-effectiveness and budget impact

7.1.1 Databases and search strategy

To identify health economic evidence, search strategies based on the PICO criteria were developed in collaboration with a medical librarian and according to current best practice guidelines (see **Appendix Chapter B** for the detailed search strategy per database).^{124–126} In addition to the search in Medline and Embase, a search was performed in the American Economic Association's electronic database EconLit, the International Network of Agencies for HTA database (INAHTA) and the National Health Service Economic Evaluation Economic Database (NHSEED). The search strategy focused on PICO's intervention and outcome components, while population and comparators have not been specified to avoid undue narrowing of the search results. Search limits were applied to exclude animal studies, conference abstracts and studies exclusively focusing on infants. All studies were imported to CADIMA for study selection.

The inclusion and exclusion criteria have been defined according to the PICO framework (Section 4) and are presented in **Table 66**. Although some valerian-containing medicines in Switzerland are specifically indicated for symptoms related to mental stress or test anxiety (PICO 3 and 4), the literature search included a broader population (anxiety in general) to optimise the pool of evidence, in case little evidence for the subpopulation is available. There were no restrictions on the country,

setting, sample size or publication period. The publication language had to be English, French, German, or Italian. Studies were included if they fell into the category of original health economic evaluation, budget impact analysis or HTA of medicines containing valerian (alone or in combination).

Table 66: Inclusion criteria for health economic evidence

	Inclusion	Exclusion
Population	Human patients (≥ 6 years) with symptoms of insomnia, mental stress or test anxiety/anxiety	Animal studies or patients with symptoms not related to insomnia, mental stress or test anxiety/anxiety or patients below 6 years of age
Intervention	Medicines containing valerian extract alone and medicines in which valerian is combined with either: 1) Lemon balm 2) Hops 3) Lemon balm, butterbur and passionflower	Any other intervention including medicines combined with non-herbal medication
Comparator	• Placebo • Lifestyle adaptation • Improvement of sleep hygiene • Other herbal medicines • Cognitive behaviour therapy • Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), sedative antidepressants, selective serotonin reuptake inhibitors or tricyclic antidepressants) • No treatment Only comparators approved for use in Switzerland will be considered.	Any other comparator or comparators not approved for use in Switzerland
Outcomes	Total and incremental costs, total and incremental QALYs and effects, ICER, budget impact.	Patient satisfaction, biological or surrogate outcomes, narrative or qualitative outcomes.
Study design	HTAs, health economic evaluations, including within-trial or model-based cost-effectiveness, -utility, -benefit, -minimization, comparison and budget impact analyses	Not a health economic evaluation or budget impact analysis, for example cost-of-illness and resource use studies
Language	English, French, German, or Italian	All other languages
Country	No restrictions	—
Setting	No restrictions	—
Publication period	No restrictions	—
Publication status	Published in a scientific, peer-reviewed journal or as HTA report with full-text or essential content available	Published as a book, conference abstract, or journal article without full-text or essential content available

Abbreviations: QALY: Quality-Adjusted Life Year, ICER: Incremental Cost-effectiveness Ratio, HTA: Health Technology Assessment.

Study selection

In a first step, the studies were screened by title and abstract in duplicate according to the inclusion/exclusion criteria. In a second step, full texts of studies retained from the first step were reviewed in duplicate. Any disagreement was resolved by consensus. Where consensus could not be found, a third reviewer was consulted. To increase consistency between reviewers, prior training sessions were held.

7.1.2 Other sources

Health insurance claims data provided by SWICA and SASIS for the years 2018–2023 were used. These data contained information on utilisation and reimbursed volumes of valerian-containing medicines. The data providers extracted the relevant outcomes and conducted plausibility checks before sharing the data for analysis. Because several products are reimbursed for multiple

indications, claims data alone were insufficient to derive indication-specific treatment patterns. To address this, a Computer-Assisted Web Interviewing (CAWI) survey of 80 general practitioners (GPs) from Switzerland was commissioned, carried out by an independent market research company, MIS Trend SA. GPs were randomly selected from the Swiss register of medical professions (MedReg) using randomly generated letter combinations in their last names (e.g., “AE,” “CU”), ensuring representativeness. The sampling strategy incorporated balanced representation across all Swiss language regions for comprehensive national coverage. Selection criteria included: profession = physician, specialist title = general internal medicine OR general practitioner, and professional license = granted and active. The survey was developed and translated by the Zurich University of Applied Sciences (ZHAW) and consisted of a 7-minute questionnaire with only closed questions on the indication for prescribing valerian-containing medicines and the distribution of treatment alternatives.

In addition, targeted literature was used to inform prevalence estimates and substitution patterns. This included, for example, international evidence on benzodiazepine substitution following valerian delisting, which was adapted to the Swiss context.

Together, the claims data, GP survey responses and literature evidence were extracted, analysed and synthesised to generate epidemiological estimates, indication-specific treatment distributions and alternative treatment scenarios for the budget impact analysis.

7.1.3 Assessment of quality of evidence

n.a.

7.1.4 Methodology data extraction, analysis and synthesis of health economic data

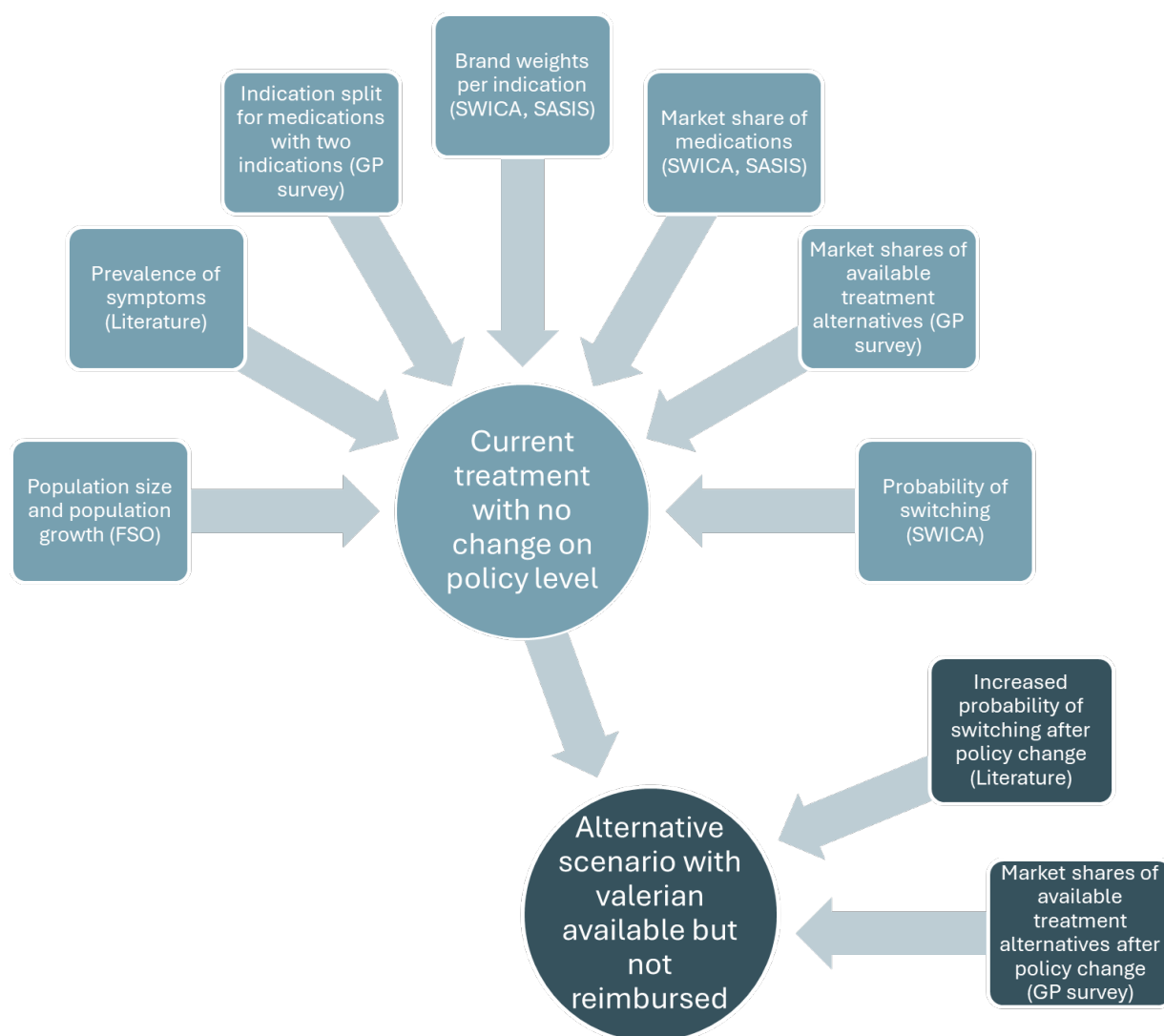
7.1.4.1 Cost-effectiveness

The cost-effectiveness analysis aimed to present the best available published data from cost-effectiveness analyses retrieved from the scientific literature. To provide an overview, a narrative summary of the findings was planned if suitable studies were identified.

7.1.4.2 Budget impact

A de novo Budget impact model has been developed. As an overview, **Figure 18** shows the input parameters for the budget impact analysis. The light-shaded boxes display the input parameters for the current treatment scenario. The dark-shaded boxes represent additional parameters required to model the alternative scenario in which valerian-containing medicines remain available but are excluded from reimbursement. The details of the input parameters are presented in the following chapters.

Figure 18: Input parameters for budget impact analysis



Abbreviations: FSO: Federal statistical office, GP: general practitioner

Perspective

The Budget impact analysis was built from a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis did not include indirect costs due to productivity losses and additional non-medical costs for patients, such as travel costs.

Time horizon

The time horizon for the BIA was 5 years.

Target population

Epidemiological inputs were identified through a targeted review of Swiss data sources (claims databases, surveys, published reports). The focus was on the symptoms rather than on formal

diagnoses. A constant annual prevalence was assumed in the base case scenario, reflecting treatment durations of less than one year and the expectation that patients either recover or progress to more severe conditions. Chronic insomnia and severe mental health disorders were excluded.

Insomnia prevalence was estimated using a 2018 cross-sectional Sentinella survey of Swiss primary care physicians, restricted to adults (≥ 18 years) with subjective sleep problems but excluding chronic insomnia. Prevalence of mental health problems was taken from the AXA Mind Health Report¹²⁷, based on a representative Swiss sample aged 18–75. For test anxiety, no prevalence data were available for the general Swiss population. We therefore used data from adolescent populations as a proxy. A study of 259 secondary school students aged 11–16 in Vaud reported 22% with high test anxiety¹²⁸, while PISA data from Swiss school students (mean age 15 years) indicated 33% prevalence of pre-exam anxiety. For the base case analysis, the lower estimate (22%) was selected as a conservative approach. The estimated number of people with symptoms of insomnia, mental stress or test anxiety, and the proportions of patients seeking treatment, are presented in **Table 67**. In the absence of data specific to insomnia symptoms in the Sentinella-study, data on treatment-seeking behaviour from chronic insomnia studies were applied. Population growth per year was 1% as calculated from the population statistics from the federal office of statistics. Due to the model structure, in which patient numbers were calibrated to SWICA and SASIS data rather than derived independently from prevalence and treatment-seeking rates, changes to these parameters do not affect the budget impact results. Prevalence and treatment-seeking assumptions therefore serve as contextual parameters to characterise the target population but are not direct drivers of the model output.

Table 67: Estimated number of prevalent cases

Symptoms	Prevalence [%]	Proportion of patients seeking treatment [%]	Prevalence [No. of cases >6 years]	Source
Prevalence of insomnia symptoms	25%	78%	1'645'981	Maire et al. 2020 ²⁰
Prevalence of mental stress symptoms	27%	52%	1'185'107	AXA. Mind health report 2024 ¹²⁷
Prevalence of test anxiety symptoms	22%	16%	297'121	Valls 2023 ¹²⁸ Blanco et al. 2008 ¹²⁹

Current treatment mix

Treatment patterns were derived from complementary sources. Claims data indicated that 4.74% of patients purchased a reimbursed valerian-containing product during the year, but indication was not available. Prescribing distributions by indication were therefore derived from the GP survey of 80 Swiss GPs (see **Chapter 7.1.2**), which captured brand-specific use by indication and overall prescribing allocations across alternatives. Claims data provided an objective utilisation anchor, while survey responses informed indication splits and relative proportions. The current market shares are presented in **Table 68** and

Table 69. The reference product in the following tables refers to the valerian-containing medicine(s) reimbursed for the corresponding indication, comprising both monotherapy and combination preparations as applicable.

Table 68: Current marked shares of available treatment alternatives for symptoms of insomnia

Treatment option	Current market shares insomnia	SD	Source
Reference product	6.08%	n.a.	Calculation based on SWICA and SASIS data
Benzodiazepines	6.84%	8.03	Shares from GP survey re-scaled based on claims data
Z-drugs	13.99%	14.55	
Sedative antidepressants	21.92%	17.89	
CBT	6.35%	10.48	
Sleep hygiene/lifestyle adaptation	37.00%	25.14	
No treatment	5.98%	16.18	
Other	1.84%	17.93	

Abbreviations: CBT: cognitive behavioural therapy, GP: general practitioner, n.a.: not applicable, SD: standard deviation

Table 69: Current marked shares of available treatment alternatives for symptoms of mental stress and test anxiety

Treatment option	Current market shares mental stress	SD	Current market shares test anxiety	SD	Source
Reference product	2.42%	n.a.	24.98%	n.a.	Calculation based on SWICA and SASIS data
CBT	26.66%	24.82	21.37%	24.51	Shares from GP survey rescaled based on claims data
SSRIs	20.08%	18.77	4.23%	12.16	
Benzodiazepines	8.64%	13.34	11.80%	21.10	
Tricyclic antidepressants	8.44%	14.27	2.03%	6.25	
No treatment	13.13%	21.22	23.71%	29.84	
Other	21.42%	29.58	10.04%	26.30	

Abbreviations: CBT: cognitive behavioural therapy, GP: general practitioner, n.a.: not applicable, SD: standard deviation, SSRIs: Selective serotonin reuptake inhibitors

Alternative treatment mix

Survey responses for the alternative scenario introduced new categories (other reimbursed phytotherapy, over the counter (OTC) valerian), which may have underestimated some comparators. Adjustments were therefore made by rescaling responses while retaining the overall direction of switching. Most substitution was toward other phytotherapy and OTC valerian, with modest increases in CBT and lifestyle measures. Based on the survey responses, other treatment options such as benzodiazepine, Z-drugs or antidepressants do not increase.

While the surveyed GPs for this HTA did not anticipate increased switching to benzodiazepines following valerian delisting, this assumption was adjusted based on empirical evidence. França et al. reported an odds ratio (OR) of 1.46 for benzodiazepine prescribing after valerian was removed

from reimbursement in France.¹³⁰ To account for this observed substitution effect, increased switching to benzodiazepines was incorporated into the model. To adapt these findings to the Swiss setting, baseline switching probabilities were estimated from SWICA claims data (**Table 70**) and the OR from França et al.¹³⁰ was converted into a relative risk (**Appendix F, Table A 6**) using the formula proposed by Zhang and Kai¹³¹. Combining this information, the incremental increases in benzodiazepine prescribing were quantified (**Table 71**). Using the brand weights by indication (**Table 75**) increased probability of switching by indication by 7.20% for symptoms of insomnia and 7.18% for symptoms of mental stress (**Appendix F, Table A 7**). This adjustment was applied to redistribute valerian market share in the alternative scenario. For test anxiety, no benzodiazepine shift was modelled, as this indication was outside the French study scope; GP survey responses were used instead.

Table 70: Probability of switching from valerian-containing medicines to benzodiazepines under the current treatment scenario

Valerian-containing medicines	Probability of switching under current treatment mix (Data from SWICA)
Dormiplant	0.22
Hova	0.20
Redormin	0.22
Relaxane	0.22
Sedonium	0.24

Table 71: Probability of switching from valerian-containing medicines to benzodiazepines after policy change

Valerian-containing medicines	Probability of switching after policy change (calculation)	Increase in probability of switching [%]
Dormiplant	0.30	7.23%
Hova	0.26	6.67%
Redormin	0.29	7.22%
Relaxane	0.29	7.21%
Sedonium	0.31	7.52%

Table 72 and **Table 73** present alternative scenario in case that medicines containing valerian (alone or in combination), would continue to be available but no longer reimbursed by the mandatory health insurance.

Table 72: Alternative marked shares of available treatment alternatives for symptoms of insomnia

Treatment option	Alternative market shares insomnia	Source
Reference product	0.00%	Assumption (from a healthcare payer perspective)
Other herbal medicines	6.08%	Switching analysis from claims data and shares from GP survey rescaled based on claims data multiplied with odds ratios from França et al. ¹³⁰ for switch to benzodiazepine
Benzodiazepines	7.28%	
Z-drugs	13.99%	
Sedative antidepressants	21.92%	
CBT	6.69%	
Sleep hygiene/lifestyle adaptation	37.00%	
No treatment	5.98%	
Continue prescribing reference product	1.06%	

Table 73: Alternative marked shares of available treatment alternatives for symptoms of mental stress and test anxiety

Treatment option	Alternative market shares mental stress	Alternative market shares test anxiety	Source
Reference product	0.00%	0.00%	Assumption (from a healthcare payer perspective)
Other herbal medicines	23.02%	27.87%	Switching analysis from claims data and shares from GP survey rescaled based on claims data. For mental stress: multiplied with odds ratios from França et al. ¹³⁰ for switch to benzodiazepine
CBT	26.66%	21.37%	
SSRIs	20.08%	4.23%	
Benzodiazepines	8.82%	11.80%	
Tricyclic antidepressants	8.44%	2.03%	
No treatment	13.13%	23.71%	
Continue prescribing reference product	0.65%	17.83%	

Indication split and brand weights

Valerian-containing medicines (Hova, Dormiplant, Relaxane) are multi-indication products. Indication-specific splits were derived from the GP survey (**Table 74**). Claims data were used to weight brand shares: patient counts were applied for epidemiological estimates (SWICA data) (**Table 75**), while prescribed quantities were used for cost estimates (SASIS data) (**Table 76**).

Table 74: Estimated number of prevalent cases

Indication split, % (SD)	Insomnia	Mental stress	Test anxiety	Source
Dormiplant	83% (6.3)	17% (6.3)	-	GP survey
Hova	76% (8.7)	24% (8.7)	-	GP survey
Relaxane	-	26% (n.a.)	73% (n.a.)	GP survey

Abbreviations: n.a.: not applicable, SD: standard deviation

Table 75 Brand weights by indication in terms of patient count

	Dormiplant	Hova	Redormin	Relaxane	Sedonium
Insomnia symptoms	7%	4%	88%	-	1%
Mental stress symptoms	5%	4%	-	91%	-
Test anxiety symptoms	-	-	-	100%	-

Table 76: Brand weights by indication in terms of prescribed quantities

	Dormiplant	Hova	Redormin	Relaxane	Sedonium
Insomnia symptoms	5%	2%	92%	-	1%
Mental stress symptoms	4%	3%	-	93%	-
Test anxiety symptoms	-	-	-	100%	-

Assumptions and limitations

Key assumptions included: (i) constant annual prevalence equal to incidence due to short treatment durations; (ii) exclusion of chronic insomnia and severe mental health problems; (iii) GP survey responses as representative of prescribing patterns, acknowledging the potential contribution of other specialties; and (iv) application of French social security data¹³⁰ adapted to Swiss data. Limitations include potential reporting bias in survey responses, lack of indication-specific claims data and limited sample sizes for some epidemiological estimates (e.g. test anxiety).

Uncertainty analysis

Sensitivity analysis

Standard probability distributions were fitted to input parameters to represent uncertainty around base case estimates and applied in one-way deterministic sensitivity analyses. Where available, 95% confidence intervals informed upper and lower bounds. Probability distributions were fitted to input parameters as follows: normal distributions for continuous unbounded parameters (population numbers, prescription volumes, patient numbers) and beta distributions for proportions constrained between 0 and 1 (prevalences, market shares, probability of switching to psychotropic drugs). Beta distribution parameters (α , β) were derived from reported means and standard deviations, while normal distributions were parameterized directly from reported means and standard deviations. Medication prices were varied by $\pm 20\%$. **Table A 8** in the appendix provides detailed specification of distributions, bounds, and rationale for each parameter included in sensitivity analyses.

Scenario analysis

Consumption of valerian-containing medicines has been increasing over the last 10 years. Therefore, a scenario analysis was conducted to estimate the potential budget impact assuming continued prevalence growth at the observed rate. A linear function was fitted to the 10-year consumption data for valerian-containing medicines, and an annual growth factor was derived. This factor was applied to each year of the budget impact analysis to project consumption over the 5-year time horizon.

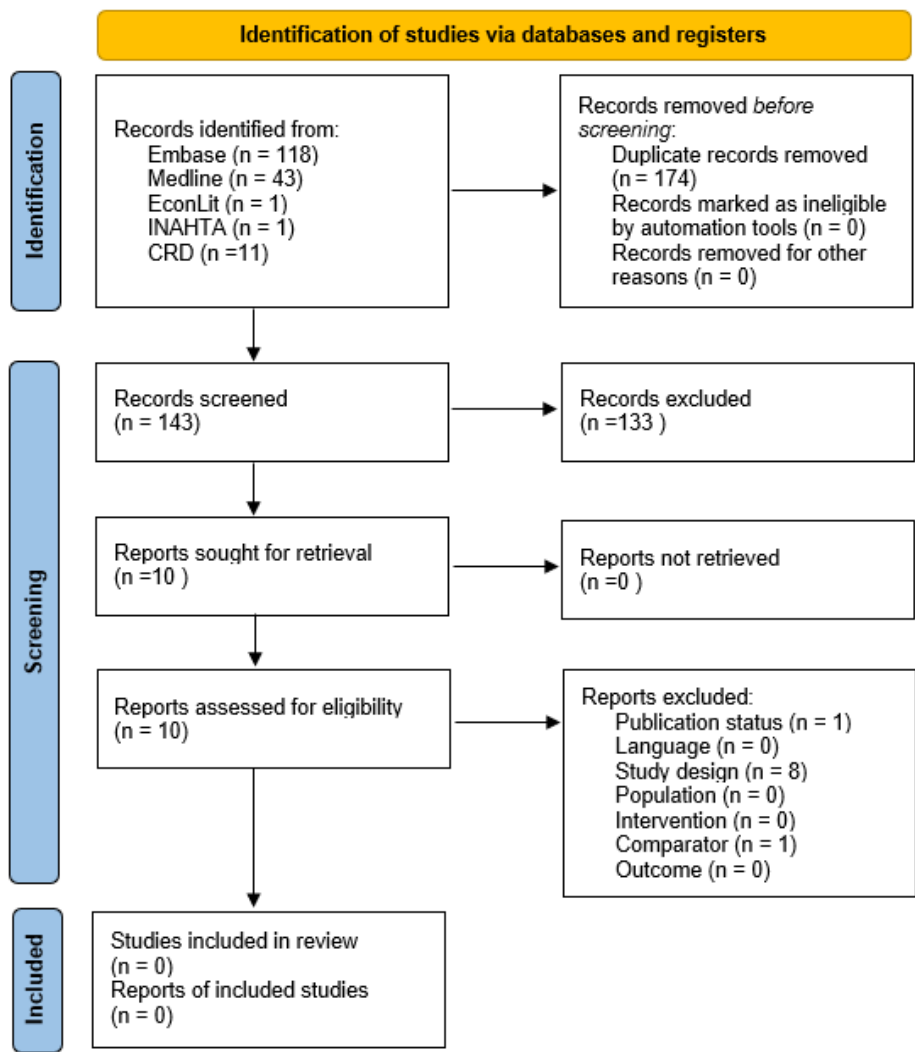
An additional scenario analysis was conducted aligning the modelled medication sales volumes more closely with real-world claims data from SASIS, to assess the sensitivity of results to the assumed market shares of valerian-containing medicines.

7.2 Results costs, cost-effectiveness and budget impact

7.2.1 PRISMA flow diagram

Figure 19 shows the PRISMA flow diagram. Of the 143 unique records, 133 were excluded during title-abstract screening. Of the remaining 10 articles, all were excluded, most frequently because of the study design (e.g. review instead of a health economic analysis, such as cost-effectiveness, -utility, -minimisation, -benefit or budget impact analysis) or the comparator or publication status did not match the inclusion criteria.

Figure 19: PRISMA flow diagram costs



7.2.2 Study characteristics and quality assessment of included studies

No studies or reports were included.

7.2.3 Evidence table

No studies or reports were included.

7.2.4 Findings costs

It was estimated, in consultation with clinical experts, that the mean treatment duration (TD) with a valerian-containing medicine in insomnia is approximately 3 months. This TD halved in the case of the medication being used to treat symptoms of mental stress and reduced further to around a month in the case of test anxiety.

Considering TD, label dosages and corresponding public prices¹³², current mean medication costs that ranged from CHF 88 for insomnia to CHF 59 for test anxiety per patient per year were estimated (*Table 77*).

Table 77: Estimated costs per drug per patient per year in CHF

Mean costs (in CHF)	Insomnia	Mental stress	Test anxiety
Sedonium	74.4	-	-
Dormiplant	97.4	57.7	-
Hova	74.5	38.8	-
Redormin	88.2	-	-
Relaxane	-	85.6	58.9

Additional costs for physician visits were assumed for all valerian-containing drugs. This was because in Switzerland it is necessary to get a prescription for any of these drugs to be reimbursed. Considering the previously mentioned TD an average of 4 and a half physician visits (GP visits) during one year was assumed for patients with symptoms of insomnia. Unit costs for a physician visit were estimated at CHF 41.01, based on a 15-minute consultation using current TARMED tariffs¹³³ and cantonal tax point values.¹³⁴ The tax point value was calculated as a population-weighted average across cantons, yielding a value of 0.881. Based on consultation with clinical experts, it was assumed that 50% of the patients being treated for symptoms of insomnia would be referred to a specialist consultation and 25% of patients under treatment for symptoms of mental stress. Specialist consultation costs were estimated at CHF 456.12 per patient, based on an assumed two consultations (initial consultation: 90 minutes; follow-up: 60 minutes) using current TARMED tariffs and cantonal tax point values. The estimated costs for physician visits for valerian-containing drugs per patient per year were CHF 412.61 due to treatment for symptoms of insomnia, CHF 278.08 due to treatment for symptoms of mental stress and, CHF 123.03 due to treatment for test anxiety.

Similarly, costs for alternative treatment for each indication were calculated, with benzodiazepines, Z-drugs and sedative antidepressants as alternative for treating symptoms of insomnia. Benzodiazepines, SSRIs and tricyclic antidepressants were taken as alternative for treating symptoms of mental stress and test anxiety. After consultation with 3 clinical experts specialising in sleep medicine, psychiatry, and general medicine, it was assumed that a negligible number of patients would

be treated with tricyclic antidepressants. Costs by drug class are displayed in **Table 78**. It is important to consider the longer TD assumed for sedative antidepressants and SSRIs when looking at their estimated costs, since this drug classes have generally a very different side effect profile to benzodiazepines and Z-drugs. As per consultation with the 3 clinical experts, the 2 latter drug classes are recommended for a maximum of 4 weeks or to be used sporadically for acute treatment of symptoms. As these have a higher potential for dependency, they also carry with them higher costs for physician visits, with patients needing careful monitoring. Estimated annual costs per patient for physician visits varied by indication and treatment. For insomnia symptoms, GP visit costs were estimated at CHF 471.63 for patients treated with benzodiazepines or Z-drugs and CHF 307.59 for those treated with sedative antidepressants. Specialists visit costs were estimated at CHF 228.06. For mental stress symptoms, GP visit costs were CHF 287.08 for benzodiazepine treatment and CHF 205.06 for SSRI treatment, with specialist visits costs estimated at CHF 114.03. For test anxiety symptoms, GP visit costs for benzodiazepine treatment were estimated at CHF 205.06.

Table 78: Estimated costs per drug class per patient per year in CHF

Mean costs (in CHF)	Insomnia	Mental stress	Test anxiety
Benzodiazepines	19.75	13.55	13.55
Z-Drugs	31.03	-	-
Sedative antidepressants	391.63	-	-
SSRIs	-	249.54	-

Prolonged use of benzodiazepines and Z-drugs carries a risk of dependence, which generates additional healthcare costs. To capture these long-term sequelae costs, the model incorporated two parameters: the transition rate from short-term to long-term use, derived from Rosenqvist et al.¹³⁵ and annual healthcare costs attributable to benzodiazepine dependence, obtained from Berger et al.¹³⁶ As cost data were reported in 2007 US dollars, a two-step currency conversion was applied: inflation adjustment using the US Medical Care Consumer Price Index, followed by conversion to 2025 Swiss francs using OECD purchasing power parities (**Table 79**).

Table 79: Costs associated with a possible dependency when treated with benzodiazepines or Z-drugs

Costs due to drug dependency	Input parameter	Source
Proportion of patients treated with benzodiazepines who developed dependency	13.1%	Rosenqvist et al. 2024 ¹³⁵
Proportion of patients treated with Z-drugs who developed dependency	17.8%	Rosenqvist et al. 2024 ¹³⁵
Increased healthcare costs due to long-term treatment	US dollar 4'668	Berger et al. 2012 ¹³⁶
Medical care consumer price index	2007 = 359 2025 = 585 Factor = 1.63	Federal Reserve Bank of St. Louis ¹³⁷
Purchasing power parities	1.10	Federal statistical office ¹³⁸
Increased healthcare costs due to long-term treatment for Switzerland	CHF 8402	Calculation

In the case of cognitive behavioural therapy, the average of group and individual therapy was calculated, estimating costs of CHF 588.24 per patient per year. In the absence of medication treatment, medication costs would be saved.

Additionally, Laitea was considered as an alternative herbal medicine, with costs estimated at CHF 49.48 and CHF 45.18 for symptoms of mental stress and test anxiety, correspondingly.

Lifestyle adaptation and improvement of sleep hygiene were assumed to be treatment alternatives recommended by the GPs.

Treatment costs

For each treatment option, costs were estimated by combining medication costs and physician visits (GPs and specialists, referred to as “additional costs” in the tables). Treatment duration, dosage, medication and visit frequency were estimated based on clinical guidelines, pharmaceutical compendium and structured interviews with clinical experts. **Table 80** to **Table 82** present the total costs for each treatment option per patient and year. The analysis assumes constant costs over time.

Table 80: Costs of treatment options for symptoms of insomnia

Treatment option	Costs (CHF) per patient and year
Reference product	88.24
Additional costs reference product	412.61
Other herbal medicines	0.00
Additional costs other herbal medicines	0.00
Benzodiazepines	19.75
Additional costs benzodiazepines	699.69
Z-drugs	31.03
Additional costs Z-drugs	699.69
Sedative antidepressants	391.63
Additional costs antidepressants	535.65
CBT	588.24
Sleep hygiene/lifestyle adaptation	82.02
No treatment	0.00

Table 81: Costs of treatment options for symptoms of mental stress

Treatment option	Costs (CHF) per patient and year
Reference product	83.13
Additional costs reference product	278.08
Other herbal medicines	49.48
Additional costs other herbal medicines	278.08
CBT	588.24
SSRIs	249.54
Additional costs SSRIs	319.09
Benzodiazepines	13.55
Additional costs benzodiazepines	401.11
Tricyclic antidepressants	0.00
Additional costs tricyclic antidepressants	0.00
No treatment	0.00

Table 82: Costs of treatment options for symptoms of test anxiety

Treatment option	Costs (CHF) per patient and year
Reference product	58.93
Additional costs reference product	123.03
Other herbal medicines	45.18
Additional costs other herbal medicines	123.03
CBT	588.24
SSRIs	0.00
Additional costs SSRIs	0.00
Benzodiazepines	13.55
Additional costs benzodiazepines	205.66
Tricyclic antidepressants	0.00
Additional costs tricyclic antidepressants	0.00
No treatment	0.00

7.2.5 Findings cost-effectiveness

No cost-effectiveness results are reported due to the absence of studies meeting the inclusion criteria.

7.2.6 Findings budget impact

7.2.6.1 Base case

The budget impact analysis projected substantial savings when valerian-containing medicines would stay available but would not be reimbursed anymore. For insomnia symptoms, estimated savings totalled CHF 174.05 million over 5 years, based on approximately 1.7 million annual prevalent patients (**Table 83**). Mental stress showed potential savings of CHF 6.14 million for approximately 1.2 million prevalent patients (**Table 84**), while test anxiety generated estimated savings of CHF 22.28 million for 0.3 million prevalent patients (**Table 85**).

Table 83: Budget impact of valerian-containing medicines for symptoms of insomnia

Cost of treatment [Million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent insomnia individuals >6 years	1.65	1.66	1.68	1.70	1.71
With no change on policy level					
Valerian-containing medicines	8.83	8.92	9.00	9.09	9.19
Additional costs valerian (GP and specialist visits)	41.28	41.69	42.11	42.53	42.95
Alternatives (medications, CBT and sleep hygiene)	242.79	245.22	247.67	250.15	252.65
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	798.22	806.20	814.26	822.41	830.63
Total	1'091.11	1'102.02	1'113.04	1'124.18	1'135.42
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (medications, CBT and sleep hygiene)	246.28	249.20	251.70	254.21	256.75
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	810.35	818.45	826.63	834.90	843.25
Total	1'056.62	1'067.65	1'078.33	1'089.11	1'100.00
Budget impact	-34.49	-34.37	-34.72	-35.06	-35.41
Budget impact over 5 years	-174.05				

Table 84: Budget impact of valerian-containing medicines for symptoms of mental stress

Cost of treatment [Million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent mental stress individuals >6 years	1.19	1.20	1.21	1.22	1.23
With no change on policy level					
Valerian-containing medicines	2.39	2.41	2.44	2.46	2.48
Additional costs valerian (GP and specialist visits)	7.99	8.07	8.15	8.23	8.31
Alternatives (medications and CBT)	251.41	253.92	256.46	259.03	261.62
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	280.52	283.33	286.16	289.02	291.91
Total	542.31	547.73	553.21	558.74	564.33
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (medications and CBT)	252.38	254.91	257.45	260.03	262.63
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	288.70	291.62	294.53	297.48	300.45
Total	541.08	546.52	551.99	557.51	563.08
Budget impact	-1.23	-1.21	-1.22	-1.23	-1.25
Budget impact over 5 years	-6.14				

Table 85: Budget impact of valerian-containing medicines for symptoms of test anxiety

Cost of treatment [Million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent test anxiety individuals >6 years	0.30	0.30	0.30	0.31	0.31
With no change on policy level					
Valerian-containing medicines	4.37	4.42	4.46	4.51	4.55
Additional costs valerian (GP and specialist visits)	9.13	9.22	9.31	9.41	9.50
Alternatives (medications and CBT)	39.15	39.54	39.94	40.33	40.74
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	46.47	46.93	47.40	47.88	48.36
Total	99.12	100.11	101.11	102.13	103.15
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (medications and CBT)	41.54	42.03	42.45	42.88	43.31
Additional costs alternatives (GP and specialist visits and costs caused by dependency)	52.99	53.72	54.26	54.80	55.35
Total	94.53	95.76	96.72	97.68	98.66
Budget impact	-4.59	-4.36	-4.40	-4.44	-4.49
Budget impact over 5 years	-22.28				

The combined 5-year budget impact for all 5 valerian-containing medicines currently listed on the SL amounts to CHF 202.47 million in savings, with insomnia symptoms representing the largest component (**Table 86**). Total costs across all 3 indications could be summed because the model allocated actual sales volumes of valerian-containing medicines to each indication based on approved uses, minimizing potential overlap between indication-specific estimates.

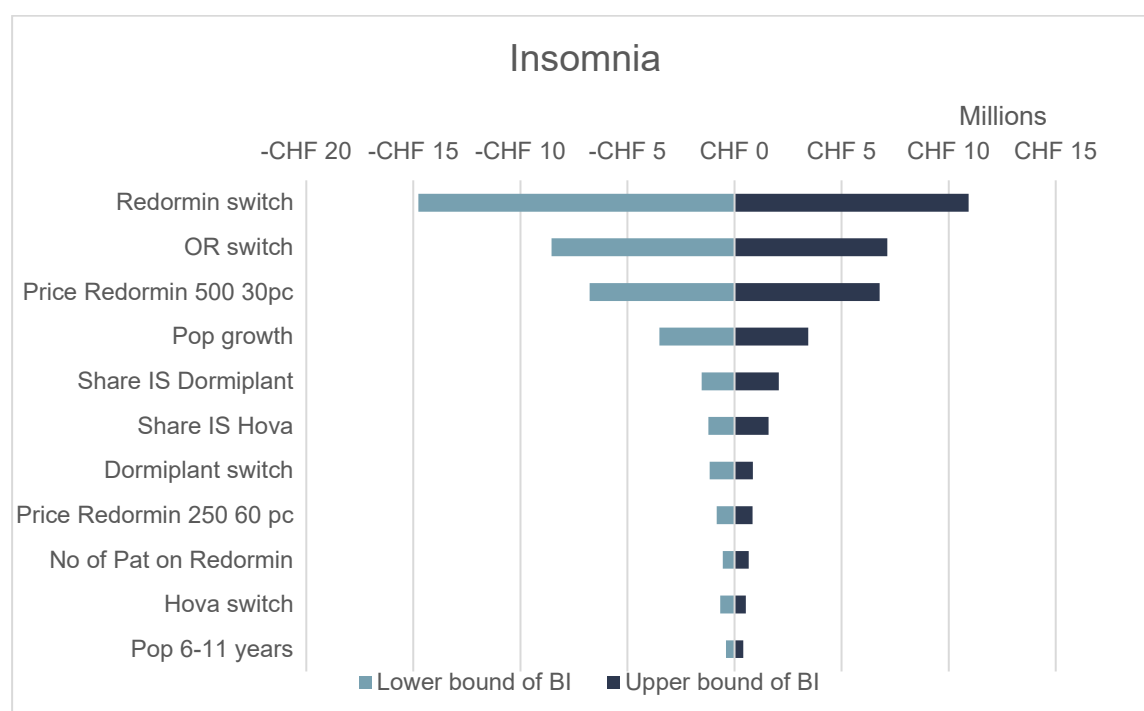
Table 86: Budget impact of valerian-containing medicines for the symptoms of insomnia, mental stress and test anxiety over 5 years

Indication	Brands in scope	Budget impact (CHF)
Insomnia symptoms	Dormiplant, Hova, Redor-min, Sedonium	-174.05 million
Mental stress symptoms	Dormiplant, Hova, Relaxane	-6.14 million
Test anxiety symptoms	Relaxane	-22.28 million
Total	Dormiplant, Hova, Redor-min, Relaxane, Sedonium	-202.47 million

7.2.6.2 Sensitivity analysis

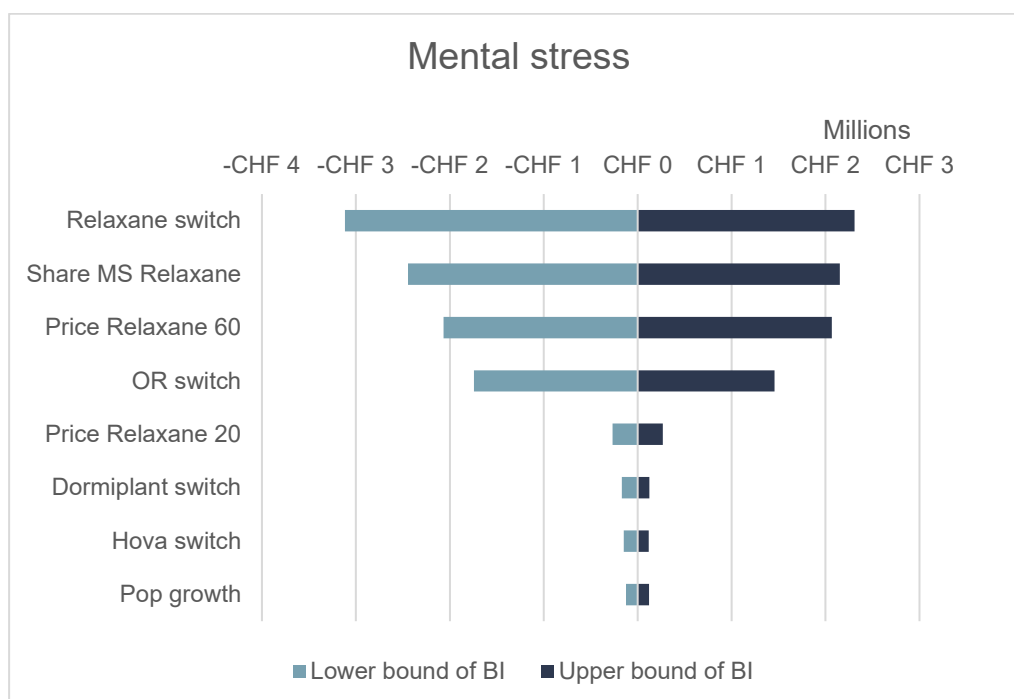
When considering the uncertainty behind the eligible patient population, indication split shares, switching probabilities, alternative treatment mix and prices of medications, cost savings varied from CHF -14.8 million to 10.9 million for symptoms of insomnia (current probability of switching from Redormin to benzodiazepines, **Figure 20**), from CHF -3.1 to +2.3 million for symptoms of mental stress (current probability of switching from Relaxane to benzodiazepines, **Figure 21**) and CHF $\pm$ 3.8 million for symptoms of test anxiety (price of Relaxane 60 pills, **Figure 22**).

Figure 20: Univariate sensitivity analysis for symptoms of insomnia



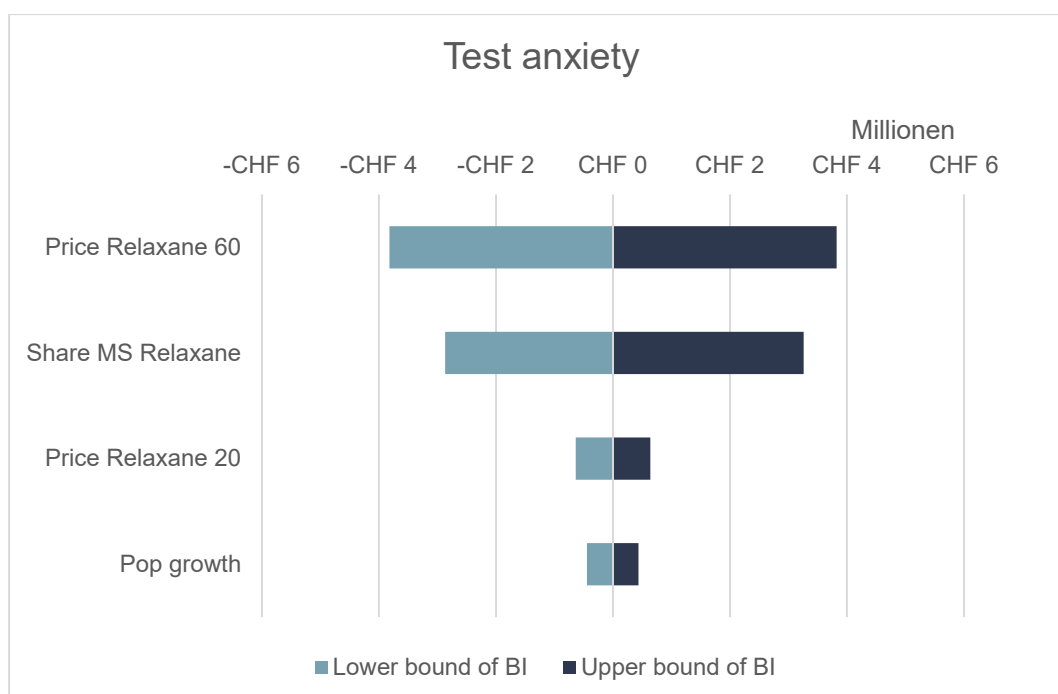
Abbreviations: BI: budget impact, IS: insomnia, pc: pieces, Pop: population, OR: odds ratio

Figure 21: Univariate sensitivity analysis for symptoms of mental stress



Abbreviations: IS: insomnia; MS: mental stress; Pop: population; OR: odds ratio

Figure 22: Univariate sensitivity analysis for symptoms of test anxiety



Abbreviations: MS: mental stress; Pop: population

7.2.6.3 Scenario analyses

Continued, linear consumption growth of valerian-containing medicines

Consumption of valerian-containing medicines has been on the ascendancy over the last 10 years. The following scenario analysis calculates the potential budget impact of a disinvestment from the SL if the observed prevalence growth would continue with the same rate.

As expected, this additional budget impact analysis projected higher savings compared to the base case scenario with total savings of CHF 243.73 million over 5 years. For insomnia symptoms, estimated savings totalled CHF 209.65 million, based on approximately 2.0 million annual prevalent patients (**Table 87**). Mental stress showed potential savings of CHF 7.34 million for approximately 1.5 million prevalent patients (**Table 88**), while test anxiety generated estimated savings of CHF 26.74 million for 0.36 million prevalent patients (**Table 89**). Total savings across all indications were estimated at CHF 243.73 million (**Table 90**).

Table 87: Budget impact of valerian-containing medicines for symptoms of insomnia – scenario analysis: continued consumption growth

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent insomnia individuals >6 years	1.75	1.88	2.01	2.16	2.32
With no change on policy level					
Valerian-containing medicines	9.38	10.06	10.80	11.59	12.43
Additional costs valerian	43.85	47.05	50.49	54.17	58.13
Alternatives (incl. CBT and sleep hygiene)	257.94	276.77	296.97	318.65	341.92
Additional costs alternatives (incl. costs caused by dependency)	848.01	909.92	976.35	1'047.63	1'124.11
Total	1'159.18	1'243.81	1'334.61	1'432.04	1'536.59
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT and sleep hygiene)	261.64	281.26	301.80	323.83	347.47
Additional costs alternatives (incl. costs caused by dependency)	860.90	923.75	991.19	1'063.55	1'141.19
Total	1'122.54	1'205.01	1'292.98	1'387.38	1'488.66
Budget impact	-36.64	-38.79	-41.63	-44.66	-47.93
Budget impact over 5 years	-209.65				

Table 88: Budget impact of valerian-containing medicines for symptoms of mental stress – scenario analysis: continued consumption growth

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent mental stress individuals >6 years	1.26	1.35	1.44	1.54	1.65
With no change on policy level					
Valerian-containing medicines	2.53	2.71	2.90	3.11	3.33
Additional costs valerian	8.47	9.07	9.71	10.39	11.13
Alternatives (incl. CBT)	266.51	285.34	305.51	327.10	350.21
Additional costs alternatives (incl. costs caused by dependency)	297.37	318.38	340.88	364.97	390.76
Total	574.88	615.51	659.00	705.57	755.43
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT)	267.54	286.45	306.69	328.36	351.57
Additional costs alternatives (incl. costs caused by dependency)	306.04	327.70	350.86	375.65	402.20
Total	573.58	614.15	657.55	704.01	753.76
Budget impact	-1.30	-1.36	-1.45	-1.56	-1.67
Budget impact over 5 years	-7.34				

Table 89: Budget impact of valerian-containing medicines for symptoms of test anxiety – scenario analysis: continued consumption growth

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent test anxiety individuals >6 years	0.32	0.34	0.36	0.39	0.42
With no change on policy level					
Valerian-containing medicines	4.64	4.98	5.34	5.72	6.13
Additional costs valerian	9.69	10.39	11.14	11.95	12.81
Alternatives (incl. CBT)	41.56	44.56	47.77	51.22	54.91
Additional costs alternatives (incl. costs caused by dependency)	49.33	52.89	56.70	60.79	65.18
Total	105.22	112.81	120.95	129.67	139.03
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT)	44.10	47.36	50.78	54.45	58.37
Additional costs alternatives (incl. costs caused by dependency)	56.25	60.54	64.91	69.59	74.61
Total	100.34	107.90	115.69	124.03	132.98
Budget impact	-4.88	-4.91	-5.26	-5.64	-6.05
Budget impact over 5 years	-26.74				

Table 90: Budget impact of valerian-containing medicines for the symptoms of insomnia, mental stress and test anxiety over 5 years – scenario analysis: continued consumption growth

Indication	Brands in scope	Budget impact (CHF)
Insomnia symptoms	Dormiplant, Hova, Redor-min, Sedonium	-209.65 million
Mental stress symptoms	Dormiplant, Hova, Relaxane	-7.34 million
Test anxiety symptoms	Relaxane	-26.74 million
Total	Dormiplant, Hova, Redor-min, Relaxane, Sedonium	-243.73 million

Consumption volume aligned with real-world claims data from SASIS

In the base case, the number of patients per valerian-containing medicine was derived from SWICA claims data and scaled to the Swiss population using SASIS claims data as a conversion factor (SWICA-to-SASIS sales volume ratio applied to patient counts). In this scenario analysis, patient numbers per valerian-containing medicine were adjusted upward such that the resulting sales volume exactly matches the total sales volume observed in the SASIS data. This approach provides an alternative estimate of the budget impact under the assumption that SASIS sales volumes represent the most accurate reflection of real-world consumption in Switzerland.

This budget impact analysis revealed higher savings compared to the base case scenario with total savings of CHF 222.37 million over 5 years. For insomnia symptoms, estimated savings totalled CHF 172.60 million (**Table 91**). Mental stress showed potential savings of CHF 10.29 million (**Table 92**), while test anxiety generated estimated savings of CHF 39.48 million (**Table 93**). The higher savings observed for test anxiety in this scenario reflect the upward adjustment of Relaxane® consumption volumes to align with the SASIS data. Since the majority of Relaxane® prescriptions are attributed to the test anxiety indication, this adjustment disproportionately increased the patient numbers and associated savings for this indication compared to the base case. Total savings across all indications were estimated at CHF 222.37 million (**Table 94**).

Table 91: Budget impact of valerian-containing medicines for symptoms of insomnia – scenario analysis: SASIS-aligned consumption volume

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent insomnia individuals >6 years	1.65	1.66	1.68	1.70	1.71
With no change on policy level					
Valerian-containing medicines	8.76	8.84	8.93	9.02	9.11
Additional costs valerian	40.94	41.35	41.77	42.18	42.61
Alternatives (incl. CBT and sleep hygiene)	242.92	245.35	247.80	250.28	252.78
Additional costs alternatives (incl. costs caused by dependency)	798.63	806.62	814.69	822.83	831.06
Total	1'091.25	1'102.16	1'113.19	1'124.32	1'135.56
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT and sleep hygiene)	246.38	249.30	251.79	254.31	256.85
Additional costs alternatives (incl. costs caused by dependency)	810.67	818.78	826.97	835.24	843.59
Total	1'057.05	1'068.08	1'078.76	1'089.55	1'100.44
Budget impact	-34.20	-34.08	-34.42	-34.77	-35.12
Budget impact over 5 years	-172.60				

Table 92: Budget impact of valerian-containing medicines for symptoms of mental stress – scenario analysis: SASIS-aligned consumption volume

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent mental stress individuals >6 years	1.19	1.20	1.21	1.22	1.23
With no change on policy level					
Valerian-containing medicines	4.02	4.06	4.10	4.14	4.18
Additional costs valerian	13.44	13.57	13.71	13.85	13.98
Alternatives (incl. CBT)	247.15	249.62	252.12	254.64	257.18
Additional costs alternatives (incl. costs caused by dependency)	275.77	278.52	281.31	284.12	286.96
Total	540.37	545.77	551.23	556.74	562.31
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT)	248.77	251.27	253.78	256.32	258.88
Additional costs alternatives (incl. costs caused by dependency)	289.54	292.48	295.40	298.36	301.34
Total	538.31	543.75	549.19	554.68	560.22
Budget impact	-2.06	-2.03	-2.05	-2.07	-2.09
Budget impact over 5 years	-10.29				

Table 93: Budget impact of valerian-containing medicines for symptoms of test anxiety – scenario analysis: SASIS-aligned consumption volume

Cost of treatment [million CHF]	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent test anxiety individuals >6 years	0.30	0.30	0.30	0.31	0.31
With no change on policy level					
Valerian-containing medicines	7.75	7.83	7.91	7.98	8.06
Additional costs valerian	16.18	16.34	16.51	16.67	16.84
Alternatives (incl. CBT)	29.08	29.37	29.67	29.96	30.26
Additional costs alternatives (incl. costs caused by dependency)	34.52	34.87	35.22	35.57	35.92
Total	87.54	88.41	89.30	90.19	91.09
With valerian available but not reimbursed					
Valerian-containing medicines	0.00	0.00	0.00	0.00	0.00
Alternatives (incl. CBT)	33.33	33.79	34.13	34.47	34.82
Additional costs alternatives (incl. costs caused by dependency)	46.07	46.90	47.37	47.84	48.32
Total	79.40	80.69	81.50	82.32	83.14
Budget impact	-8.14	-7.72	-7.80	-7.87	-7.95
Budget impact over 5 years	-39.48				

Table 94: Budget impact of valerian-containing medicines for the symptoms of insomnia, mental stress and test anxiety over 5 years – scenario analysis: SASIS-aligned consumption volume

Indication	Brands in scope	Budget impact (CHF)
Insomnia symptoms	Dormiplant, Hova, Redor-min, Sedonium	-172.60 million
Mental stress symptoms	Dormiplant, Hova, Relaxane	-10.29 million
Test anxiety symptoms	Relaxane	-39.48 million
Total	Dormiplant, Hova, Redor-min, Relaxane, Sedonium	-222.37 million

8. Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

The ELSO analysis of this HTA identified several significant aspects of potential reimbursement changes for valerian-containing preparations. From an ethical perspective, the current system presents concerns regarding inequitable resource allocation when supporting interventions lacking robust effectiveness evidence. Another argument discussed in the context of the indications examined in this HTA is the question to what extent common experiences such as insomnia, test anxiety, and mental stress should be understood and met as medical problems, and thereby pathologizing these phenomena of human life. Tendencies towards overdiagnosis, pathologisation and medicalisation may impact health-seeking behaviour and clinical decision-making and potentially discourage more effective non-pharmacological approaches. Legally, reimbursement withdrawal is fundamentally possible when robust evidence demonstrates that effectiveness criteria are no longer met. Social aspects highlighted potential financial challenges for vulnerable populations and the need for careful transition planning to maintain continuous patient care. Organisationally, possible increased consultation time and additional strain on already overburdened mental health services were identified.

8.1 Methodology ethical, legal, social and organisational issues

8.1.1 Databases and search strategy

To assess the ELSO aspects, pertinent issues were identified from the studies included in the clinical and economic evaluations. Additionally, targeted, selective searches in MEDLINE, Swisslex and Legalis were performed.

A single researcher screened and reviewed the literature and identified studies relevant to the ELSO aspects. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, reports, legal documents, narrative research and case studies were considered for inclusion. The publication language had to be English, French, German, or Italian.

To answer the relevant legal questions, a search of materials and literature was carried out in national and international databases to identify publications dealing with legal questions related to Valerian preparations. With a view to the Swiss context, the following sources and databases were used for the legal search:

- Legal texts and materials of the Confederation (in particular laws, ordinances and justifications for enactments);
- Jurisprudence of the Federal Supreme Court (database);
- Jurisprudence of the Federal Administrative Court (database);
- PubMed (database);

- Swisslex (database);
- Legalis (database);
- Weblaw (database);
- Beck-Online (database).

Although court decisions and expert publications on the legal classification of Valerian preparations are manageable, the multitude of possible legal norms with significance for these medicinal products makes it necessary to limit the legal clarification to a selection of the most important enactments. Taking into account the objective according to the HTA Core Model (**Chapter 8.1.4**) and in the sense of a relevance review according to the HTA checklist (**Chapter 8.1.4**), only the most important legal questions are identified and analysed here.

8.1.2 Other sources

In addition to the searches in the databases mentioned above, information was gathered from relevant websites (those of health authorities, research groups and non-governmental organisations). National and international regulations, guidelines and recommendations as well as judgements, reports and (specialist and grey) literature related to these domains were identified and reviewed. Furthermore, social and organisational considerations were identified using the assessment framework provided by the HTA Core Model.¹³⁹

8.1.3 Assessment of quality of evidence

No quality assessment of the evidence was conducted. The focus of the ELSO-part was to provide a comprehensive overview of ethical, legal, social and organisational aspects related to this HTA.

8.1.4 Methodology data extraction, analysis and synthesis of the domains ethical, legal, social and organisational issues

The main ELSO aspects identified through this targeted search was reported in a descriptive manner. Key issues were summarised narratively, analysed and discussed.

For the analysis of ethical issues, an axiological approach based on the “Hofmann catalogue” was used, comprising 33 questions designed to identify characteristics of a health technology, involved interests and stakeholders. All relevant questions of the catalogue were addressed.¹⁴⁰

With regard to the reimbursement of costs for valerian-containing preparations by mandatory healthcare insurance (OKP), a large number of international guidelines and national regulations at the federal and cantonal levels must be included in the analysis. The HTA Core Model was used here for the clarification and answering of the relevant legal questions.

The objective defined in the HTA Core Model¹³⁹ served as a guideline here: " The objective of the Legal Aspects (LEG) domain is to assist the HTA doers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of

implementing a health technology."^e The concept further states: "The aim within LEG is not and indeed cannot be, to give or even propose a binding legal solution to a given question. Instead, the aim is to guide the HTA doers in recognising the relevant legal questions they need to consider when evaluating the technology and providing advice for decisionmakers."

Against this background, this HTA examines the essential legal questions in connection with valerian-containing preparations (monopreparations and combination preparations). The "Checklist for Legal Analysis in the Sense of a Relevance Review," as developed in Swiss legal literature, was used for this purpose.^f The checklist, which is structured according to areas of law, distinguishes 8 review steps: "(1) Right of self-determination, (2) Doctor-patient relationship, (3) Therapeutic Products Act, (4) Health Insurance Act, (5) Constitution, (6) Cantonal legal enactments/recommendations, (7) Other legal enactments and (8) Other legal questions to be reviewed".^g

With the help of the HTA Core Model's objective and the checklist for HTA legal review, several questions were formulated to answer the central research question regarding Valerian preparations from a legal perspective step by step.

8.2 Results ethical, legal, social and organisational issues

8.2.1 PRISMA flow diagram

n.a.

8.2.2 Study characteristics and risk of bias of included studies

n.a.

8.2.3 Evidence table

n.a.

8.2.4 Findings ethical issues

Introduction and theoretical background

The ethical aspects of this HTA mainly concern issues arising in relation to fair and sustainable allocation of healthcare resources and costs. Schröder-Bäck¹⁴¹ proposed 5 principles specific to public health ethics, which serve as theoretical background for the ethical analysis:

1. Maximisation of overall health benefits and population protection (principle of utility)

^e EUnetHTA, HTA Core Model, S. 371.

^f Widrig, HTA, Anhang, S. 461 ff.

^g Widrig, HTA, Anhang, S. 461 ff.: «(1) Selbstbestimmungsrecht, (2) Arzt-Patientenbeziehung, (3) Heilmittelrecht, (4) Krankenversicherungsgesetz, (5) Verfassung, (6) Kantonale Rechtserlasse/Empfehlungen, (7) Weitere Rechtserlasse und (8) Weitere zu prüfende Rechtsfragen».

2. Respect for human dignity (self-determination)
3. Justice (reduction of health inequalities)
4. Efficiency (as a criterion for the allocation of public resources)
5. Proportionality (appropriateness of means to ends)

The first principle integrates a utilitarian perspective (produce the greatest good for the greatest number of people) as a basic orientation for public health. The second and third principles reflect the core concerns of a Kantian deontological approach (adhere to rules and duties, regardless of consequences). The fourth and fifth principles further develop and refine the principle of utility by emphasising the importance of responsible resource management.

Approach of the ethical analysis

For the ethical analysis of this HTA, an axiological approach based on the "Hofmann catalogue" was employed. This framework comprises 33 questions designed to identify characteristics of a health technology as well as the involved interests and stakeholders.¹⁴⁰ Pertinent questions from this catalogue were selected for the present assessment.

Selected questions for this HTA

Q1 What are the morally relevant consequences of a de-implementation of the technology?

As the present analysis concerns de-implementation, Hofmann's questions were adapted to address the morally relevant aspects of de-implementation of the technology from reimbursement coverage. "De-implementation is the systematic process of discontinuing low-value care (LVC), namely, to remove (i.e. stop the delivery entirely), replace (i.e. stop an inappropriate intervention and start a new, evidence-based intervention targeting similar aims), reduce (i.e. change the practice frequency and/or intensity), or restrict (i.e. specify a particular setting/population) LVC practices (see Kien et al. 2024¹⁴⁵ on the basis of Norton and Chambers (2020)¹⁴⁶)."

For this HTA, it is essential to distinguish between prescribing and reimbursement: valerian-containing products may be prescribed without being reimbursed within the healthcare system. Additionally, the psychological and social effects of prescriptions (both positive (e.g., validation of symptoms) and negative (e.g., pathologisation)), were examined. In this HTA, de-implementation refers to the anticipated reduction in valerian use as a consequence of suspension of reimbursement. While valerian-containing medicines would remain available on the market and could still be prescribed by medical professionals, the recipient of the prescription would have to pay fully out of pocket. Alternatively, reimbursement suspension could be implemented as a restriction, limiting coverage to specific populations, e.g. elderly or pregnant persons.

As noted by Kien et al.¹⁴⁵: "Reducing low-value care (LVC) is crucial to improve the quality of patient care while increasing the efficient use of scarce healthcare resources.", de-implementation is a moral desideratum in the same way as early health technology assessment of a new technology is vital for patients." The moral implications and consequences of a de-implementation include: Policy

makers, insurers, providers and patients must be able to develop a commonly shared transparent de-implementation strategy. As patients and physicians can no longer resort to managing the phenomena through treatment with prescribed and reimbursed medications, they must change their behaviour and patients will need to be sensitised to other ways of dealing with symptoms of insomnia, mental stress, or test anxiety, e.g., via working on their sleep hygiene, etc.

In addition, the practice of prescribing and reimbursing valerian-containing products raises the question of fair allocation of resources for drugs vs. other kinds of therapies for insomnia, mental stress and test anxiety. Delisting valerian-containing products would imply equality with other measures, which are not reimbursed, such as sleep hygiene. This needs to be taken in consideration when justice and equity in healthcare are discussed (see also questions below, especially Q14).

Furthermore, from a public health ethics perspective, social and political determinants of health must also be addressed at a structural level. In societies where individuals face significant pressure to perform efficiently, factors such as availability and performance expectations play a critical role in shaping health outcomes. Therefore, it is essential to foster health promoting working and living environments, e.g., by organisational health management strategies, strengthening health literacy and individual resilience. For individuals experiencing insomnia, test anxiety, and mental stress, the development of supportive living environments that strengthen psychological well-being, reduce stressors, and enhance coping capacities are significant.¹⁴⁷

Ethical implications of pathologisation

The following section covers questions 4, 5 and 7-9 of the Hofmann catalogue.

Q4 Does the technology challenge human integrity?

Q5 Does the technology challenge human dignity?

Q7 Does the technology challenge social values and arrangements?

Q8 Does the widespread use of the technology change our conception of certain persons?

Q9 Does the technology contest religious, social, or cultural convictions (because they interfere with foundations of communities)?

The ethical challenges associated with these questions are closely interrelated. Prescription and reimbursement of valerian-containing products by Swiss mandatory health insurance for treating symptoms related to insomnia, mental stress or test anxiety, means pathologizing these phenomena of human life. The above discussed de-implementation by reducing the use of valerian as a consequence of the suspension of its reimbursement would mean to de-pathologize these phenomena. Symptoms related to insomnia, mental stress or test anxiety exist on a continuum between normal stress responses and pathological conditions. The current procedure of prescribing and reimbursing valerian-containing products may contribute to a perception of individuals as passive

recipients of care and contribute to internalisation of an illness-centered identity. Questions 4, 5 and 7 to 9 from Hofmann's catalogue address the ethical implications of this pathologisation.

Q7 Does the technology challenge social values and arrangements?

Hofmann elaborates this question further by asking: Does the technology change the social status of certain conditions? The key question for this HTA is what (social, cultural and) ethical significance does the pathologisation or the de-pathologisation of experiences and treatment of insomnia, mental stress and test anxiety have? To what extent are affected persons stigmatised and to what extent are they respected, recognised and supported in coping with these conditions?

Insomnia, psychological stress and test anxiety are aspects of human life and represent common experiences. Treating them with (prescribed) pharmaceuticals means to view these conditions as psychological or medical problems. This is referred to as pathologisation, medicalisation or pharmaceuticalisation. Even if persistence or severity (see elaborations below under Q8) may vary, a differentiated diagnosing is necessary. The ethical questions to consider are whether such practices genuinely benefit the individuals affected, whether they pose any potential harm and how they influence the well-being of individuals experiencing insomnia, mental stress and test anxiety in varying severity and persistence, as well as the broader implications for society and the healthcare system.

Suhr and Johnson (2022) define medicalisation regarding insomnia as the expansion of medical categories to include non-medical problems, often resulting in inappropriate diagnoses and treatments.¹⁴⁸ While severe insomnia might demand medical diagnosis and treatment, this process might be inadequate in episodic cases, which can lead to ethical concerns on individual and societal level. The current procedure of reimbursed prescription of valerian-containing products without the baseline of a diagnosis contributes to over-pathologisation. This can lead individuals to adopt an illness identity, interpreting negative experiences as pathological, potentially affecting self-perception. On a societal-level social inequalities may be reinforced and trust in mental healthcare might be negatively affected. By reducing the use of valerian-containing preparations as a consequence of the suspension of its reimbursement, these negative effects of pathologisation may be mitigated.

Q8 Does the widespread use of the technology change our conception of certain persons (e.g., with certain diseases)?

Regarding insomnia, Coveney et al. (2019) explored the historical and sociocultural change of sleeplessness into the medical condition 'insomnia', which they identify as a 'more modern matter'. While sleeplessness has existed throughout human history, the term "insomnia" only emerged as a formal medical diagnosis in the late nineteenth century.¹⁴⁹ This shift marks a broader process of medicalisation, wherein natural variations in sleep began to be redefined as pathological. The authors describe ambiguities both in affected people and healthcare providers. On one hand the perception of poor sleep as a normal and inevitable part of life leads to scepticism towards pathologisation and medicalisation. On the other hand, healthcare providers are confronted with

expectations to recognise and solve the experienced disruptions as a pathological problem. Thus, although the prescription of hypnotics may be perceived as an act of empathy, it is accompanied by a professional obligation to limit their use due to unfavourable side effects, such as addiction.¹⁴⁹ The suspension of reimbursement for valerian-containing medications would effectively reduce the possibility of prescription for these substances as some people may not be able to afford or would not be willing to pay the product out of pocket.

Nevertheless, this may help mitigate the negative consequences associated with patients' expectations and the pressure they place on physicians. Furthermore, it could change the socially established practice of consulting medical professionals for common human experiences such as insomnia. Whether this would lead to heightened pressure to prescribe stronger hypnotics and what the implications of such a development might be, remains uncertain. In case of delisting valerian-containing products, the potential risk of increasing prescription of stronger hypnotics will have to be carefully observed, but this does not alter the identified ethical problems with reimbursement of valerian-containing products.

Q4/Q5 Does the technology challenge human integrity and/or human dignity?

Pathologisation of human experiences can contribute to stigmatisation as individuals are labelled and treated primarily through the lens of disease. Such labelling may be associated with negative connotations and stigmatisation and may compromise human integrity and dignity by neglecting the complexity of personal identity and reducing individuals to persons with perceived deficits or disorders. Stigma can manifest as prejudices and rejection from society towards patients suffering from a specific pathology, as well as patients internalising this discrimination, which has repercussions for their state of mind and quality of life.^{150–152}

Concerning this HTA, pathologisation and prescription of valerian-containing products or other pharmaceuticals may be viewed as inconsistent with a broader and more holistic approach. This medicalised response not only represents a less satisfactory alternative to addressing underlying social problems, but it may also contribute to the reinforcement of stigma.

Gabe et al. (2016) explore how the use or avoidance of sleep medications is morally framed, identifying 6 user identities shaped by themes of addiction, control and ambivalence.¹⁵³ Their findings show that sleep and its pharmaceutical management are deeply moralised and the authors emphasise that pharmaceuticals are socially embedded, influenced by cultural norms and expectations around informed, responsible use. The identification of 6 distinct repertoires as a result of the qualitative study about use of hypnotics illustrates the moral dimensions associated with pharmaceutical treatment of insomnia: the 'deserving' patient, the 'responsible' user, the 'compliant' patient, the 'addict', the 'sinful' user and the 'noble' non-user. These users and non-users are constructed drawing on cross-cutting themes of addiction and control, ambivalence and reflexivity. The authors conclude that persons' management of sleep disorders and prescriptions of pharmaceuticals is embedded in social norms and that there is a moral dimension of sleep.¹⁵³

In summary, while persons suffering from insomnia should be respected and receive support, the practice of prescribing valerian containing preparations may express a narrow focus on a biomedical explanation. This may on the one hand express recognition and thus reducing blame, but on the other hand it also appears to be linked to pathologisation and stigmatisation. It is therefore essential to address the social dimensions associated with insomnia and its medicalisation.

Q9 Does the technology contest religious, social, or cultural convictions (because they interfere with foundations of communities)?

Social values such as effectiveness, efficiency and high-performance expectations characterise contemporary culture. The pathologisation of conditions like insomnia or mental stress through medical prescription of valerian-containing medicines may reinforce stigmatisation and delay more systemic approaches to addressing these issues, raising concerns about human dignity and the principle of proportionality. Importantly, insomnia, test anxiety and mental stress exist on a continuum from normal human experiences to clinically significant disorders. While severe cases can meet ICD-11 diagnostic criteria (e.g. insomnia with persistent sleep difficulties despite adequate opportunity, resulting in daytime impairment), the boundary between transient symptoms and pathological conditions remains difficult to define. The Swiss practice of prescribing valerian-containing medicines without clear diagnostic criteria raises concerns regarding disproportionate pathologisation and medicalisation of normal stress responses. While severe and persistent cases meeting diagnostic criteria require evidence-based medical intervention, milder presentations could be addressed within broader social and cultural contexts, including societal expectations that may contribute to these experiences.

Q11 How does the technology assessed relate to more general challenges of modern medicine?

Q13 Does the technology in any way challenge or change the relationship between physician and patient?

A systematic review by Winkler and Rief¹⁵⁴ revealed that nearly 64% of drug responses in patients with insomnia are attributable to placebo effects across various pharmacological treatments, including hypnotics, antidepressants, benzodiazepines and valerian-containing preparations. This raises fundamental ethical questions about the prescription and reimbursement of treatments primarily working through placebo mechanisms.

From a legal perspective, prescribing placebo without patient knowledge is not permitted in Switzerland. According to legal expert Juana Vassella (has written the chapter of legal issues of the present HTA), placebo use in clinical care must comply with constitutional rights to autonomy (Art. 10 Abs. 2 BV) and professional obligations to inform patients (Art. 19c, 28 ZGB; Art. 97 Abs. 1 OR). Prescribing placebo without prior information could be perceived as deceit (Art. 19c ZGB i.V.m. Art. 28 ZGB). An exception exists for "open placebo treatment" where patients willingly consent with full understanding that the treatment lacks proven effectiveness or when used as an adjuvant to evidence-based psychotherapeutic regimens. In this case the physician must have a clear

diagnosis and adhere to professional diligence (Art. 40 lit. a MedBG, Art. 27 lit. a PsyG and Art. 16 lit. a GesBG; see also SAMS-Guidelines and FMH-professional guidelines).

Current bioethical standards foster shared decision-making and patient autonomy: this necessitates full information about therapeutic interventions. Prescribing treatments without proven effectiveness based solely on anticipated placebo responses contradicts both Swiss law and fundamental medical ethics' principles.

The nature of placebo effects requires careful consideration. According to Benedetti et al. (2005)¹⁵⁵, placebo responses encompass any positive reaction attributable solely to psychosocial context rather than drug effectiveness. However, effects observed in placebo arms of trials often include regression to the mean, natural disease course, spontaneous remission and effects of additional therapeutic measures, rather than "true" placebo responses.¹⁵⁶ This complexity challenges simplistic interpretations of placebo effects.

Regarding the physician-patient relationship, shared decision-making including more intensive physician-patient discussions about alternative evidence-based approaches such as CBT, sleep hygiene and lifestyle modifications may be necessary. While this requires additional consultation time and access to specialised services, it promotes evidence-based care aligned with ethical principles of informed consent and transparent resource allocation.

Q12 Are there any related technologies that have turned out to be morally challenging?

Concerns have been raised that delisting valerian containing products would increase prescription of benzodiazepines. As these have stronger side effects, substitution of the use of valerian containing products with benzodiazepines is medically clearly not desirable. However, this substitution risk and measures to prevent such substitutional prescription practice require independent analysis. This does not alter the ethical concern: prescribing valerian containing products without robust evidence remains problematic. Furthermore, it is ethically not legitimate to continue the current practice in order to avoid a potentially worse scenario. This position is further reinforced by the EAE criteria (effectiveness, appropriateness, economic effectiveness), which explicitly require demonstrated effectiveness as a prerequisite for reimbursement. The hypothetical risk that ineffective products may be substituted with alternative medications following delisting does not constitute sufficient justification for maintaining reimbursement status.

Q14 How does the de-implementation of the technology affect the distribution of healthcare?

Regarding Q1 this question is relevant, as this HTA was motivated by uncertain clinical effectiveness and rising expenses of valerian-containing products for symptoms of insomnia, test anxiety and mental stress. Moreover, it is a more general question when it comes to problems at the interface of disease and well-being: how should decisions be made in a system with mandatory insurance based on premiums in a solidary manner?

Currently reimbursement for symptoms of insomnia, mental stress and test anxiety is not in line with the European and Swiss guidelines, as it is based on inconsistent evidence. The findings of this HTA confirm that evidence demonstrating superiority of valerian-containing medicines over placebo is largely absent. Meta-analyses conducted where sufficient data were available failed to demonstrate statistically significant advantages over placebo for most outcomes, with the exception of sleep quality at post-intervention assessment and PSQI total score. A comprehensive discussion about allocation, distribution, prioritisation, and rationing principles is beyond the scope of this HTA. These issues are connected to basic decisions on ethical theories such as utilitarianism (actions are morally right if they produce the greatest good for the greatest number of people) and deontological ethics (actions are morally right based on adherence to rules and duties irrespective of consequences).^{1,3,4,6,49} Distribution of health refers to ensuring fair and equitable access to healthcare, especially with regard to the section of healthcare that is reimbursed by insurance funds. The Swiss health insurance system is based on solidarity, raising the ethical question of transparent and fair criteria for reimbursement.

The so called EAE criteria can be of help: The Swiss Health Insurance Act (HIA)¹⁵⁷ (articles 32 and 33) requires that services that are reimbursed must be effective, appropriate and economically effective. In this context, solidarity includes practices which are based on the willingness to absorb “costs” (whether financial, social, emotional, or even of any other kind) to support others with whom similarities in relevant aspects are shared.¹⁵⁸ According to Daniels and Sabin (2002) decision-making need to be fair and transparent which is considered warranted if decisions can be made on the basis of an HTA.¹⁵⁹

Public health ethics, offers a framework for decision-making. Schröder-Bäck¹⁴⁷ proposes a set of principles that balance efficacy, justice and individual interests. The principles 2 (respect for human dignity [self-determination]) and 3 (justice [reduction of health inequalities]) create a counterweight to the utilitarian principles 1 (maximization of overall health benefits and population protection [principle of utility]), 4 (efficiency [as a criterion for the allocation of public resources]) and 5 (proportionality [appropriateness of means to ends]).

The definition of the legal obligation to provide reimbursed medical services is rather vague. According to Swiss court precedent, treatment is deemed necessary when health impairment substantially restricts physical or mental function such that: (a) the insured person requires medical assistance, (b) recovery without medical intervention is unlikely or cannot reasonably be expected within an appropriate timeframe, or (c) it would be unreasonable to expect the individual to forgo at least an attempt at treatment (Judgment 9C_465/2010, 6 December 2010, section 4.1). The applicability of these criteria to symptoms of insomnia, mental stress and test anxiety requires further examination. The subsequent ethical analysis addresses the criteria for prioritisation, respectively rationing, severity, and reliability of diagnoses.

Would the de-implementation of valerian containing products for treating symptoms of insomnia, mental stress and test anxiety be a form of rationing? Rationing refers to the situation when services

are not provided, even though they might be effective, appropriate and economically effective, due to limited resources. In the context of the introduction of health economics into decision-making processes in Germany around the year 2010, the German Ethics Council contributed with valuable expertise on benefits and costs (see Deutscher Ethikrat (2011)¹⁵⁸). They observed an ongoing debate on rationing in the UK since the 1980ies. Against this background, the concept of rationing is viewed rather negative in German speaking countries (pg. 21). Robert Brook and Kathleen Lohr (pg. 15) define rationing as “any set of activities that determines who gets needed medical care when resources are insufficient to provide for all”.¹⁶⁰ Prioritisation (German Ethics Council, pg. 23), to the contrary, is defined as a ranking on the basis of criteria that could end in rationing if those low on the list are no longer reimbursed. The authors note that the definition and thus the limitations, of the reimbursement basket are widely accepted by populations in countries with solidarity-based insurance systems, albeit to varying degrees (p. 24). This acceptance depends on shared cultural values and social expectations, as well as the status quo of healthcare delivery and the sort of reduction.¹⁶¹

International criteria include appropriateness, effectiveness / benefit, cost effectiveness. These international criteria, though still hard to operationalise, are rather similar to those in the Swiss HIA.¹⁵⁷

When it comes to exclusion from reimbursement in a solidary system there are various criteria based on the Swiss law¹⁵⁷ and international literature^{159,161}:

- A) Any technology that has no (proven) effect according to current evidence should be delisted from reimbursement. According to this HTA, statistically significant superiority of valerian-containing products over placebo could only be proven for two outcomes.
- B) Where is the border between disease and lifestyle or enhancement (see questions 7 to 9)? The question needs to be raised if the practice of prescription and reimbursement of valerian-containing products based on subjective reports of symptoms of insomnia, mental stress and test anxiety is consistent with criteria of transparency and fairness in the solidarity system. Furthermore, the symptoms are not as clearly defined and operationalised as many diseases that have a clear set of symptoms, signs, and can be verified via markers or tests.^{14,31–33} Nevertheless, reimbursement of services would need to be based on clear criteria and categories for need for treatment.
- C) Where is the border to out-of-pocket costs? Given that the indication for valerian-containing products are symptoms of insomnia, mental stress and test anxiety, it could be argued that these symptoms could be treated via out-of-pocket expenses, to avoid putting a burden on the solidarity system. This would be in accordance with the ethical deliberations on prioritisation.
- D) Overall, the criterion of the severity of symptoms could be introduced into the debate around de-implementation of valerian-containing products. As Sören Holm pointed out severity is open to different interpretations.¹⁶² In a more recent study by Barra and colleagues (2019)

the question on severity as a priority setting criterion is taken up anew.¹⁶³ Their motive is to widen the discussion from merely utilitarian criteria. “Safety, efficiency, cost and budgetary constraints together constitute classical cost-effectiveness, which in priority setting ethics is built upon utilitarian considerations. In Norway and Sweden, however, considerable efforts have been made to integrate non-utilitarian ethical principles into the nations’ priority setting policies ...” (pg. 26).

The authors further state: “One concept they include is “mestring” (Norwegian) – which is perhaps better translated as coping, although coping here does not quite capture the full connotations of the Norwegian “mestring” – which suggests getting ‘on top of’ (e.g. capability to meet social roles, conduct activities of daily life and find meaning and dignity) rather than merely ‘getting by’. ‘Self-management’ is also a candidate term. ... the Blankholm commission insists that a notion of basic needs should be defined and take precedence over severity (and equity) concerns in a priority setting context.” (pg. 30). In Sweden “it is also claimed that severity can be judged according to the suffering of the patient, the medical prognosis, the disability and the existential despair experienced” (pg. 32).¹⁶³ Through these deliberations, it is shown that the often simplified concept of severity needs a perspective for its definition, social context and criteria. As Barra et al go on (pg. 32): “One issue is whether the severity of a condition may depend on individual desires or preferences, or if severity is something which applies to a medical condition independent of the perceptions of the patient’s attitudes towards his/her condition. For example, the severity of infertility seems to depend on whether there is a desire for having children or not; if the individual has no desire of having biologically related children whatsoever, it is highly unlikely that the individual in question will perceive the condition of infertility as severe and unclear why anyone else should consider it so. It seems plausible to consider desires relevant for determining severity, at least sometimes and to some degree. But: when and how much? Moreover, will severity also depend on the strength of such a desire? The general point about the relationship between subjective well-being and severity is thus addressed.”¹⁶³

Translating this idea of including personal preference into the appraisal of disease severity to the question of whether valerian-containing products should be reimbursed for symptoms of insomnia, mental stress and test anxiety, questions of severity can be taken into account but may vary across patients and patient groups. An additional aspect to characterise severity in terms of impact on a person, one could differentiate between populations: an adult who has to perform at work could be considered different from a retired person who does not have to comply with the requirements of a full working day.

An additional consideration is the extent to which subjective evaluation should be used to assess the severity of a condition. Barra et al. (pg. 33) continue: “For example, placing too much emphasis on subjective evaluation of one’s own health may discriminate against those who adapt well, or are endowed with a naturally positive disposition, while ‘objective

measures of health' may not measure what people in fact care about."¹⁶³ The debate on severity can contribute to the debate on reimbursement of valerian-containing products but cannot determine it.

With regard to the present HTA's remit: "Medicines containing valerian extract, either alone or in combination with lemon balm, hops and/or other herbs, are reimbursed by Switzerland's mandatory health insurance for the treatment of symptoms related to insomnia, mental stress or test anxiety. Notably, a formal diagnosis of either condition is not required for prescribing these medicines and it can also be prescribed for mild symptoms." Given that formal diagnosis is not required, the aforementioned concept of severity supports non-reimbursement: when severity is not operationalised or merely based on mild symptoms excluding valerian-containing products from reimbursement is justified – particularly given the absence of demonstrated effectiveness.

- E) Where is the border between medical and non-medical therapies? For insomnia, valerian is just one intervention, while subsequent lifestyle adaptations or improved sleep hygiene could be more effective but would be paid respectively would currently have to be paid by the patients themselves. As long as valerian and other preparations are reimbursed, people who do not use these drugs, while paying for interventions like lifestyle adaptation or improved sleep hygiene, are at a financial disadvantage versus those who ask for a drug of questionable effectiveness when they could probably benefit from a larger effect based on a lifestyle adaptation. This raises the question of equity in treatment of insomnia.
- F) Limit the reimbursement to certain subgroups. Often, the elderly, children and pregnant women are mentioned when it comes to subgroups. This could be addressed when there is a scientific basis (compare question 23).

Q20 What are the interests of the producers of the technology?

Q23 Is the symbolic value of the technology of any moral relevance?

These questions are addressed jointly. In a previous HTA report¹⁶⁴, this question was answered as follows: "It is obvious that an industry has an interest in the distribution of the drugs, while it might be more feasible to test combined strategies of non-pharmacological interventions for the patients and educational programs for their caring relatives in randomised controlled trials." That report acknowledged the scarcity of evidence for comparator interventions to anti-dementia drugs. Yet for insomnia, mental stress and test anxiety there is clear evidence that CBT is the preferred treatment strategy compared to drugs.¹⁶⁴

If valerian-containing products are no longer reimbursed based on the results of this HTA, this will have an effect on a symbolic level, as its de-implementation might raise questions concerning the reimbursement of other herbal medicines. It might put pressure on producers to prove the effect of other herbal medicines which are reimbursed under the current reimbursement schemes.

Q29: What are the reasons this technology is selected to be assessed?

The technology was selected due to uncertain clinical effectiveness and increasing expenditure (from CHF 7 million in 2014 to CHF 21 million in 2023) of medicines containing valerian. This reflects recognition that rising prescriptions rates warrant closer examination, particularly regarding whether insurance funds should support products lacking evidence.

8.2.5 Findings legal issues

Legal Classification: How are valerian-containing preparations to be classified from a legal perspective and what are the consequences for cost coverage?

The valerian herbal medicinal products (HMP) evaluated in this HTA are registered medicinal products in accordance with Swissmedic requirements and applicable national and EU regulations. Valerian-containing preparations in general are medicinal products of complementary medicine. "Complementary medicine" is not characterised by a uniform medical concept, which makes a definition difficult.¹⁶⁵ Corresponding to this broad scope of complementary medicine, "complementary medicinal products" cover a wide range. These include, in particular, herbal and homeopathic medicinal products. As a typical example of herbal medicinal products with exclusively herbal active ingredients, also known as phytomedicines, valerian is mentioned, among others.¹⁶⁶

Swiss law does not generally recognise complementary and phytomedicinal products (CPM) as a distinct group of medicinal products. However, in individual areas, the legislator has also established special regulations for complementary medicinal products due to their special position. For example, certain complementary medicinal products are reimbursed by the OKP according to special rules.

The legal review of the eligibility for reimbursement of medicinal products with valerian extract within the scope of mandatory health insurance is based primarily on the HIA, in particular Art. 24 para. 1 HIA (principle of the scope of benefits), Art. 25 para. 1 HIA (general benefits in the event of illness), Art. 32 HIA (prerequisites for cost coverage) and Art. 34 HIA (scope of cost coverage), as well as the Health Insurance Ordinance (HIO), in particular Art. 52 et seq. HIO. In doing so, criteria of EAE must be observed. If the EAE criteria are met, medicinal products are included in the SL of the FOPH (Art. 25 para. 2 lit. b and 52 para. 1 lit. b HIA in conjunction with Art. 34 and 65 para. 3 HIO).

When including complementary medicinal products in the SL, special conditions apply – in comparison with allopathic medicinal products – according to Art. 35a HIO (Complementary Medicine), in that the following criteria are of particular importance when assessing their effectiveness, appropriateness, and economic effectiveness:

- the tradition of application and research of the field in which the services are provided;
- the services being based on scientific evidence and medical experience;
- the knowledge, skills and abilities necessary to provide the services being conveyed in a specific supplementary postgraduate training.

This means that the effectiveness review is carried out using scientific methods (beyond a natural science or conventional medicine perspective, for example, through scientific publications) and that clinically controlled studies do not necessarily have to be available.¹⁶⁶

As far as can be seen, valerian-containing preparations in general are only explicitly mentioned in federal laws in "Annex 1: Plants and plant parts as well as preparations and substances made from them whose use in food is not permitted" of the Ordinance of the Federal Department of Home Affairs (FDHA) on foods of plant origin, mushrooms and table salt (VLpH) under "Part A: Plants, plant parts and preparations made from them whose use in food is not permitted" as "valeriana edulis subsp. procera (Kunth) F.G. Mey. | Mexican valerian | root". Therefore, this does not provide any further insights regarding the registered valerian-containing preparations investigated in this HTA, and this legal issue will not be addressed further.

Patient Rights: Are human and fundamental rights aspects to be considered when reimbursing/not reimbursing the costs of valerian-containing preparations?

General Constitutional Principles

The decision of the competent authorities on the future reimbursement or non-reimbursement of costs for valerian-containing preparations must take into account essential human and fundamental rights guarantees. The Swiss Federal Constitution (FC) is the primary basis for this.

The guarantees for the protection of particularly vulnerable groups of people are of particular importance in this respect. In connection with the use of valerian-containing preparations, one must think primarily of children and adolescents, pregnant women and elderly or chronically ill people. The state has a special duty to protect their fundamental rights towards these persons in accordance with its constitutional mandate. They must be specially protected in legislative and official measures due to (temporary or permanent) physical or mental conditions.

A decision on the future reimbursement or non-reimbursement of costs can affect fundamental rights guarantees, for example, due to faulty, limited, or omitted effective medical treatment with a valerian-containing preparation. In particular, human dignity (Art. 7 FC), legal equality and the prohibition of discrimination (Art. 8 FC), personal rights such as physical and mental integrity, self-determination, or privacy (Art. 10 para. 2 FC and Art. 13 FC) and the right to assistance in times of need (Art. 12 FC) may be affected.¹⁶⁷

However, the consulted sources, as far as can be seen, do not explicitly comment on these questions in connection with the cost reimbursement of valerian-containing preparations. In this respect, reference can therefore be made to the general health law literature on patient rights.^{167,168}

Constitutional Provision on Complementary Medicine

In the constitutional context, it should also be noted that with the adoption of the federal popular initiative "Yes to Complementary Medicine" in May 2009, the Confederation and the cantons were obliged to give greater consideration to complementary medicine in the healthcare system. In

addition to enshrining complementary medicine in the Federal Constitution, the key elements of this initiative were to ensure that complementary medicine methods are taken into account in primary care and to recognise complementary medicine remedies and treatment methods. Based on the vote, the new Article 118a was incorporated into the Federal Constitution in 2012. Following the adoption of Article 118a, certain complementary medical services in the fields of anthroposophic medicine, traditional Chinese medicine, homeopathy and phytotherapy were provisionally reimbursed by mandatory health insurance until the end of July 2017.

The new constitutional provision is to be understood as a target and programme norm that is intended to provide the state with guidance for its actions.¹⁶⁹ The requirement to take complementary medicine into account, as stipulated in Article 118a of the Federal Constitution, therefore defines a value that public authorities must act upon in an appropriate manner. However, the meaning of the norm is extremely vague and the wording is unclear. The term "consideration", in this case of complementary medicine, is even described in specialist literature as an empty phrase whose concrete content varies depending on the area of application and which can take on any extent.¹⁶⁹ Due to the low regulatory density and the open wording of the norm, Article 118a of the Federal Constitution does not establish any individually enforceable rights.¹⁶⁹

In June 2017, the Federal Council decided to revise the relevant provisions of the ordinance on the reimbursement of complementary medicine methods under mandatory health insurance. It approved amendments to the HIO and Ordinance on Healthcare Benefits (OHB) with effect from August 2017, thereby placing complementary medical services on an equal footing with other medical disciplines reimbursed by the mandatory health insurance (in the sense of a permanent inclusion). The adjustments were made to the HIO (Art. 35a HIO), which sets out the application of the EAE criteria and the principle of trust for complementary medical services, as well as to the Health Care Services Ordinance (Art. 4b OHB and Annex 1 of the OHB).

Since the revision, medical services provided in the fields of anthroposophic medicine, traditional Chinese medicine, homeopathy and phytotherapy have been covered by mandatory health insurance under the principle of trust, provided that the requirements of Art. 35a letters a–c HIO are fulfilled (tradition of use and research, scientific evidence and medical experience, as well as specific supplementary medical training; see above re. Legal Classification). According to the principle of trust, the mandatory nature of diagnostic and therapeutic services is implicitly assumed; they are generally reimbursed unless special provisions are set out in Annex 1 of the OHB. The principle of trust requires that doctors only provide services that meet the EAE criteria. As in other medical disciplines, only individual, controversial services should be reviewed upon justified request.

The amendments to the HIO and OHB, including Annex 1, which were enacted on the basis of the constitutional provision, essentially lay down the conditions for the reimbursement of complementary medical services, taking into account the principle of trust and the EAE criteria. Articles 35a HIO and 4b OHB and Annex 1 to the OHB do not specifically address the recognition of individual services, such as the use of valerian-containing preparations, as services covered by mandatory

health insurance. However, when assessing the obligation to provide benefits, it is necessary to specify and operationalise the EAE criteria with regard to their application to complementary medical services.¹⁷⁰ The present HTA serves precisely this purpose of conducting a detailed assessment, initiated upon request, of certain phytotherapy services whose effectiveness, appropriateness and economic effectiveness are controversial.

Health Insurance: From a legal perspective, should valerian-containing preparations be reimbursed even if the clinical benefit is unclear or minor?

Principle

In the legal review of the eligibility for reimbursement of medicinal products with valerian extract, the aforementioned provisions on the entitlement to benefits in the event of illness (Art. 25 para. 1 HIA) and the EAE criteria (Art. 32 HIA) must be observed in particular. The likewise mentioned provisions on inclusion in the SL by the FOPH (Art. 25 para. 2 lit. b and 52 para. 1 lit. b HIA in conjunction with Art. 34 and 65 para. 3 HIO) contain supplementary regulations.

Limitations

In addition, the conditions for limitations (Art. 73 HIO) must be observed, for example, with regard to the quantity or the medical indications. However, limitations may not lead to a violation of statutory provisions (EVGer, K 156/2001, 30.10.2003, E. 3.3.1). According to established jurisprudence, it would be inadmissible to include a medicinal product in the SL whose effectiveness has not been sufficiently proven by scientific methods, with the condition that the missing proof must be provided within a certain period (BGE 128 V 159 E. 5c/bb/bbb).

The FOPH can limit the inclusion in the SL for certain areas of application or groups of people and can also generally attach conditions and requirements. Such limitations of the main regulation (Art. 73 HIO) and ancillary provisions to the decision can be an expression of the principle of proportionality, the application of which must in turn be reviewed objectively and may not have a discriminatory effect.

- From a legal perspective, limitations are permissible if they appear suitable and necessary to ensure the effectiveness, appropriateness and economic effectiveness of a therapy in an individual case, primarily to promote the cost-efficient use of the medication.¹⁷¹
- Furthermore, the design of the limitation must be reasonable for the insured person and, with regard to the therapeutic freedom of the treating physician, must be proportionate. In this regard, the competent authorities have a certain margin of discretion.^{171,172}
- As a result, restrictions as well as conditions and comparisons with a complete refusal of cost reimbursement are to be considered "milder means" in the context of the proportionality review.

In the proportionality review, it should be explained in detail why the chosen measure for cost reimbursement (delisting, limitation, time limit or price specifications) is appropriate. In this context, transitional periods and individual case regulations can also be used.

Case-by-case reimbursement

If a medication is not included in the SL, cost reimbursement for therapeutic products in individual cases is only possible under certain conditions in the sense of a "hardship regulation". The regulations on "reimbursement of medicinal products in individual cases" (Art. 71a–71d HIO) establish various requirements:

- For such an exception, according to Art. 71a para. 1 lit. b HIO, a "significant therapeutic benefit" of the valerian-containing preparations must be affirmed in the case. According to jurisprudence, a significant therapeutic benefit also requires a favourable cost-benefit ratio, in the sense that the higher the costs, the more a significant therapeutic benefit must be expected (BGE 143 V 130 E. 11).
- It should be noted in this respect that in an individual case, according to Art. 71a para. 1 lit. b HIO, a "significant treatment success must be proven". This proof is likely to be difficult to provide in the case of valerian-containing preparations, as the therapeutic benefit of these medicinal products is unclear or minor according to the present analysis.
- It would also have to be ensured that effective and equal access for insured persons to treatment options with valerian-containing preparations reimbursed on a case-by-case basis is guaranteed. In general, a benefit is to be denied according to jurisprudence if there is a gross disproportion between effort and success of the cure (BGE 145 V 116 E. 5.1; BGE 137 V 295 E. 6.3.2). As far as can be seen, jurisprudence has not yet developed or adopted an established method for quantifying the "gross disproportion" (BGE 145 V 116 E. 5.2 ff.).

There are still no clear criteria for the necessary assessment of cost-effectiveness in the context of the economic effectiveness review. It is therefore important that the competent authorities, when assessing a reimbursement decision, include a human rights-based approach and carry out a corresponding weighing of interests between the individual patient's interest in a treatment and the state's interest in a cost-sensitive assessment.

Many valerian-containing preparations are not prescription-only, i.e. Over-the-Counter (OTC) available. However, in health insurance law, according to Art. 25 para. 2 lit. b HIA, there is the principle that a doctor's prescription is necessary for cost coverage. However, according to the HTA protocol, it is assumed as a starting point for the present HTA that a prescription is required for the reimbursement of the preparations to be examined. It must therefore also be clarified whether only the prescription-only valerian-containing preparations on the Specialties List are affected by a possible end of cost reimbursement or whether the costs for non-prescription valerian-containing preparations can also be covered by the OKP in individual cases and whether these should also be covered by the reimbursement stop.

The administrative separation between OTC availability (according to the Therapeutic Products Act) and eligibility for reimbursement (according to the HIA) must be observed. This creates a tension between free access vs. reimbursement under insurance law, which can also have an impact on doctors' prescribing practices and possible claims for reimbursement.

Constitution: Do the popular vote and the constitutional provisions concerning complementary medicine imply a legal obligation for cost reimbursement?

The Federal Constitution establishes a duty for the state in the article on complementary medicine (Art. 118a FC) to "take complementary medicine into account". In 2009, the people and the cantons decided that complementary medicine should be taken into account in the healthcare system, specifically with regard to the freedom of choice of therapy and consumer protection.¹⁷³ In view of this constitutional mandate, the question therefore arises to what extent this constitutional obligation must be taken into account in decisions on cost coverage by means of an ordinance amendment or decision and whether there is even an increased duty to review in favour of complementary medical services. According to voices from expert literature, the legally established reimbursement only of costs caused by the application of ineffective methods could run counter to the constitutional goal of increased consideration of complementary medicine.¹⁷³ By requiring that complementary medicine be taken into account in political, legal and official healthcare, the constitutional provision does not, in any case, provide for an automatic entitlement to reimbursement of costs for complementary medicinal products. The constitutional provision requires, rather, a margin of discretion when considering complementary medical therapies and is thus intended to ensure an appropriate weighing within the legal EAE criteria. The mention of complementary medicine in the FC therefore does not establish an obligation to reimburse for valerian-containing preparations in the sense of an automatism, but the constitutional context must be transparently included in reimbursement decisions for complementary medicinal products. Although Art. 118a FC on the consideration of complementary medicine creates a legal obligation for a benevolent appraisal in reimbursement decisions and a certain political expectation in favour of cost coverage, it does not establish an automatic entitlement to inclusion in the SL and reimbursement by the OKP. In the justification for any ordinance amendment and delisting concerning valerian-containing preparations, it should therefore be explicitly mentioned that the decision is in line with the constitutional requirements and health policy expectations.

Other Legal Enactments: What are the prerequisites and legal consequences for the classification of valerian-containing preparations as a placebo?

Legal Classification of Placebos

In view of the starting point that a therapeutic benefit of valerian-containing preparations is in question, it must be clarified from a legal perspective whether these medicinal products are to be classified as a placebo in the event of a missing or unclear proof of effectiveness. In this case, the legal prerequisites for the use of placebos and the legal consequences of an inadmissible use of a placebo must be reviewed.

If "placebos" are used in medical practice, this is legally considered a medical procedure that can only bring about a health improvement in relation to the disease to be treated due to the associated context (treatment environment, persons involved, information given, etc.).¹⁷⁴ From a therapeutic point of view, a distinction can be made between placebo medications and placebo procedures. "Placebo medication" means a "medicinal product" in the sense of Art. 4 para. 1 lit. a TPA; all other placebo therapies belong to the "placebo procedures".¹⁷⁴ In the case of a placebo treatment with valerian-containing preparations, it would be a matter of "placebo medications".

According to the highest court's jurisprudence and legal doctrine, the use of placebos – like all other medical treatments – therefore constitutes an unlawful interference with the personal rights of the person concerned, unless there is a corresponding justification ground (so-called justification solution) (BGE 133 III 121 E. 4.1.1; 117 Ib 197 E. 2a).³¹ The explicit consent of the patient (concerning a mere attempt at healing and not a verum) or at least a presumed or hypothetical consent is therefore required for a permissible use of a placebo (BGE 133 III 121 E. 4.1.1).³² The intention to heal of the treating professional (in the sense of the intention of a therapy and recovery) is not relevant for the legal justification (BGE 117 Ib 197 E. 2c).

In non-research-related medical practice, the use of placebos is less clearly regulated. There are no explicit legal or ordinance provisions in Switzerland; the use of a placebo is, however, limited by general legal principles and professional norms. However, even without an explicit regulation, binding legal frameworks apply, such as the civil law duty to inform (Art. 19c, 28 Civil Code and Art. 97 para. 1 Code of Obligations), the criminal law duties of protection (Art. 122 et seq. Criminal Code), the professional duties of care (MedPA, PsyPA and NuPA) and the constitutional right to self-determination (Art. 10 para. 2 FC).

General Legal Principles

The following general legal principles must be observed when considering placebo use in clinical practice:[172]

- *Information and consent* (Art. 7 para. 1 TPA analogously; Art. 321 Criminal Code): The patient must be fully informed about the type, scope, purpose, etc. of the treatment. The person concerned must be able to decide for themselves – after being informed accordingly by the doctor ("informed consent") – whether to use a valerian-containing preparation with a questionable therapeutic benefit. The administration of a placebo without disclosure can constitute a deception and violate the patient's rights of self-determination (Art. 19c Civil Code in conjunction with Art. 28 Civil Code).
- *Indication and duty of care* (Art. 40 lit. a MedPA, Art. 27 lit. a PsyPA and Art. 16 lit. a NuPA; cf. also SAMS Guidelines and FMH professional code): The use of placebo must be medically indicated, performed according to professional standards (de lege artis), and compatible with the duty of care. For example, the FMH professional code requires that treatments correspond to the state of science and serve patient well-being.

- *Potentially permissible constellations*: The use of a placebo may be exceptionally permitted in clinical practice under specific conditions: when the patient expressly agrees (e.g. in the context of a so-called "open placebo treatment"), when no other effective therapy is available, or when the use is supportive (e.g. to reinforce psychotherapeutic effects in an evidence-based intervention). For example, a patient with chronic tension headaches may be informed about an open placebo treatment and provide explicit consent.
- *Generally impermissible constellations*: Placebo use is not permitted when: the patient has not been adequately informed, an effective alternative therapy is withheld, the placebo serves merely to "calm" or deceive the patient, or the primary purpose is cost savings. For instance, administering a placebo instead of an indicated antibiotic to a patient with bacterial infection without disclosure would be impermissible.

Summary and Conclusions

From a legal perspective, a restriction or withdrawal of reimbursement for valerian-containing preparations by the mandatory health insurance is not only fundamentally possible, but also legally appropriate, provided that the FOPH, on the basis of a robust HTA dossier and a well-founded analysis, determines that the EAE criteria are not or are no longer fulfilled. However, the decisive factor for legal defensibility is not merely the legal possibility of a reimbursement decision, but rather the legal procedural quality and the methodological rigour of the HTA as well as the proportionality of the resulting measure taken.

8.2.6 Findings social issues

Patient perspectives

The discontinuation of reimbursement for valerian-containing medications is likely to generate emotional and psychological responses among affected patient populations.¹⁷⁵ Patients who have successfully managed symptoms of insomnia, mental stress and test anxiety with these preparations may experience disappointment, particularly as they perceive the withdrawal of support for established, gentle therapeutic options that have proven effective in their personal care regimens.

Patients may express concerns about transitioning to potentially dependency-inducing alternatives, particularly prescription sleep medications, benzodiazepines, or antidepressants. The fear of iatrogenic dependency may have led individuals to specifically choose valerian-containing preparations over conventional psychoactive medications to avoid the risks associated with these medications.¹⁷⁶ Additionally, patients may perceive a sense of injustice, feeling disadvantaged compared to users of conventional medications who continue to receive reimbursement coverage for their treatments.

Financial burden and accessibility

The transition to self-payment for valerian-containing medications may create financial barriers that disproportionately affect vulnerable populations.^{3,177} Low-income households may be unable to

afford valerian-containing preparations without reimbursement support, limiting their access to their preferred therapeutic approach.¹⁷⁸ This economic barrier may result in either discontinuation of treatment or transition to alternative therapies that would not reflect their preferences.¹⁷⁷

Elderly patients, who often have fixed incomes and limited financial flexibility, may be particularly affected by potential access restrictions.¹⁷⁹ This demographic often has fewer suitable therapeutic alternatives due to age-related contraindications, comorbidities, or comedications, which could make changes to the reimbursement of valerian-containing preparations more challenging for their care management.

Support during treatment transitions

The policy change may encourage transitions to prescription medications as patients and healthcare providers may seek reimbursed alternatives.¹⁸⁰ Careful clinical supervision and transition planning is necessary to ensure that patients do not inappropriately switch to prescription sleep aids or hypnotics that carry higher risks of dependency, tolerance and adverse effects.¹⁸¹ This ensures the policy aims at improving evidence-based care without inadvertently leading to the use of more problematic therapeutic agents. Healthcare providers should not give in to pressure to prescribe conventional medications solely to maintain treatment accessibility for their patients, as this could potentially compromise individualised care approaches and the principles of shared decision-making that prioritise patient preferences and values.

Vulnerable population groups

Should this policy change be implemented, several demographic groups may require particular attention.¹⁷⁸ Individuals with low socioeconomic status could face financial challenges. Healthcare providers should ensure continuity of care for these patients by exploring alternative treatment pathways. Healthcare planners should consider that senior populations may lose reimbursement to a well-tolerated therapeutic option for extended periods. For elderly patients who may have contraindications to conventional sleep medications or experience side effects from alternatives, maintaining access to suitable treatment options would require careful consideration of individual patient needs and potential alternative pathways.¹⁷⁹

Users of complementary and alternative medicine may perceive changes in phytopharmaceutical reimbursement as affecting their preferred healthcare approach.¹⁷⁸ Communication strategies that address concerns about the continued role of traditional and natural therapeutic modalities within the healthcare system could be helpful in ensuring that evidence-based decision-making processes are clearly explained to maintain confidence in integrative care approaches.

8.2.7 Findings organisational issues

8.2.7.1 Intra-organisational level

Healthcare providers

The discontinuation of reimbursement for valerian-containing medications presents some organisational challenges at the healthcare provider level. Primary care physicians and specialists may need to allocate additional consultation time to discuss the implications of the policy change and explore alternative treatment pathways with affected patients seeking management for sleep disorders, mental stress and test anxiety.¹⁸² This educational process necessitates thorough discussion of both pharmacological and non-pharmacological interventions, including evidence-based alternatives such as CBTI, sleep hygiene measures, benzodiazepine and antidepressants where clinically appropriate. Healthcare providers will need more time in discussing multiple treatment pathways, including the option of continuing valerian therapy as an out-of-pocket expense or switching to reimbursed alternatives such as prescription medications or non-pharmacological interventions.¹⁸² This expanded counselling scope may require additional resources to ensure that providers are fully informed about the comparative effectiveness, safety profiles and cost implications of each treatment option.

Pharmaceutical dispensing services

Pharmacy operations may face immediate practical challenges regarding inventory management of valerian-containing medications.¹⁸³ Existing stock levels could require strategic adjustment to minimise financial losses while ensuring continued availability for patients choosing to purchase these medications without reimbursement.¹⁸⁴ Pharmacists may need to enhance their counselling capabilities to provide comprehensive information about self-payment options and alternative therapeutic approaches. Additionally, they may experience increased consultation demands as patients seek guidance on cost-effective alternatives and the relative merits of continuing valerian therapy versus switching to reimbursed alternatives.

8.2.7.2 Inter-organisational level

Care coordination

The policy change may require enhanced communication between healthcare providers and pharmacists to ensure seamless patient care for patients choosing alternative reimbursed therapy. Coordination mechanisms could help to ensure continuity of care, particularly for individuals with sleep disorders or mental stress conditions who have been successfully managed with valerian-containing medicines. Healthcare organisations may need to develop standardised protocols for managing the transition, including alternative treatment pathways and follow-up monitoring to assess treatment outcomes and patient satisfaction with alternative therapies.¹⁸⁴

8.2.7.3 Healthcare System level

Regulatory and policy implications

The discontinuation of reimbursement for valerian-containing medications represents a potentially significant regulatory decision that may have broader implications for the phytopharmaceutical sector. This policy change could trigger systematic reviews of other herbal and traditional medications currently included in reimbursement schedules, potentially leading to comprehensive reassessment of the evidence base supporting coverage decisions for phytopharmaceuticals. Such regulatory scrutiny may establish new evaluation criteria for herbal medicines, potentially requiring enhanced clinical evidence standards for continued reimbursement eligibility.¹⁸⁵ The approach could influence future health technology assessment processes for complementary and alternative medicine products, necessitating more rigorous evidence requirements for market access and coverage decisions.

System-wide resource allocation

The policy change may result in cost shifting within the healthcare system, as patients may transition to more expensive prescription alternatives or increase utilisation of non-pharmacological services such as psychology consultations, sleep disorder clinics and CBTI. Healthcare planners must consider the potential for increased demand on mental health services and CBTI providers, recognising that these services are already experiencing capacity constraints with existing waiting lists for evidence-based psychological interventions.¹⁸⁶ This increased demand may further strain already overburdened providers and potentially create access barriers for patients seeking non-pharmacological alternatives.

Implementation Considerations

The successful management of a potential organisational transition requires coordinated planning across all healthcare system levels, with particular attention to patient communication, provider education and system capacity to accommodate changed treatment patterns. Stakeholder engagement throughout the implementation process could be helpful to ensure continuous patient care and maintain public confidence in healthcare decision-making processes.

9. Additional issues

9.1 Existing HTA reports on the same topic/ Reimbursement of drugs containing valerian in other countries

A comprehensive literature search was conducted to assess the reimbursement status of valerian-containing products across European countries. Initial searches using the term 'valerian' in the INAHTA database yielded one inaccessible publication. The search was subsequently expanded using "benzodiazepines" as a search term, identifying HTAs that included valerian as a comparator.

The identified HTAs exclusively focused on insomnia as the indication; mental stress and test anxiety were not evaluated in any HTA.

A UK HTA examined cognitive behavioural therapy for sleep disorders, but included only one participant receiving valerian, rendering the data inconclusive.¹⁸⁷ A German HTA from the Federal Institute for Drugs and Medical Devices (BfArM) focused on post-menopausal complaints, which was deemed irrelevant to valerian's primary indications.¹⁸⁸ Analysis of Federal Joint Committee (G-BA) data in Germany revealed no specific HTAs for valerian. One systematic review⁶⁰ of sleep-promoting agents referenced a study on valerian that demonstrated no efficacy.¹⁰³

The National Institute for Health and Research (NIHR) in the UK published an HTA based on 39 studies of interventions for sleep disturbances.¹⁸⁹ The single study evaluating valerian found no improvement in sleep quality and highlighted insufficient methodological quality for drawing definitive conclusions.¹⁹⁰

In summary, the limited available evidence from HTAs, primarily based on RCTs, demonstrates insufficient efficacy data to support reimbursement of valerian products by health insurance systems in Europe. While valerian-containing preparations remain available throughout Europe, costs are typically borne directly by patients.

9.2 Summary of the observational studies reported in EMA HMPC monographies and systematic reviews and meta-analysis

9.2.1 Methods and results

To ensure comprehensive evidence capture for this HTA, secondary search strategies were employed to supplement the primary systematic literature review. Reference lists of all included systematic reviews and meta-analyses were manually screened, and EMA HMPC monographs were examined to identify studies that fulfilled the PICO criteria but did not meet the predefined methodological inclusion criteria regarding study design, i.e. they lacked a control group. This complementary approach yielded eight additional relevant studies: three from EMA HMPC monographs and five from reference list screening of systematic reviews and meta-analyses. All 8 observational studies were published between 2000 and 2020.¹ Full text access was unavailable for 2 studies.

9.2.2 Study characteristics

Three studies examined the effect of valerian in children (ages 6 to 12 years) and 5 studies in adults (ages 18 to 65 years). Study duration ranged from 2 to 12 weeks, with most lasting 4 weeks. The indications varied across studies: Wegener¹⁹¹ investigated anxiety; Wheatly¹⁹² and Abedallah et al.¹⁹³ examined both anxiety and insomnia; Trompetter et al.¹⁹⁴ assessed anxiety, insomnia and nervous restlessness and Müller et al.¹⁹⁵ focused on depression. Only Dominiguez et al.¹⁹⁶ used valerian as monotherapy; all other studies employed combination preparations with various herbal

agents, including lemon balm, hops, *eschscholtzia californica* cham., *hypericum perforatum*, *passiflora incarnata* and St. John's Wort.

9.2.3 Dosing regimens

Dosing protocols varied considerably. The lowest doses were administered in paediatric studies by Trompetter et al.¹⁹⁴ (28 mg per tablet, dried extract *valeriana officinalis* L. root: 3.8-5.6:1) and Abdellah et al.¹⁹³ (32 mg per tablet, *valeriana officinalis* L. root), with weight-adjusted dosing. Conversely, Gromball et al.¹⁹⁷, administered 640 mg valerian plus 320 mg lemon balm to children (mean age of 8 years), a dose comparable to adult regimens. Adult studies employed doses ranging from 160 mg to 1000 mg valerian with Müller et al.¹⁹⁵ administering the highest dose. The absence of comparator groups in these studies limits their interpretability.

9.2.4 Outcomes and measurement tools

Different assessment instruments were employed across studies. Wegener¹⁹¹ used an anxiety score reporting a 56.2% reduction in anxiety symptoms with 225 mg valerian and 30 mg hop extract, alongside approximately 60% improvements in well-being and performance. Wheatley¹⁹² used a visual analogue scale (VAS) stress measurement plus assessments of sleep latency, sleep duration and morning mood. This study found that stress reduction with kava, but not valerian alone, though combined kava-valerian treatment improved sleep disorders after 6 weeks.

Trompetter et al.¹⁹⁴ employed a Child Behaviour Questionnaire due to varied indications, demonstrating that herbal triplet extract significantly improved 81.6% to 93.3% of symptoms including depression, anxiety, sleep disorders and other somatic complaints. Müller and Klement¹⁹⁸ investigated the effects of valerian-lemon balm in children under 12 years for sleep disorders and restlessness, finding significant symptom reduction. Gromball et al.¹⁹⁷ used questionnaires to assess valerian-lemon balm for pediatric insomnia, demonstrating reduced inability to concentrate (75% to 14%), decreased hyperactivity (61% to 13%), reduced impulsive behaviour (59% to 22%) and improvements in social and sleeping behaviours.

Studies using *eschscholtzia californica* cham.-valerian combination, reported 30% reductions in Insomnia Severity Index (ISI) score and 50% reductions in Hamilton Anxiety Rating Scale (HAM-A) scores, with improved sleep quality, except for sleep latency.¹⁹³ Müller et al.¹⁹⁵ compared valerian monotherapy, versus valerian-St. John's Wort combination in depressed patients, finding significant reduction in depression and anxiety symptoms with good tolerability. Dominiguez et al.¹⁹⁶ observed moderate improvements in sleep disorders using sleep questionnaires.

9.2.5 Conclusion

All studies showed improvements in sleep disorders and anxiety symptoms with valerian-containing preparations. However, significant methodological limitations constrain interpretation: 1) substantial heterogeneity in active ingredient combinations and dosing regimens, 2) wide variation in

sample sizes, 3) absence of control groups. These factors considerably limit the generalisability and clinical significance of these findings.

9.3 Ongoing clinical trials

Ongoing RCTs related to the PICOs investigated in this HTA were identified on Clinicaltrials.gov and on the WHO International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform) (**Table 95**). A total of 8 trials were initiated within the last 5 years, while all other registered studies are of earlier origin.

Table 95: Ongoing RCTs

Main ID	Title	Date of registration	Current status	Publication status
NCT00070928	Valerian to Improve Sleep in Patients with Parkinson's Disease	2003-10-09	Recruitment complete	Unknown
NCT00097604	Effects of Valerian on Sleep in Healthy Older Adults	2004-11-24	Recruitment complete	Unknown
NCT00075842	(Valerian) for Improving Sleep in Patients with Cancer Receiving Adjuvant Therapy	2004-01-09	Recruitment complete	Unknown
NCT00483964	A Safety and Efficacy Study of Bacopa Monnieri and Nardostachys Jatamansi to Treat Schizophrenia	2007-06-06	Recruitment complete	Unknown
NCT00794456	Association of Passiflora Incarnata L; Crataegus Oxyacantha L and Salix Alba L. on Mild and Moderate Anxiety	2008-11-19	Recruitment complete	Unknown
NCT00782080	Efficacy and Safety of St. John's Wort/Valerian Extract Versus Placebo in Children and Adolescents With ADHD	2008-10-29	Recruitment complete	Unknown
NCT00997256	Study to Investigate Effects of an Herbal Drug Compared to Placebo on Sleep (sleep-EEG)	2009-10-16	Recruitment complete	Unknown
NCT00997490	Study of the Antidepressant Efficacy of a Combination Herbal Drug Preparation (NEURAPAS Balance)	2009-10-16	Prematurely Ended	-
NCT01178632	Therapeutic Effect of an Herbal Medicine on Anxiety	2010-08-08	Unknown	Unknown
NCT01100645	Efficacy and Safety of the Herbal Medicine Sominex® (Passiflora Incarnata L., Valeriana Officinalis L. and Crataegus Oxyacantha L.), Manufactured by the Laboratory EMS S / A in Patients with Psychophysiological Insomnia	2010-04-07	Unknown	Unknown
NCT01047605	Pharmacological Effects of Neurapas® Balance and Pascoflair® 425 mg on Brain Activity in Healthy Volunteers (NCAG 5209)	2010-01-12	Recruitment complete	Unknown
NCT01612130	Valerian for Conscious Sedation in Patients Submitted to Impacted Lower Third Molars Surgery	2012-06-01	Recruitment complete	Published: https://pmc.ncbi.nlm.nih.gov/articles/PMC3983740/
NCT02273453	Study to Evaluate the Presence of a Hangover Effect in Healthy Adults After Administration of Songha® Night Tablets	2014-10-23	Recruitment complete	Unknown
NCT02981238	Phytotherapy Strategy for Sleep Disorders Related to Anxiety with a Combination of Eschscholtzia and Valerian Extracts	2016-11-22	Recruitment complete	Unknown
NCT04093271	Investigating the Efficacy of Rest-ZZZ Formula in Healthy Participants with Difficulty Falling Asleep or Stayasleep-sleep	2019-09-16	Recruitment complete	Published: https://pmc.ncbi.nlm.nih.gov/articles/PMC10900002/
NCT03909906	Chronic Effects of Euphytose® on Psychological and Physiological Measures of Stress	2019-04-04	Recruitment complete	Published: https://pmc.ncbi.nlm.nih.gov/articles/PMC9643820/

Main ID	Title	Date of registration	Current status	Publication status
NCT05109923	Onnit Labs New Mood Supplementation in Healthy College Students	2020-12-10	Recruitment complete	Unknown
NCT05185219	The Effect of Valerian on Insomnia in Menopausal Women	2021-12-03	Recruiting	-
NCT05194618	Efficacy and Safety of Valerian Root Extract and Lavender Essential Oil Combination, over 4 Weeks in Subjects with Sleep Complaints (PHY-TOSOM)	2021-11-30	Recruitment complete	Unknown
NCT05684523	Feasibility Study on the Use of Redomin®500 on Day-time Cognition	2022-12-20	Recruitment complete	-
NCT05609890	Novel Formulation for Sleep Among People with Poor Sleep Quality	2022-08-25	Recruitment complete	Published: https://www.nature.com/articles/s41598-024-58661-z
NCT05459272	Clinical Trial on a Food Supplement with Melatonin and Herbal Products to Improve Sleep Quality	2022-07-11	Unknown	Unknown
ACTRN12612001199808	A study to evaluate the safety and efficacy of a complementary medicine formulation, to help relieve cold & flu symptoms and reduce duration of a cold, in otherwise healthy adults	2012-11-14	Recruitment complete	Unknown
EUCTR2011-000037-36-DE	Open label clinical trial to investigate the physiological effects on sleep of Nervenruh Baldrian Forte 600 in patients with primary insomnia	2011-03-15	Recruiting	-
ISRCTN72748991	A televised, web-based randomised trial of an herbal remedy (valerian) for insomnia	2007-01-03	Recruitment complete	Published: https://pmc.ncbi.nlm.nih.gov/articles/PMC2002515/
JPRN-UMIN000049908	Safety evaluation of the capsules containing Valeriana fauriei root (VF) extract.	2022-12-26	Not recruiting yet	-
NCT00997256	Study to Investigate Effects of an Herbal Drug Compared to Placebo on Sleep (sleep-EEG)	2009-10-16	Recruitment complete	Unknown
NCT02189239	Efficacy Study of Zeller Entspannung Film Coated Tablets on Acute Stress	2014-07-10	Recruitment complete	Unknown
ACTRN12620000884909	Optimisation and validation of a nutritional intervention to enhance sleep quality and quantity	2020-09-07	Recruitment complete	Published: https://pmc.ncbi.nlm.nih.gov/articles/PMC7551573/

10. Discussion

This health technology assessment evaluated the clinical effectiveness and budget impact of valerian-containing preparations for symptoms of insomnia, mental stress and test anxiety. The systematic review and meta-analyses of 33 RCTs demonstrated no statistically significant clinical benefits of valerian-containing preparations compared to placebo except for post-intervention sleep quality and PSQI scores, which favoured valerian. Meta-analyses of valerian monotherapy versus placebo for most insomnia outcomes showed no statistically significant benefits: sleep latency (MD: -0.99 minutes, 95% CI -5.41 to 3.44, moderate certainty), sleep duration (MD: 3.16 minutes, 95% CI -7.07 to 13.39, moderate certainty), sleep quality reported as change from baseline (SMD: -0.03, 95% CI -0.21 to 0.15, moderate certainty), night awakenings (SMD for outcomes reported as post-intervention: -0.20, 95% CI -0.65 to 0.25, moderate certainty, SMD for outcomes reported as change from baseline: -0.06, 95% CI -0.42 to 0.30, low certainty), and sleep efficiency (MD: 1.36, 95% CI -2.58 to 5.30, low certainty). Two exceptions favoured valerian: sleep quality at post-intervention assessment (SMD: -1.51, 95% CI -2.84 to -0.17, low certainty) and the PSQI total score (MD: -3.67, 95% CI -5.22 to -2.13, moderate certainty). Valerian combinations with lemon balm or hops showed no superiority over placebo for insomnia parameters. Few comparisons with benzodiazepines were available, revealing no significant differences in sleep quality (MD: 0.04, 95% CI -0.16 to 0.25, moderate certainty). Meta-analysis for mental stress and test anxiety/anxiety was not possible due to inconsistent outcome reporting across the identified studies. The overall certainty of evidence was judged as very low to moderate, reflecting methodological limitations and substantial inconsistencies regarding outcome measurements, dosage and follow-up periods across the included studies. Regarding safety, a meta-analysis could only be computed for valerian combined with lemon balm, passionflower and butterbur versus placebo in patients with test anxiety/anxiety. However, no statistically significant difference was observed (risk ratio: 0.96, 95% CI 0.31 to 2.96, very low certainty). For other comparisons, meta-analyses could not be computed due to fewer than two eligible studies being available.

Three observational studies were included in the systematic literature review but because they had different comparators, pooling was not possible, and no meta-analysis was conducted.

The economic evaluation revealed substantial potential savings if valerian-containing medicines remained available in Switzerland as out of pocket purchases but were no longer reimbursed by mandatory health insurance. The budget impact analysis projected total savings of CHF 202.47 million, comprising CHF 174.1 million for 1.7 million annual prevalent patients for insomnia symptoms, CHF 6.1 million for 1.2 million prevalent patients with mental stress symptoms and CHF 22.3 million for 0.3 million prevalent patients with test anxiety. Sensitivity analyses confirmed the robustness of these findings, with an uncertainty of CHF -14.8 million to +10.9 million for insomnia symptoms, CHF -3.1 million to +2.3 million for mental stress symptoms and CHF $\pm$ 3.8 million for test anxiety symptoms. Two scenario analyses projected higher savings compared to the base case. The first scenario, assuming continued prevalence growth, estimated total savings of CHF 244

million (210 million for insomnia, CHF 7 million for mental stress and CHF 27 million for test anxiety). The second scenario, aligning consumption volumes to real-world claims data from SASIS, projected total savings of CHF 222 million (CHF 173 million for insomnia, CHF 10 million for mental stress and CHF 39 million for test anxiety).

The ELSO analysis identified no insurmountable barriers to delisting given the insufficient evidence to demonstrate consistent effectiveness over placebo across outcomes, though considerations for vulnerable populations and transition planning were noted.

Efficacy, effectiveness and safety

The meta-analyses conducted in this HTA demonstrated no statistically significant differences between valerian and placebo for most outcomes. Two exceptions were observed: sleep quality at post-intervention assessment and PSQI total score, both favouring valerian. The post-intervention sleep quality finding warrants methodological consideration. Post-intervention scores reflect the absolute outcome level at the end of the study, whereas change-from-baseline scores reflect each participant's individual change from their starting point, thereby accounting for baseline differences between treatment arms. When baseline values differ between groups, even slightly as can occur by chance, post-intervention SMDs may overestimate the treatment effect. The divergence between the two sleep quality analyses – significant for post-intervention but not for change from baseline – is therefore likely explained by this statistical property, with the change-from-baseline analysis representing the more conservative and methodologically robust estimate. Furthermore, two of the three studies contributing to the post-intervention analysis had a follow-up of only one day, leaving only one study with a clinically meaningful follow-up, resulting in high uncertainty around this finding.

A recent randomized controlled feasibility trial by Schick Tanz et al. (2025) investigated the effects of valerian combined with hops on sleep duration and daytime cognitive performance in individuals with occasional sleep problems (n=40).¹⁹⁹ Exploratory analyses showed a statistically significant increase in sleep duration of 21.7 minutes per night compared to placebo measured by a sleep tracker (Fitbit Charge 5). However, given the feasibility design, small sample size and industry funding, these findings should be interpreted with caution and warrant replication in adequately powered confirmatory trials.

The findings of the present analysis are consistently aligned with high-quality systematic reviews examining valerian's effectiveness. Leach and Page (2015) conducted a systematic review and meta-analysis specifically focused on herbal medicine for insomnia, including valerian studies.⁴⁹ Their analysis similarly found insufficient evidence to support valerian's effectiveness for sleep disorders, noting significant methodological limitations across included studies. This concordance strengthens confidence in the present conclusions despite using a broader search strategy and more recent studies.

The umbrella review by Ell et al. (2023) examined complementary and alternative treatments for insomnia disorder, providing a comprehensive overview of existing systematic reviews.⁴ Their evaluation of valerian evidence reached comparable conclusions regarding the lack of robust evidence for effectiveness, while highlighting the persistent methodological challenges in phytotherapy research. These findings are extended by the present meta-analyses through the provision of updated pooled estimates incorporating more recent trials.

Shinjo et al. (2020) performed a systematic review and meta-analysis specifically targeting valerian root for sleep problems.¹ Similar studies to those included in the present review were analysed and the authors concluded that valerian could be a safe and effective herb to promote sleep and prevent associated disorders. However, their meta-analysis of sleep quality across all included studies yielded a non-significant combined effect size with high heterogeneity. Their positive conclusion was primarily driven by a subgroup analysis of studies using whole root/rhizome preparations (4 studies only), which showed a higher effect size than valerian extracts but remains based on very limited evidence. The findings of the present analysis are therefore consistent with Shinjo et al.'s primary meta-analytic findings.

Zhang et al. (2022) conducted a network meta-analysis of medicinal herbs for anxiety treatment, including valerian-containing preparations.⁶ Their findings regarding valerian's limited effectiveness for anxiety symptoms correspond with the present results for mental stress and test anxiety indications.

Most notably, the umbrella review by Valente et al. (2024) specifically addressed the question "Does valerian work for insomnia?" using rigorous umbrella review methodology.³ Their comprehensive evaluation of existing systematic reviews concluded that current evidence does not support valerian's effectiveness for insomnia, confirming the present meta-analytic findings.

The present systematic review also included observational studies, of which 3 were identified for inclusion.^{110,111,120} One study used lavender as comparator, one used melissa and/or passion flower as well as other herbal remedies and one used Neurexan. As none of these comparators had a sufficient number of studies for meta-analysis, no further analysis has been done.

The EMA HMPC monographs on valerian-containing preparations acknowledge 2 regulatory pathways: well-established medicinal use, supported by controlled clinical evidence and traditional use, based on long-standing historical application. These monographs represent an important regulatory framework and reflect a different evidentiary standard than that applied in this HTA. While the HMPC "well-established use" designation indicates that a body of clinical evidence was considered sufficient for regulatory approval, it does not require demonstration of superiority over placebo in RCTs, which is the standard applied in HTAs. The present findings therefore do not contradict the regulatory status of valerian-containing medicines but apply a more stringent evidentiary framework consistent with EAE criteria, which require demonstrated comparative effectiveness as a prerequisite for reimbursement by mandatory health insurance. The insufficient evidence identified in this

HTA thus pertains specifically to reimbursability under Swiss law, not to regulatory approval or traditional use.

Health economic analysis

The budget impact analysis demonstrated substantial financial implications. The model allocated dispensed packages of valerian-containing medicines across the 3 indications based on approved therapeutic uses. For medicines approved for multiple indications, the allocation was informed by indication splits reported in the GP survey. This distribution approach accounts for actual utilisation patterns, minimizing overlap between indication-specific cost estimates and permitting summation to total cost savings of CHF 202 million over 5 years for all 5 reimbursed valerian-containing medicines. For insomnia symptoms, the model estimated savings of CHF 174.05 million over 5 years, based on approximately 1.7 million annual prevalent patients. Mental stress showed potential savings of CHF 6.14 million for approximately 1.2 million prevalent patients and test anxiety generated estimated savings of CHF 22.28 million for 0.3 million prevalent patients.

The sensitivity analyses revealed an uncertainty of CHF -3.1 million to +2.3 million for mental stress, CHF $\pm$ 3.8 million for test anxiety and CHF -14.8 million to +10.9 million for insomnia, demonstrating moderate uncertainty.

The scenario analysis projected higher savings compared to the base case scenario due to increased prevalence growth. For insomnia symptoms, cost savings were estimated at CHF 209.65 million, based on approximately 2.0 million annual prevalent patients. Mental stress showed potential savings of CHF 7.34 million for approximately 1.5 million prevalent patients and test anxiety generated estimated savings of CHF 26.74 million for 0.36 million prevalent patients. A second scenario analysis, aligning consumption volumes to real-world claims data from SASIS, projected total savings of CHF 222 million, comprising CHF 173 million for insomnia, CHF 10 million for mental stress and CHF 39 million for test anxiety. The higher savings for test anxiety relative to the base case reflect the proportionally greater consumption of Relaxane® observed in the SASIS data.

Even though the model accounted for increased switching to benzodiazepines and Z-drugs following delisting, and incorporated the substantial long-term costs of benzodiazepine dependence, the analysis still projected cost savings when valerian-containing medicines are not reimbursed anymore. This finding is explained by GP survey data indicating that a substantial proportion of patients would switch to other herbal medicines or purchase valerian-containing medicines out-of-pocket rather than switching to hypnotics such as benzodiazepines or z-drugs. While benzodiazepine-related costs are considerably higher on a per-patient basis, including both medication costs and long-term sequelae from dependence, the relatively smaller proportion of patients actually switching to these alternatives results in net cost savings from delisting valerian-containing medicines.

Ethical, legal, social and organisational issues

The ethical analysis reveals interconnected moral considerations regarding the discontinuation of reimbursement for valerian-containing medications. A central tension emerges around the medicalisation of common human experiences such as sleep difficulties, mental stress and test anxiety, where current reimbursement without formal diagnosis requirements may contribute to pathologising variations in human functioning. The analysis through public health ethics principles reveals competing values: while utility and efficiency principles support evidence-based reimbursement policies, the EAE criteria must be balanced with considerations of health equity and individual autonomy. Given the insufficient evidence for consistent effectiveness of valerian-containing preparations, their continued reimbursement may represent inequitable allocation of collective resources. Furthermore, current reimbursement structures may inadvertently discourage patients from pursuing more effective non-pharmacological interventions such as cognitive-behavioural approaches or sleep hygiene measures. The discussion of placebo effects raises additional questions about informed consent and medical transparency when healthcare providers prescribe preparations whose effects may not be clearly distinguishable from placebo responses.

From a legal perspective, a restriction or withdrawal of reimbursement for valerian-containing preparations by the mandatory health insurance is not only fundamentally possible, but also legally appropriate, provided that the FOPH, on the basis of a robust HTA dossier and a well-founded analysis, determines that the EAE criteria are no longer fulfilled. However, the decisive factor for legal defensibility is not merely the legal possibility of a reimbursement decision, but rather the legal-procedural quality and the methodological rigour of the HTA as well as the proportionality of the resulting measure.

The social analysis identified potential access barriers for vulnerable populations, particularly low-income households and elderly patients, who may face financial constraints when valerian-containing preparations require out-of-pocket payment. While these medications remain available, economic barriers could result in treatment discontinuation or transitions to alternatives that may not reflect patient preferences. Careful transition planning to maintain patient-centred care, with healthcare providers ensuring continuity by exploring alternative, evidence-based treatment pathways are important. Transparent communication about the evidence base underlying reimbursement decisions is essential to maintain confidence in healthcare decision-making processes.

The organizational analysis revealed that physicians may require additional consultation time to discuss policy implications and alternative treatment pathways, while pharmacies face inventory management adjustments. At the system level, the policy change could increase demand on already overburdened mental health services and CBT providers. Successful transition management requires coordinated planning across healthcare system levels. The decision following this HTA may also establish precedents for future HTAs of complementary and alternative medicine products.

Strength of this HTA

This HTA has several strengths. It systematically reviews the specific research questions posed by the FOPH and evaluates the identified literature in-depth. The newly conducted meta-analyses assess the existing evidence. Furthermore, a de novo budget impact model was built. This is the first budget impact analysis in the field of phytopharmacology in Switzerland. The comprehensive and thorough research on Swiss data including SASIS data, SWICA data and the survey among general practitioners allowed the budget impact model to be parametrised with Swiss specific data on valerian use. In addition, the ethical and legal domains, which are especially important when evaluating complementary or alternative medicine interventions, were assessed and discussed in detail.

Methodological limitations

The present systematic review revealed 3 critical methodological issues that substantially limit the reliability of available evidence on valerian-containing preparations, challenges that have been consistently identified across multiple independent reviews in this field.

Firstly, meta-analyses demonstrated substantial statistical heterogeneity across most outcomes, with I^2 values frequently exceeding acceptable thresholds: sleep latency ($I^2 = 89.75\%$), sleep duration ($I^2 = 96.06\%$) and PSQI total scores ($I^2 = 84.15\%$). This heterogeneity reflects the inherent challenges in valerian research, including enormous variation in dosing regimens from 300 mg¹⁰³ to 1060 mg²⁰⁰ daily and diverse patient populations ranging from healthy adults to patients with complex comorbidities including HIV, cancer and chronic heart failure.

Shinjo et al. (2020) and Leach and Page (2015) similarly identified significant methodological diversity as a persistent challenge in valerian research.^{1,49} The consistency of this finding across multiple independent reviews suggests that heterogeneity represents a fundamental characteristic of the valerian literature, reflecting both the complexity of herbal preparations and the diversity of research approaches in this field.

Secondly, risk of bias assessment revealed systematic challenges across the evidence base. Most notably, 93% of outcomes showed concerns regarding selection of reported results due to absent pre-specified analysis plans, a pattern that Valente et al. (2024) also identified as a critical limitation in their umbrella review.³ For insomnia studies, only 7% achieved "low risk" overall ratings, while mental stress studies showed no studies achieving "low risk" status. The randomisation process proved particularly challenging, with 67% of mental stress outcomes showing concerns and 75% of test anxiety/anxiety outcomes demonstrating high risk patterns. Missing outcome data handling varied considerably across studies. In studies examining mental stress, this domain was rated as high risk of bias in 75% of cases. Ell et al. (2023) noted similar methodological limitations as a consistent theme across complementary insomnia treatments, emphasising that these quality concerns represent broader challenges in the field rather than isolated issues.⁴

Thirdly, incomplete results reporting presented systematic challenges for evidence synthesis, a pattern that Zhang et al. (2022) also identified in their network meta-analysis of herbal anxiety treatments.⁶ Many studies provided only intervention group values with p-values while omitting control group data necessary for meta-analysis. For example, Aliakbari et al. reported sleep latency improvements with significance ($p=0.001$) and sleep duration increases ($p<0.05$) but provided only intervention group means (0.74 and 5.38 hours, respectively) without corresponding control values.¹⁰⁸ Results of these studies could not be incorporated into meta-analyses due to inadequate reporting of numerical results and outcome measures. Some studies showed inconsistencies between planned and reported outcomes. Aliakbari et al. included PSQI measurement in their methodology but ultimately did not report these results, while Coxeter et al. consistently reported only "proportion of treatment success" values for intervention groups across multiple sleep outcomes without providing control group data.^{90,108} These reporting challenges necessitated extensive use of SWiM approaches for 29 separate outcome comparisons across the 4 PICOs. This pattern appears widespread in complementary medicine research, demonstrating that rigorous adherence to established reporting guidelines and standardised methods is imperative for meaningful progress in evidence quality.

Several methodological limitations should be acknowledged when interpreting the budget impact analysis results. Regarding data sources and representativeness, the GP survey responses are subject to measurement and reporting bias. The forced allocation requirement asking GPs to distribute 100% of patients across different treatment options can artificially exaggerate small categories while depressing others. Additionally, responses reflect perceptions and recall rather than recorded prescriptions, likely including some over-the-counter use that may not accurately mirror reimbursed utilisation captured in claims data.

The survey covered general practitioners only, while psychiatrists, paediatricians and other specialists may manage a non-trivial proportion of cases with different prescribing patterns. This specialty limitation means the model may under- or overestimate the use of comparators influenced by specialty practice patterns.

Paediatric populations are under-represented in the GP survey data, yet some treatment alternatives such as sleep hygiene and non-pharmacological interventions may be used differently in paediatric settings. Generalising adult-dominated treatment patterns to paediatric populations introduces potential bias in budget impact estimates.

The linkage of different data sources presents additional challenges. The analysis anchored valerian's market share to claims data (approximately 4% of reimbursed users) and rescaled remaining alternatives proportionally based on GP survey responses. However, claims data exclude over-the-counter purchases and do not capture indication information, while GP survey responses appear to include over-the-counter use and are subjective in nature. Combining these sources assumes proportionality between perceived treatment shares and actual reimbursed utilisation within

indications - an assumption that may not hold if over-the-counter use patterns or specialty referral patterns differ across indications.

Brand-specific weighting approaches differed between epidemiological estimates (weighted by patient counts) and cost calculations (weighted by dispensed quantities). Applying indication splits derived from patient data to volume data assumes homogeneous dosing and pack sizes across brands and indications. If dose intensity varies systematically, budget impact estimates may be biased.

Category definitions and mapping present further limitations. The broad "other" categories in the alternative treatment mix questionnaire, including "other reimbursed phytotherapy" and "over-the-counter valerian", cannot be cleanly disentangled from baseline medication categories. Multi-indication products such as valerian-containing medicines (Hova, Dormiplant and Relaxane) span multiple therapeutic areas and the indication-specific allocation relies on survey-based patient shares that may be subject to misclassification at the respondent level, particularly given potential symptom overlap between conditions.

The epidemiological assumptions underlying the model provide context for characterising the target population. The analysis used point prevalence of symptoms rather than diagnosed disease, assumed constant prevalence across years and equated prevalence with annual incidence for mild and acute conditions. Test anxiety prevalence estimates were derived from a small secondary school cohort ($n \approx 59$) in a single canton, limiting generalisability to the broader Swiss population. Due to the model's calibration to observed SWICA and SASIS data, however, epidemiological parameters such as prevalence and treatment-seeking rates do not independently drive budget impact estimates and changes to these parameters do not affect the results. These assumptions therefore serve to characterise the target population rather than as direct model inputs.

The analysis reports indication-specific estimates separately, which could theoretically lead to double-counting if patients experience symptoms across multiple indications simultaneously. This represents a common challenge in health economic evaluations of medications with multiple approved indications. However, unlike prevalence-based approaches that would multiply distinct patient populations by per-patient costs, this analysis allocates actual dispensed packages across indications. This distribution approach, informed by approved therapeutic uses and observed prescribing patterns, accounts for real-world utilization patterns and substantially reduces the impact of patient overlap. Consequently, while some degree of overlap between indication populations cannot be entirely excluded, its effect on the summed budget impact is minimal, and aggregation across indications remains justified for decision-making purposes.

Regarding switching patterns to benzodiazepines, the French odds ratio from França et al. (2018) was transported to the Swiss healthcare context. Converting odds ratios to relative risks requires baseline switching risk estimates and while SWICA data were used with aligned definitions, residual mismatches in practice patterns and baseline risk levels may bias the relative risk estimates. No benzodiazepine substitution was modelled for test anxiety due to lack of evidence, though if

such switching occurs in clinical practice, the modelled alternative treatment mix would understate benzodiazepine utilisation in this patient subgroup.

Finally, the model assumes identical treatment patterns across all 5 analysis years, which simplifies interpretation but ignores potential diffusion and decay dynamics such as seasonal effects, policy learning curves, or substitution inertia that may influence treatment choices over time.

An important consideration not formally incorporated into this HTA concerns vulnerable patient populations for whom treatment alternatives are particularly limited or contraindicated. Valerian-containing medicines represent one of few options with acceptable safety profiles for pregnant women, breastfeeding mothers, elderly patients, and children; populations for whom benzodiazepines and Z-drugs pose substantial risks including neonatal complications, falls, cognitive impairment, and unknown long-term developmental effects. This population therefore warrants particular attention in transition planning following any reimbursement decision.

Evidence Gaps

The present review identified substantial gaps in high-quality evidence for valerian-containing preparations. While 30 ongoing RCTs were identified in clinical trial registries, most were initiated years ago with unclear completion status. This substantial gap between registered and published trials may indicate publication bias. The persistent lack of pre-specified analysis plans in 93% of studies reflects broader deficiencies in research planning and conduct. Valente et al. (2024) emphasised that despite valerian's widespread use, robust clinical evidence remains elusive after years of investigation.³ The absence of adequately powered, well-designed trials with appropriate control groups continues to limit evidence-based decision-making for valerian-containing medicines. Future research must address these fundamental methodological shortcomings by ensuring adequate sample sizes for sufficient statistical power, adherence to established reporting guidelines and implementation of core outcome sets with comprehensive reporting of all pre-specified endpoints.

11. Conclusions

The review of the existing literature and the conducted meta-analysis of the important outcomes showed mostly no statistically significant benefits of valerian-containing preparations compared to placebo for insomnia, mental stress or test anxiety/anxiety symptoms across 36 included studies. Meta-analyses examined various sleep parameters including sleep latency, duration, quality, efficiency, night awakenings and PSQI scores, as well as adverse events, mostly showing no superiority over placebo. Two measures showed statistically significant improvements in favour of valerian: sleep quality at post-intervention assessment and PSQI total score. Comparisons with benzodiazepines were limited but showed no significant differences for insomnia symptoms. For symptoms of mental stress and test anxiety/anxiety, meta-analyses could not be computed. The certainty of evidence for critical outcomes was judged as very low to moderate, reflecting methodological limitations and inconsistencies across studies.

The de novo budget impact analysis demonstrated the financial implications of discontinued reimbursement of valerian-containing medicines across all three indications. Total savings were estimated at CHF 202 million over 5 years. For insomnia symptoms, the model estimated savings of CHF 174 million, based on approximately 1.7 million annual prevalent patients, with sensitivity analyses indicating an uncertainty of CHF -15 million to +11 million. For mental stress, estimated savings were CHF 6 million for approximately 1.2 million prevalent patients, with an uncertainty of CHF -3 million to +2 million. For test anxiety, estimated savings were CHF 22 million for approximately 0.3 million prevalent patients, with an uncertainty of CHF $\pm$ 4 million. Two scenario analyses projected higher savings than the base case. The first, assuming continued prevalence growth, estimated total savings increased to CHF 244 million (CHF 210 million for insomnia, CHF 7 million for mental stress and CHF 27 million for test anxiety), reflecting the observed upward trend in valerian consumption over the past decade. The second, aligning consumption volumes to real-world claims data from SASIS, projected total savings of CHF 222 million (CHF 173 million for insomnia, CHF 10 million for mental stress and CHF 39 million for test anxiety).

From an ethical standpoint, the analysis reveals 3 primary considerations regarding valerian reimbursement. First, the current system may contribute to the pathologisation of experiences such as sleep difficulties, mental stress and test anxiety. While these conditions exist on a continuum and can represent clinically significant disorders meeting diagnostic criteria, the Swiss practice of reimbursing valerian-containing medications without requiring formal diagnosis risks medicalising transient symptoms that represent common variations in human functioning, potentially undermining individuals' capacity for self-management and non-medical coping strategies. Second, given that valerian-containing preparations lack robust evidence for effectiveness from high-quality studies, their continued reimbursement represents an inequitable allocation of collective resources within the solidarity-based healthcare system. Third, the current reimbursement structure may inadvertently discourage patients from pursuing more demanding but potentially more effective approaches such as cognitive-behavioural interventions, sleep hygiene modifications, or lifestyle adaptations.

From a legal perspective, a restriction or withdrawal of reimbursement for valerian-containing preparations by the mandatory health insurance is not only fundamentally possible, but also legally appropriate, provided that the FOPH, on the basis of a robust HTA dossier and a well-founded analysis, determines that the EAE criteria are no longer fulfilled. However, the decisive factor for legal defensibility is not merely the legal possibility of a reimbursement decision, but rather the legal-procedural quality and the methodological rigour of the HTA as well as the proportionality of the resulting measure. Identified social issues were associated with continuous care for vulnerable groups and well supported transition for patients currently on valerian. Organisational aspects were identified including increased consultation time with healthcare providers for discussing treatment alternatives, enhanced care coordination between stakeholders and potential strain on already overburdened mental health services due to increased demand for non-pharmacological interventions. Broader regulatory questions about the systematic evaluation of phytopharmaceuticals within the healthcare system may be rising additionally. While this HTA demonstrates potential cost

savings from discontinued reimbursement of valerian-containing medicines, the clinical effectiveness evidence remains inadequate to establish definitive efficacy. Well-designed, adequately powered studies with rigorous methodology are urgently needed to close this evidence gap.

12. References

- 1 Shinjyo N, Waddell G, Green J. Valerian Root in Treating Sleep Problems and Associated Disorders—A Systematic Review and Meta-Analysis. *J Evid Based Complementary Altern Med* 2020;25:2515690X20967323. doi:10.1177/2515690X20967323
- 2 Mikoteit T, Acker JG, Castelnovo A, *et al.* Behandlungsempfehlungen Insomnie der Gruppe «Schlaf & Psychiatrie» der SGSSC. *Swiss Med Forum* Published Online First: 13 December 2023. doi:10.4414/smf.2023.1316824571
- 3 Valente V, Machado D, Jorge S, *et al.* Does valerian work for insomnia? An umbrella review of the evidence. *European Neuropsychopharmacology* 2024;82:6–28. doi:10.1016/j.euro-neuro.2024.01.008
- 4 Ell J, Schmid SR, Benz F, *et al.* Complementary and alternative treatments for insomnia disorder: a systematic umbrella review. *Journal of Sleep Research* 2023;32:e13979. doi:10.1111/jsr.13979
- 5 Valente V, Machado D, Jorge S, *et al.* Does valerian work for insomnia? An umbrella review of the evidence. *European Neuropsychopharmacology* 2024;82:6–28. doi:10.1016/j.euro-neuro.2024.01.008
- 6 Zhang W, Yan Y, Wu Y, *et al.* Medicinal herbs for the treatment of anxiety: A systematic review and network meta-analysis. *Pharmacological Research* 2022;179:106204. doi:10.1016/j.phrs.2022.106204
- 7 Savage K, Firth J, Stough C, *et al.* GABA-modulating phytomedicines for anxiety: A systematic review of preclinical and clinical evidence. *Phytotherapy Research* 2017;32:3–18.
- 8 Mulder F, Löwinger D, Jenkinson SP, *et al.* Counselling for Chronic Insomnia in Swiss Pharmacies: A Survey Study Based on Case Vignettes. *Pharmacy (Basel)* 2023;11:105. doi:10.3390/pharmacy11030105
- 9 Riemann D, Espie CA, Altena E, *et al.* The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023. *Journal of Sleep Research* 2023;32:e14035. doi:10.1111/jsr.14035
- 10 Federal Office of Public Health. Arzneimittelliste mit Tarif (ALT). <https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Arzneimittel/arzneimittellistemittarif.html> (accessed 13 June 2024).
- 11 Federal Office of Public Health. Spezialitätenliste (SL). <https://www.xn--spezialittenliste-yqb.ch/ShowPreparations.aspx?searchType=Substance&searchValue=Valeriana+extrac-tum+ethanolicum+siccum> (accessed 13 June 2024).
- 12 SASIS AG. Tarifpool: © SASIS AG – data processing: © COGE GmbH. 2024.
- 13 Holder S, Narula NS. Common Sleep Disorders in Adults: Diagnosis and Management. *afp* 2022;105:397–405.

- 14 Substance Abuse and Mental Health Services Administration. *Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health*. Rockville (MD): : Substance Abuse and Mental Health Services Administration (US) 2016. <http://www.ncbi.nlm.nih.gov/books/NBK519697/> (accessed 1 Oct 2024).
- 15 Sutton EL. Insomnia. *Ann Intern Med* 2021;174:ITC33–48. doi:10.7326/AITC202103160
- 16 Singareddy R, Vgontzas AN, Fernandez-Mendoza J, *et al*. Risk factors for incident chronic insomnia: A general population prospective study. *Sleep Medicine* 2012;13:346–53. doi:10.1016/j.sleep.2011.10.033
- 17 Federal Statistical Office. Swiss Health Survey 1997-2022: Sleep disorders. Swiss Health Survey 1997-2022: Sleep disorders - GNP Diffusion. <https://www.bfs.admin.ch/news/en/2024-0165> (accessed 3 Oct 2024).
- 18 Delini-Stula A, Bischof R, Holsboer-Trachsler E. Sleep behavior of the Swiss population: Prevalence and the daytime consequences of insomnia. *Somnologie* 2007;11:193–201. doi:10.1007/s11818-007-0297-5
- 19 ICD-11 for Mortality and Morbidity Statistics. <https://icd.who.int/browse/2025-01/mms/en#1038292737> (accessed 20 Oct 2025).
- 20 Maire M, Linder S, Dvořák C, *et al*. Prevalence and management of chronic insomnia in Swiss primary care: Cross-sectional data from the ‘Sentinella’ practice-based research network. *J Sleep Res* 2020;29:e13121. doi:10.1111/jsr.13121
- 21 Schweizerisches Gesundheitsobservatorium (Obsan). Einschlaf- oder Durchschlafstörungen. 2025.<https://ind.obsan.admin.ch/indicator/obsan/einschlaf-oder-durchschlafstoerungen> (accessed 7 Apr 2025).
- 22 American Psychiatric Association. What are Sleep Disorders? <https://www.psychiatry.org/443/patients-families/sleep-disorders/what-are-sleep-disorders> (accessed 2 Oct 2024).
- 23 Baglioni C, Battagliese G, Feige B, *et al*. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011;135:10–9. doi:10.1016/j.jad.2011.01.011
- 24 Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol* 2014;13:1017–28. doi:10.1016/S1474-4422(14)70172-3
- 25 Li M, Zhang X-W, Hou W-S, *et al*. Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *Int J Cardiol* 2014;176:1044–7. doi:10.1016/j.ijcard.2014.07.284
- 26 Hafner M, Romanelli RJ, Yerushalmi E, *et al*. The societal and economic burden of insomnia in adults: An international study. RAND Corporation 2023. https://www.rand.org/pubs/research_reports/RR2166-1.html (accessed 7 Apr 2025).
- 27 Hertenstein E, Trinca E, Wunderlin M, *et al*. Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis. *Sleep Med Rev* 2022;62:101597. doi:10.1016/j.smr.2022.101597
- 28 Pascoe MC, Thompson DR, Jenkins ZM, *et al*. Mindfulness mediates the physiological markers of stress: Systematic review and meta-analysis. *Journal of Psychiatric Research* 2017;95:156–78. doi:10.1016/j.jpsychires.2017.08.004
- 29 Khoury B, Sharma M, Rush SE, *et al*. Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *Journal of Psychosomatic Research* 2015;78:519–28. doi:10.1016/j.jpsychores.2015.03.009

- 30 What's the difference between stress and anxiety? Clinical Partners. <https://www.clinical-partners.co.uk/insights-and-news/anxiety/what-is-the-difference-between-stress-and-anxiety> (accessed 7 Apr 2025).
- 31 Von Der Embse N, Jester D, Roy D, *et al.* Test anxiety effects, predictors, and correlates: A 30-year meta-analytic review. *Journal of Affective Disorders* 2018;227:483–93. doi:10.1016/j.jad.2017.11.048
- 32 Thomas CL, Cassady JC, Finch WH. Identifying Severity Standards on the Cognitive Test Anxiety Scale: Cut Score Determination Using Latent Class and Cluster Analysis. *Journal of Psychoeducational Assessment* 2018;36:492–508. doi:10.1177/0734282916686004
- 33 Szuhany KL, Simon NM. Anxiety Disorders: A Review. *JAMA* 2022;328:2431–45. doi:10.1001/jama.2022.22744
- 34 Putwain D, Daly AL. Test anxiety prevalence and gender differences in a sample of English secondary school students. *Educational Studies* 2014;40:554–70. doi:10.1080/03055698.2014.953914
- 35 Hamilton N, Freche R, Zhang Y, *et al.* Test Anxiety and Poor Sleep: A Vicious Cycle. *IntJ Behav Med* 2021;28:250–8. doi:10.1007/s12529-021-09973-1
- 36 Javaid SF, Hashim IJ, Hashim MJ, *et al.* Epidemiology of anxiety disorders: global burden and sociodemographic associations. *Middle East Current Psychiatry* 2023;30:44. doi:10.1186/s43045-023-00315-3
- 37 Federal Statistical Office. Psychische Gesundheit. 2022. <https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitszustand/psychische.html> (accessed 4 Oct 2024).
- 38 Swiss Health Observatory (Obsan). 5.2 Prävalenz psychischer Gesundheit und Krankheit | Nationaler Gesundheitsbericht 2020. Nationaler Gesundheitsbericht 2020. 2023. <https://www.gesundheitsbericht.ch/de/05-psychische-gesundheit/52-praevalenz-psychischer-gesundheit-und-krankheit.html> (accessed 4 Oct 2024).
- 39 Young LM, Pipingas A, White DJ, *et al.* A Systematic Review and Meta-Analysis of B Vitamin Supplementation on Depressive Symptoms, Anxiety, and Stress: Effects on Healthy and 'At-Risk' Individuals. *Nutrients* 2019;11:2232. doi:10.3390/nu11092232
- 40 London School of Economics and Political Science (LSE). Mental health problems cost UK economy at least £118 billion a year - new research. 2022. <https://www.lse.ac.uk/News/Latest-news-from-LSE/2022/c-Mar-22/Mental-health-problems-cost-UK-economy-at-least-118-billion-a-year-new-research.aspx> (accessed 4 Oct 2024).
- 41 González-Valero G, Zurita-Ortega F, Ubago-Jiménez JL, *et al.* Use of Meditation and Cognitive Behavioral Therapies for the Treatment of Stress, Depression and Anxiety in Students. A Systematic Review and Meta-Analysis. *IJERPH* 2019;16:4394. doi:10.3390/ijerph16224394
- 42 Stubbs B, Vancampfort D, Rosenbaum S, *et al.* An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: A meta-analysis. *Psychiatry Research* 2017;249:102–8. doi:10.1016/j.psychres.2016.12.020
- 43 Seifritz E, Hättenschwiler J, Hemmeter UM, *et al.* Die Behandlung der Angsterkrankungen: Kurzversion. *Swiss Med Forum* Published Online First: 10 April 2024. doi:10.4414/smf.2024.1398963534
- 44 Bandelow B, Aden I, Alpers G, *et al.* Deutsche S3-Leitlinie Behandlung von Angststörungen, . Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

- (AWMF) 2021. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF). 2021.
- 45 Sedonium compendium.ch. <https://compendium.ch/product/93087-sedonium-drag/mpro> (accessed 25 Nov 2024).
 - 46 Hova compendium.ch. <https://compendium.ch/product/3310-hova-filmtabl/mpub> (accessed 25 Nov 2024).
 - 47 Redormin compendium.ch. <https://compendium.ch/product/1007677-redormin-filmtabl-500-mg/mpro> (accessed 25 Nov 2024).
 - 48 Relaxane compendium.ch. <https://compendium.ch/product/1122908-relaxane-filmtabl/mpro> (accessed 25 Nov 2024).
 - 49 Leach MJ, Page AT. Herbal medicine for insomnia: A systematic review and meta-analysis. *Sleep Medicine Reviews* 2015;24:1–12. doi:10.1016/j.smrv.2014.12.003
 - 50 Valerian Root in Treating Sleep Problems and Associated Disorders—A Systematic Review and Meta-Analysis. doi:10.1177/2515690X20967323
 - 51 National Institutes of Health NIH. Office of Dietary Supplements - Valerian. Fact Sheet for Health Professionals. 2013.<https://ods.od.nih.gov/factsheets/Valerian-HealthProfessional/> (accessed 30 Sept 2024).
 - 52 Hood SD, Norman A, Hince DA, *et al.* Benzodiazepine dependence and its treatment with low dose flumazenil. *Br J Clin Pharmacol* 2014;77:285–94. doi:10.1111/bcp.12023
 - 53 The German Guidelines for the treatment of anxiety disorders: first revision | European Archives of Psychiatry and Clinical Neuroscience. <https://link.springer.com/article/10.1007/s00406-021-01324-1> (accessed 16 Sept 2025).
 - 54 Everitt H, Baldwin DS, Stuart B, *et al.* Antidepressants for insomnia in adults. *Cochrane Database of Systematic Reviews Published Online First*: 2018. doi:10.1002/14651858.CD010753.pub2
 - 55 European Medicines Agency (EMA). European Union herbal monograph on Valeriana officinalis L., radix. 2016. https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-valeriana-officinalis-l-radix_en.pdf
 - 56 European Medicines Agency (EMA). European Union herbal monograph on Valeriana officinalis L., radix and Humulus lupulus L., flos. 2019.
 - 57 List of references supporting the assessment of Valeriana officinalis L., radix and Valeriana officinalis L., aetheroleum.
 - 58 Higgins J, Thomas J, Chandler J, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions*. 2024.<https://training.cochrane.org/handbook/current> (accessed 10 Aug 2024).
 - 59 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71
 - 60 Sys J, Van Cleynenbreugel S, Deschodt M, *et al.* Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review. *Eur J Clin Pharmacol* 2020;76:363–81. doi:10.1007/s00228-019-02812-z
 - 61 France KG, McLay LK, Hunter JE, *et al.* Empirical research evaluating the effects of non-traditional approaches to enhancing sleep in typical and clinical children and young people. *Sleep Medicine Reviews* 2018;39:69–81. doi:10.1016/j.smrv.2017.07.004

- 62 Leach MJ, Page AT. Herbal medicine for insomnia: A systematic review and meta-analysis. *Sleep Medicine Reviews* 2015;24:1–12. doi:10.1016/j.smrv.2014.12.003
- 63 Khadivzadeh T, Abdollahian S, Ghazanfarpour M, *et al.* A Systematic Review and Meta-analysis on the Effect of Herbal Medicine to Manage Sleep Dysfunction in Periand Post-menopause. *Journal of Menopausal Medicine* 2018;24:92–9. doi:10.6118/jmm.2018.24.2.92
- 64 Kim J, Lee SL, Kang I, *et al.* Natural Products from Single Plants as Sleep Aids: A Systematic Review. *Journal of Medicinal Food* 2018;21:433–44. doi:10.1089/jmf.2017.4064
- 65 Hu R-F, Jiang X-Y, Chen J, *et al.* Non-pharmacological interventions for sleep promotion in the intensive care unit. *Cochrane Database of Systematic Reviews Published Online First*: 2015. doi:10.1002/14651858.CD008808.pub2
- 66 Culpepper L, Wingertzahn MA. Over-the-Counter Agents for the Treatment of Occasional Disturbed Sleep or Transient Insomnia: A Systematic Review of Efficacy and Safety. *Prim Care Companion CNS Disord* 2015;17:26162. doi:10.4088/PCC.15r01798
- 67 Guadagna S, Barattini DF, Rosu S, *et al.* Plant Extracts for Sleep Disturbances: A Systematic Review. *Evidence-based Complementary and Alternative Medicine : eCAM* 2020;2020. doi:10.1155/2020/3792390
- 68 Verma K, Singh D, Srivastava A. The Impact of Complementary and Alternative Medicine on Insomnia: A Systematic Review. *Cureus* 2022;14:e28425. doi:10.7759/cureus.28425
- 69 Attarian H, Hachul H, Guttuso T, *et al.* Treatment of chronic insomnia disorder in menopause: evaluation of literature. *Menopause* 2015;22:674. doi:10.1097/GME.0000000000000348
- 70 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
- 71 Higgins JP, Savović, Jelena, Page, Matthew J, *et al.* Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)*. Cochrane 2023. www.training.cochrane.org/handbook (accessed 24 Aug 2021).
- 72 Higgins JPT, Thomas J, Chandler J, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)*. 2023.www.training.cochrane.org/handbook
- 73 Egger M, Smith GD, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34. doi:10.1136/bmj.315.7109.629
- 74 Augusteijn HEM, van Aert RCM, van Assen MALM. The effect of publication bias on the Q test and assessment of heterogeneity. *Psychol Methods* 2019;24:116–34. doi:10.1037/met0000197
- 75 Peters JL, Sutton AJ, Jones DR, *et al.* Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *Journal of Clinical Epidemiology* 2008;61:991–6. doi:10.1016/j.jclinepi.2007.11.010
- 76 Sterne JAC, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. doi:10.1136/bmj.i4919
- 77 Schünemann HJ, Higgins JPT, Vist GE, *et al.* Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Cumpston M, *et al.*, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0*

- (updated July 2019). Cochrane 2022. <http://www.training.cochrane.org/handbook> (accessed 4 Apr 2023).
- 78 McMaster University, Evidence Prime Inc. GRADEpro. GRADEpro GDT. 2024.<https://www.grade.pro/> (accessed 19 July 2024).
 - 79 University of Pittsburgh. The Pittsburgh Sleep Quality Index (PSQI). The Pittsburgh Sleep Quality Index (PSQI). <https://www.sleep.pitt.edu/psqi> (accessed 30 Oct 2025).
 - 80 American Psychological Association. The State-Trait Anxiety Inventory (STAI). <https://www.apa.org>. <https://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/trait-state> (accessed 23 Oct 2025).
 - 81 Bucher HC, Guyatt GH, Griffith LE, *et al.* The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;50:683–91. doi:10.1016/S0895-4356(97)00049-8
 - 82 Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;14:135. doi:10.1186/1471-2288-14-135
 - 83 Williams D. *Weighing the Odds: A Course in Probability and Statistics*. Cambridge University Press 2001.
 - 84 Georgiev G. P-value to Z-score Calculator. P-value to Z-score Calculator. <https://www.gigacalculator.com/calculators/p-value-to-z-score-calculator.php> (accessed 3 Jan 2025).
 - 85 Deeks J, Higgins J, Altman D, *et al.* Chapter 10: Analysing data and undertaking meta-analyses [last updated November 2024]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.5*. Cochrane 2024. Available from www.training.cochrane.org/handbook.
 - 86 Campbell M, McKenzie JE, Sowden A, *et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;368:l6890. doi:10.1136/bmj.l6890
 - 87 Ahmadi M, Khalili H, Abbasian L, *et al.* Effect of Valerian in Preventing Neuropsychiatric Adverse Effects of Efavirenz in HIV-Positive Patients: A Pilot Randomized, Placebo-Controlled Clinical Trial. *Ann Pharmacother* 2017;51:457–64. doi:10.1177/1060028017696105
 - 88 Barton DL, Atherton PJ, Bauer BA, *et al.* The Use of Valeriana Officinalis (Valerian) in Improving Sleep in Patients Who Are Undergoing Treatment for Cancer: A Phase III Randomized, Placebo-Controlled, Double-Blind Study: NCCTG Trial, N01C5. *J Support Oncol* 2011;9:24–31. doi:10.1016/j.suponc.2010.12.008
 - 89 Chandra Shekhar H, Joshua L, Thomas JV. Standardized Extract of Valeriana officinalis Improves Overall Sleep Quality in Human Subjects with Sleep Complaints: A Randomized, Double-Blind, Placebo-Controlled, Clinical Study. *Adv Ther* 2024;41:246–61. doi:10.1007/s12325-023-02708-6
 - 90 Coxeter PD, Schluter PJ, Eastwood HL, *et al.* Valerian does not appear to reduce symptoms for patients with chronic insomnia in general practice using a series of randomised n-of-1 trials. *Complementary Therapies in Medicine* 2003;11:215–22. doi:10.1016/S0965-2299(03)00122-5
 - 91 Cuellar NG, Ratcliffe SJ. Does valerian improve sleepiness and symptom severity in people with restless legs syndrome? *Altern Ther Health Med* 2009;15:22–8.

- 92 Diaper A, Hindmarch I. A double-blind, placebo-controlled investigation of the effects of two doses of a valerian preparation on the sleep, cognitive and psychomotor function of sleep-disturbed older adults. *Phytotherapy Research* 2004;18:831–6. doi:10.1002/ptr.1574
- 93 Dimpfel W. Akute Wirksamkeit eines Baldrianwurzel-Trockenextraktes auf die Schlaftiefe beim Menschen. *Z Phytother* 2007;28:7–16. doi:10.1055/s-2007-971838
- 94 Donath F, Quispe S, Diefenbach K, *et al.* Critical Evaluation of the Effect of Valerian Extract on Sleep Structure and Sleep Quality. *Pharmacopsychiatry* 2000;33:47–53. doi:10.1055/s-2000-7972
- 95 Jacobs BP, Bent S, Tice JA, *et al.* An Internet-Based Randomized, Placebo-Controlled Trial of Kava and Valerian for Anxiety and Insomnia. *Medicine* 2005;84:197–207. doi:10.1097/01.md.0000172299.72364.95
- 96 Koetter U, Schrader E, Käufeler R, *et al.* Valerian Hops Extract Combination (Ze 91019) in Patients Suffering from Non-Organic Sleep Disorder. *Phytotherapy Research* 2007;21:847–51. doi:10.1002/ptr.2167
- 97 Leathwood PD, Chauffard F, Heck E, *et al.* Aqueous extract of valerian root (*Valeriana officinalis* L.) improves sleep quality in man. *Pharmacology, biochemistry, and behavior* 1982;17:65–71. doi:10.1016/0091-3057(82)90264-7
- 98 Leathwood PD, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. *Planta medica* 1985;:144–8. doi:10.1055/s-2007-969430
- 99 Oxman AD, Flottorp S, Håvelsrud K, *et al.* A Televised, Web-Based Randomised Trial of an Herbal Remedy (Valerian) for Insomnia. *PLoS ONE* 2007;2:e1040. doi:10.1371/journal.pone.0001040
- 100 Schulz H, Stolz C, Muller J. The effect of valerian extract on sleep polygraphy in poor sleepers: a pilot study. *Pharmacopsychiatry* 1994;27:147–51. doi:10.1055/s-2007-1014295
- 101 Taavoni S, Ekbatani N, Kashaniyan M, *et al.* Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. *Menopause* 2011;18:951–5. doi:10.1097/gme.0b013e31820e9acf
- 102 Taibi DM, Bourguignon C, Gill Taylor A. A Feasibility Study of Valerian Extract for Sleep Disturbance in Person With Arthritis. *Biological Research For Nursing* 2009;10:409–17. doi:10.1177/1099800408324252
- 103 Taibi DM, Vitiello MV, Barsness S, *et al.* A randomized clinical trial of valerian fails to improve self-reported, polysomnographic, and actigraphic sleep in older women with insomnia. *Sleep Medicine* 2009;10:319–28. doi:10.1016/j.sleep.2008.02.001
- 104 Tammadon MR, Nobahar M, Hydarinia-Naieni Z, *et al.* The Effects of Valerian on Sleep Quality, Depression, and State Anxiety in Hemodialysis Patients: A Randomized, Double-blind, Crossover Clinical Trial. *Oman Med J* 2021;36:e255–e255. doi:10.5001/omj.2021.56
- 105 Vorbach EU, Görtelmeyer R, Brüning J. Therapy of insomnia. The efficacy and tolerability of valerian. *Psychopharmakotherapie* 1996;3:109–15.
- 106 Ziegler G, Ploch M, Miettinen-Baumann A, *et al.* Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia--a randomized, double-blind, comparative clinical study. *European journal of medical research* 2002;7:480–6.

- 107 Dorn M. Wirksamkeit und Verträglichkeit von Baldrian versus Oxazepam bei nichtorganischen und nichtpsychiatrischen Insomnien: Eine randomisierte, doppelblinde, klinische Vergleichsstudie. *Complement Med Res* 2000;7:79–84. doi:10.1159/000021314
- 108 Aliakbari F, Rafieian M. The effectiveness of *Valeriana officinalis* on sleep disturbance in patients with chronic heart failure. *Int J Pharma Investig* 2018;8:145. doi:10.4103/jphi.JPHI_43_18
- 109 Hajizadeh I, Jamshidi M, Kazemi M, *et al.* Comparison the effect of valerian and gabapentin on RLS and sleep quality in hemodialysis patients: A randomized clinical trial. *Ther Apher Dial* 2023;27:621–8. doi:10.1111/1744-9987.13987
- 110 Gantner G, Spiess D, Randecker E, *et al.* Use of Herbal Medicines for the Treatment of Mild Mental Disorders and/or Symptoms During Pregnancy: A Cross-Sectional Survey. *Front Pharmacol* 2021;12:729724. doi:10.3389/fphar.2021.729724
- 111 Waldschütz R, Klein P. The Homeopathic Preparation Neurexan® vs. Valerian for the Treatment of Insomnia: An Observational Study. *The Scientific World JOURNAL* 2008;8:411–20. doi:10.1100/tsw.2008.61
- 112 Jokar A, Kargosha A, Akarzadeh M, *et al.* Comparing the influence of relaxation training and consumption of valerian on insomnia of menopause women: A randomized clinical trial. *Afr J Trad Compl Alt Med* 2016;13:40. doi:10.4314/ajtcam.v13i1.6
- 113 Dressing: Verbesserung der Schlafqualitaet mit einem... - Google Scholar. https://scholar.google.com/scholar_lookup?title=Verbessering%20der%20Schlafqualit%C3%A4t%20mit%20einem%20hochdosierten%20Baldrian-Melisse-Pr%C3%A4parat%3A%20eine%20plazebokontrollierte%20doppelblinde&publication_year=1996&author=H.%20Dressing&author=S.%20Kohler&author=W.E.%20Muller (accessed 13 Feb 2025).
- 114 Taavoni S, Nazem Ekbatani N, Haghani H. Valerian/lemon balm use for sleep disorders during menopause. *Complementary Therapies in Clinical Practice* 2013;19:193–6. doi:10.1016/j.ctcp.2013.07.002
- 115 Gammoh OS, Al-Smadi A, Mukattash T, *et al.* Efficacy of single dose antihistamine vs. single dose valerian-hops in subjective sleep measures among war refugees: a comparison trial. *Arch Clin Psychiatry (São Paulo)* 2017;44:35–9. doi:10.1590/0101-60830000000114
- 116 Morin CM, Koetter U, Bastien C, *et al.* Valerian-Hops Combination and Diphenhydramine for Treating Insomnia: A Randomized Placebo-Controlled Clinical Trial. *Sleep* 2005;28:1465–71. doi:10.1093/sleep/28.11.1465
- 117 Rodenbeck A, Simen S, Cohrs S, *et al.* Alterations of the Sleep Stage Structure as a Feature for GABAergic Effects of a Valerian-Hop Preparation in Patients with Psychophysiological Insomnia. 1998.
- 118 Dos Santos AJS, Freire RT, Amorim KDS, *et al.* Anxiolytic effect of a combination of valerian officinalis L. and humulus lupulus L. in patients undergoing impacted third molar extraction. *Rev Contemp* 2023;3:9403–21. doi:10.56083/RCV3N7-106
- 119 Kennedy DO, Little W, Haskell CF, *et al.* Anxiolytic effects of a combination of *Melissa officinalis* and *Valeriana officinalis* during laboratory induced stress. *Phytotherapy Research* 2006;20:96–102. doi:10.1002/ptr.1787
- 120 Gasparini M, Aurilia C, Lubian D, *et al.* Herbal remedies and the self-treatment of stress: An Italian survey. *European Journal of Integrative Medicine* 2016;8:465–70. doi:10.1016/j.eujim.2016.01.001

- 121 Meier S, Haschke M, Zahner C, *et al.* Effects of a fixed herbal drug combination (Ze 185) to an experimental acute stress setting in healthy men – An explorative randomized placebo-controlled double-blind study. *Phytomedicine* 2018;39:85–92. doi:10.1016/j.phymed.2017.12.005
- 122 Melzer J, Schrader E, Brattström A, *et al.* Fixed herbal drug combination with and without butterbur (Ze 185) for the treatment of patients with somatoform disorders: randomized, placebo-controlled pharmaco-clinical trial. *Phytotherapy Research* 2009;23:1303–8. doi:10.1002/ptr.2771
- 123 Dreßing H, Köhler S, Müller WE. Improvement of sleep quality with a high-dose valerian/balm preparation. *Psychopharmakotherapie* 1996;3:123–30.
- 124 Thielen FW, Mastrigt GV, Burgers LT, *et al.* How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;16:705–21. doi:10.1080/14737167.2016.1246962
- 125 van Mastrigt GAPG, Hiligsmann M, Arts JJC, *et al.* How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;16:689–704. doi:10.1080/14737167.2016.1246960
- 126 Wijnen B, Van Mastrigt G, Redekop WK, *et al.* How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;16:723–32. doi:10.1080/14737167.2016.1246961
- 127 AXA. AXA Mind Health Report 2024. 2024. <https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.axa.ch/doc/anw34&ved=2ahUKEwjj-8Ob89-PAXWd2wIHHf4qBwMQFnoECBkQAQ&usg=AOv-Vaw1P6JwqrJBqVUFqrfl9b4-7>
- 128 Valls M. Exploring the psychometric properties of the French revised test anxiety + regulatory scale in Swiss secondary school students. *Front Educ* 2023;8. doi:10.3389/feduc.2023.1289892
- 129 Blanco C, Okuda M, Wright C, *et al.* Mental health of college students and their non-college-attending peers: results from the National Epidemiologic Study on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2008;65:1429–37. doi:10.1001/archpsyc.65.12.1429
- 130 França LR, Vidal C, Bourechak N, *et al.* A cohort study of therapeutic prescriptions after the end of phytotherapy drug reimbursement by French Social Security. *Pharmacoeconomics and Drug Safety* 2013;22:760–8. doi:10.1002/pds.3382
- 131 Zhang J, Yu KF. What's the Relative Risk? A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes. *JAMA* 1998;280:1690–1. doi:10.1001/jama.280.19.1690
- 132 compendium.ch. <https://compendium.ch/> (accessed 17 Sept 2025).
- 133 Tarmed 01.09_BR (KVG) Online Browser. https://browser.tartools.ch/de/tarmed_kvg (accessed 17 Sept 2025).
- 134 <https://www.newindex.ch/wp-content/uploads/2023/12/TPW-DE-2024-2013.pdf>. <https://www.newindex.ch/wp-content/uploads/2023/12/TPW-DE-2024-2013.pdf> (accessed 17 Sept 2025).
- 135 Rosenqvist TW, Wium-Andersen MK, Wium-Andersen IK, *et al.* Long-Term Use of Benzodiazepines and Benzodiazepine-Related Drugs: A Register-Based Danish Cohort Study on

Determinants and Risk of Dose Escalation. Am J Psychiatry 2024;181:246–54.
doi:10.1176/appi.ajp.20230075

- 136 Berger A, Edelsberg J, Treglia M, *et al.* Change in healthcare utilization and costs following initiation of benzodiazepine therapy for long-term treatment of generalized anxiety disorder: a retrospective cohort study. BMC Psychiatry 2012;12:177. doi:10.1186/1471-244X-12-177
- 137 Federal Reserve Bank of St. Louis. Consumer Price Index for All Urban Consumers: Medical Care in U.S. City Average. 2025.<https://fred.stlouisfed.org/series/CPIMEDSL> (accessed 22 Nov 2025).
- 138 Purchasing power parities. <https://www.bfs.admin.ch/content/bfs/en/home/statistics/prices/international-price-comparisons/purchasing-power-parities.html> (accessed 22 Nov 2025).
- 139 EUnetHTA Joint Action 2 WP 8. HTA Core Model version 3.0 for the full assessment of diagnostic technologies, medical and surgical interventions, pharmaceuticals and screening technologies. 2016.
- 140 Hofmann B. Toward a procedure for integrating moral issues in health technology assessment. Int J Technol Assess Health Care 2005;21:312–8. doi:10.1017/S0266462305050415
- 141 Schröder P, Bäck. *Ethik in den Gesundheitswissenschaften.*
- 142 Dratva J, Höglinger M, Lätsch D, *et al.*, editors. *Public Health im Kindes- und Jugendalter: Schlüsselkonzepte, Methoden und Umsetzungsstrategien.* 1st edn Hogrefe AG 2025. doi:10.1024/86294-000
- 143 Schröder P. Public-Health-Ethik in Abgrenzung zur Medizinethik. Bundesgesundheitsbl 2007;50:103–11. doi:10.1007/s00103-007-0115-z
- 144 Schröder-Bäck P. *Ethik in den Gesundheitswissenschaften.* Beltz Verlagsgruppe 2016.
- 145 Kien C, Daxenbichler J, Titscher V, *et al.* Effectiveness of de-implementation of low-value healthcare practices: an overview of systematic reviews. Implementation Sci 2024;19:56. doi:10.1186/s13012-024-01384-6
- 146 Norton WE, Chambers DA. Unpacking the complexities of de-implementing inappropriate health interventions. Implementation Sci 2020;15:2. doi:10.1186/s13012-019-0960-9
- 147 Schröder-Bäck, P., & Kuhn, J. (2016). *Ethik in den Gesundheitswissenschaften : Eine Einführung (1. Aufl.). Beltz Juventa.*
- 148 Suhr JA, Johnson EEH. First Do No Harm: Ethical Issues in Pathologizing Normal Variations in Behavior and Functioning. Psychol Inj and Law 2022;15:253–67. doi:10.1007/s12207-022-09455-z
- 149 Coveney C, Williams SJ, Gabe J. Medicalisation, pharmaceuticalisation, or both? Exploring the medical management of sleeplessness as insomnia. Sociology Health & Illness 2019;41:266–84. doi:10.1111/1467-9566.12820
- 150 He S, Ke X-J, Wu Y, *et al.* The stigma of patients with chronic insomnia: a clinical study. BMC Psychiatry 2022;22:449. doi:10.1186/s12888-022-04091-y
- 151 Kvaale EP, Haslam N, Gottdiener WH. The ‘side effects’ of medicalization: A meta-analytic review of how biogenetic explanations affect stigma. Clinical Psychology Review 2013;33:782–94. doi:10.1016/j.cpr.2013.06.002

- 152 Martínez-Fernández A, Rueda Vega M, Quintas S, *et al.* Psychosocial repercussion of migraine: is it a stigmatized disease? *Neurol Sci* 2020;41:2207–13. doi:10.1007/s10072-020-04332-6
- 153 Gabe J, Coveney CM, Williams SJ. Prescriptions and proscriptions: moralising sleep medicines. *Sociology Health & Illness* 2016;38:627–44. doi:10.1111/1467-9566.12383
- 154 Winkler A, Rief W. Effect of Placebo Conditions on Polysomnographic Parameters in Primary Insomnia: A Meta-Analysis. *Sleep* 2015;38:925–31. doi:10.5665/sleep.4742
- 155 Benedetti F, Mayberg HS, Wager TD, *et al.* Neurobiological Mechanisms of the Placebo Effect. *J Neurosci* 2005;25:10390–402. doi:10.1523/JNEUROSCI.3458-05.2005
- 156 Enck P, Zipfel S, Klosterhalfen S. Der Placeboeffekt in der Medizin. *Bundesgesundheitsbl* 2009;52:635–42. doi:10.1007/s00103-009-0849-x
- 157 KVG. Bundesgesetz über die Krankenversicherung. 1996.
- 158 Deutscher Ethikrat. Nutzen und Kosten im Gesundheitswesen – Zur normativen Funktion ihrer Bewertung. Deutscher Ethikrat 2011.
- 159 Daniels N, Sabin JE. *Setting Limits Fairly*. Oxford University Press 2002. doi:10.1093/acprof:oso/9780195149364.001.0001
- 160 Brook RH, Lohr KN. *Will We Need to Ration Effective Health Care?* Santa Monica, CA: : RAND Corporation 1991. <https://www.rand.org/pubs/notes/N3375.html>
- 161 Emanuel EJ, editor. *Rationing and resource allocation in healthcare: essential readings*. New York, NY, United States of America: : Oxford University Press 2018.
- 162 Holm S. The second phase of priority setting. Goodbye to the simple solutions: the second phase of priority setting in health care. *BMJ* 1998;317:1000–2.
- 163 Barra M, Broqvist M, Gustavsson E, *et al.* Severity as a Priority Setting Criterion: Setting a Challenging Research Agenda. *Health Care Anal* 2020;28:25–44. doi:10.1007/s10728-019-00371-z
- 164 Mattli R, Tomonaga Y, Tzogiou C, *et al.* Health technology assessment (HTA) : medicines for dementia due to Alzheimer's and Parkinson's disease. Bundesamt für Gesundheit BAG 2022. <https://digitalcollection.zhaw.ch/items/91542a6b-c852-4687-8d07-1b95323f3ea0>
- 165 Künzi M. Komplementärmedizin und Gesundheitsrecht, Basel/Frankfurt a.M. 1996.
- 166 Kieser U. Die Zulassung von Arzneimitteln im Gesundheits- und im Sozialversicherungsrecht - Unter besonderer Berücksichtigung von Arzneimitteln der Komplementärmedizin, insbesondere der Phytoarzneimittel. *AJP* 2007;;1042–50.
- 167 Widrig D, Tag B. Rechtliche Aspekte der Kosten-/Nutzenbewertung in der Medizin, Hill 2012, Nr. 65, Zürich 2012. 2012.
- 168 Gächter T, Bernhard Rütsche B. Gesundheitsrecht: Ein Grundriss für Studium und Praxis, 5. Aufl., Helbing Lichtenhahn, Basel 2023.
- 169 Waldmeier D. Art. 118a BV (Komplementärmedizin) – quo vadis?, Jusletter 16. August 2010.
- 170 Bundesamt für Gesundheit. Verordnung vom 27. Juni 1995 über die Krankenversicherung (KVV) und Verordnung des EDI vom 29. September 1995 über Leistungen in der

obligatorischen Krankenpflegeversicherung (Krankenpflege-Leistungsversicherung, KLV), Vorgesehene Änderungen per 1. August 2017, Bern 2016.

- 171 Rütsche B, Wildi A. Limitierung von Arzneimitteln im Krankenversicherungsrecht: Wo wird die Grenze zur Rationierung überschritten?, recht 2016, S. 199 ff.
- 172 Nationale Ethikkommission im Bereich der Humanmedizin NEK. Stellungnahme Nr. 35/2020 «Medikamentenpreise: Überlegungen zum gerechten Umgang mit teuren neuen Medikamenten», Bern 2. Juli 2020.
- 173 Kieser U, Nedi M. Komplementärmedizin: Was legt Art. 118a BV fest?, Hill 2013 Nr. 72, Zürich 2013.
- 174 Schöni N. Zulässigkeit von Placebos in der Humanmedizin nach schweizerischem Recht. Zurich: : University of Zurich 2014. <https://www.zora.uzh.ch/id/eprint/104457/> (accessed 9 July 2024).
- 175 Briquet L. Réactions des patients face au déremboursement des médicaments. Actualités Pharmaceutiques 2021;60:53–5. doi:10.1016/j.actpha.2021.06.014
- 176 Attele AS, Xie JT, Yuan CS. Treatment of insomnia: an alternative approach. Altern Med Rev 2000;5:249–59.
- 177 Bent S, Padula A, Moore D, *et al.* Valerian for Sleep: A Systematic Review and Meta-Analysis. The American Journal of Medicine 2006;119:1005–12. doi:10.1016/j.amjmed.2006.02.026
- 178 Levesque J-F, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. Int J Equity Health 2013;12:18. doi:10.1186/1475-9276-12-18
- 179 Vrdoljak D, Borovac JA. Medication in the elderly - considerations and therapy prescription guidelines. Acta Medica Academica 2015;44:159–159. doi:10.5644/ama2006-124.142
- 180 Tordjman L, Goltzène M-A, Ruppert E. A descriptive study of national trends in the dispensing of reimbursed hypnotics in France between 2012 and 2022. Sleep Health 2025;11:754–60. doi:10.1016/j.sleh.2025.07.002
- 181 Sirdifield C, Chipchase SY, Owen S, *et al.* A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. Patient 2017;10:1–15. doi:10.1007/s40271-016-0182-z
- 182 American Academy of Family Physicians (AAFP). Patient-Centered Formularies. 2025.<https://www.aafp.org/about/policies/all/patient-centered-formularies.html> (accessed 17 Nov 2025).
- 183 RELEX Solutions. Pharmacy inventory management: Maintaining availability despite complexity. Demand Forecasting , Supply Chain Planning. 2022.<https://www.relexsolutions.com/resources/drug-inventory-management-ensuring-availability-to-stay-competitive/> (accessed 17 Nov 2025).
- 184 American Society of Health-System Pharmacists. ASHP guidelines on medication cost management strategies for hospitals and health systems. 2008;Am J Health-Syst Pharm:1368–84.
- 185 Parveen A, Parveen B, Parveen R, *et al.* Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci 2015;7:329–33. doi:10.4103/0975-7406.168035

- 186 Koffel E, Bramoweth AD, Ulmer CS. Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *J Gen Intern Med* 2018;33:955–62. doi:10.1007/s11606-018-4390-1
- 187 Morgan K, Dixon S, Mathers N, *et al.* Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. *Health Technol Assess* 2004;8:iii–iv, 1–68. doi:10.3310/hta8080
- 188 Aidsburger P, Schauer S, Grabein K, *et al.* *Alternative Methoden zur Behandlung postmenopausaler Beschwerden*. DIMDI 2012. doi:10.3205/HTA000101L
- 189 Beresford B, McDaid C, Parker A, *et al.* Pharmacological and non-pharmacological interventions for non-respiratory sleep disturbance in children with neurodisabilities: a systematic review. *Health Technology Assessment* 2018;22:1–296. doi:10.3310/hta22600
- 190 Francis AJP, Dempster RJW. Effect of valerian, *Valeriana edulis*, on sleep difficulties in children with intellectual deficits: randomised trial. *Phytomedicine* 2002;9:273–9. doi:10.1078/0944-7113-00110
- 191 Wegener T. T. WegenerPhytopharmaka zur Anxiolyse – Baldri. *Deutsche Apotheker Zeitung*. 2003.<https://www.deutsche-apotheker-zeitung.de/daz-az/2003/daz-6-2003/uid-9136> (accessed 27 Feb 2025).
- 192 Wheatley D. Kava and Valerian in the treatment of stress-induced insomnia. *Phytotherapy Research* 2001;15:549–51. doi:10.1002/ptr.840
- 193 Abdellah SA, Berlin A, Blondeau C, *et al.* A combination of Eschscholtzia californica Cham. and Valeriana officinalis L. extracts for adjustment insomnia: A prospective observational study. *J Tradit Complement Med* 2020;10:116–23. doi:10.1016/j.jtcme.2019.02.003
- 194 Trompetter I, Krick B, Weiss G. Herbal triplet in treatment of nervous agitation in children. *Wiener medizinische Wochenschrift (1946)* 2013;163:52–7. doi:10.1007/s10354-012-0165-1
- 195 Müller D, Pfeil T, von den Driesch V. Treating depression comorbid with anxiety--results of an open, practice-oriented study with St John's wort WS 5572 and valerian extract in high doses. *Phytomedicine* 2003;10 Suppl 4:25–30. doi:10.1078/1433-187x-00305
- 196 Dominguez RA, Bravo-Valverde RL, Kaplowitz BR, *et al.* Valerian as a hypnotic for Hispanic patients. *Cultur Divers Ethnic Minor Psychol* 2000;6:84–92. doi:10.1037/1099-9809.6.1.84
- 197 Gromball J, Beschorner F, Wantzen C, *et al.* Hyperactivity, concentration difficulties and impulsiveness improve during seven weeks' treatment with valerian root and lemon balm extracts in primary school children. *Phytomedicine* 2014;21:1098–103. doi:10.1016/j.phymed.2014.04.004
- 198 Müller SF, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. *Phytomedicine* 2006;13:383–7. doi:10.1016/j.phymed.2006.01.013
- 199 Schick Tanz N, Gerhards C, Schlitt T, *et al.* Effects of a Valerian-Hops Extract Combination (Ze 91019) on Sleep Duration and Daytime Cognitive and Psychological Parameters in Occasional Insomnia: A Randomized Controlled Feasibility Trial. *Brain and Behavior* 2025;15:e70600. doi:10.1002/brb3.70600
- 200 Taavoni S, Nazem Ekbatani N, Haghani H. Effect of valerian on sleep quality in menopausal women: a randomized placebo-controlled clinical trial. *International journal of neuropsychopharmacology* 2012;15:242. doi:10.1017/S1461145712000508

13. Appendices

A. Search strategy for clinical evidence

MEDLINE (Ovid)

Population	No search string
Intervention	Valerian/ or (valerian* or valeren* or baldrian* or "V. officinalis" or "V. radix").ti,ab,kw. or (Dormiplant or Hova or Redormin or Relaxane or Sedonium).ti,ab,kw. or ("Li 156" or "Ze 91019" or "Ze 185" or "WS 1014").ti,ab,kw.
Comparator	No search string
Outcomes	No search string
Limits	<i>Limit to humans</i> not (animals not humans).sh. <i>Exclude infants</i> not (exp infant/ not (exp child/ OR exp adolescent/ OR exp adult/)) <i>Exclude conference/congress abstracts</i> limit X to (congress) → Then X not Y <i>Limit to clinical studies^a</i> (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial or (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol) or Multicenter Study).pt. or Clinical Studies as Topic/ or exp Clinical Trials as Topic/ or Clinical Trial Protocols as Topic/ or Multicenter Studies as Topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or Placebos/ or Control Groups/ or Cross-Over Studies/ or (random* or sham or placebo*).ti,ab,hw,kf. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. or (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. or (Nonrandom* or non random* or non-random* or quasirandom* or quasirandom*).ti,ab,hw,kf. or (phase adj6 (study or studies or trial*)).ti,ab,hw,kf. or ((crossover or cross-over) adj3 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.

Notes

^aThe clinical studies limit for MEDLINE via Ovid was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.²⁰¹

Modifications include addition of the term “comparison*” to the proximity searches with crossover, open label and equivalence/superiority terms and removal of the animal study exclusion search terms. The “limit to humans” filter is applied to the search results in a subsequent step.

Embase (Elsevier)

Population	No search string
Intervention	'valerian'/exp OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix"):ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium):ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	<i>Limit to humans</i> NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de)) <i>Exclude infants</i> NOT ([infant]/lim NOT ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim)) <i>Exclude conference/congress abstracts</i> NOT ([conference abstract]/lim) <i>Limit to clinical studies^a</i> 'clinical study'/exp OR 'clinical trial (topic)'/exp OR 'clinical trial protocol'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR (random* or sham or placebo*):ti,ab,kw OR ((singl* or doubl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR ((tripl* or trebl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR (control* NEAR/3 (study or studies or trial* or group*)):ti,ab,kw OR (Nonrandom* or "non random*" or non-random* or quasi-random* or quasirandom*):ti,ab,kw OR (phase NEAR/6 (study or studies or trial*)):ti,ab,kw OR ((crossover or cross-over) NEAR/3 (study or studies or trial* or comparison*)):ti,ab,kw OR ((multicent* or "multi-cent*") NEAR/3 (study or studies or trial*)):ti,ab,kw OR allocated:ti,ab OR ("open label" or "open-label") NEAR/5 (study or studies or trial* or comparison*)):ti,ab,kw OR ((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial* or comparison*)):ti,ab,kw OR (pragmatic study or pragmatic studies):ti,ab,kw OR ((pragmatic or practical) NEAR/3 trial*):ti,ab,kw OR ((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)):ti,ab,kw OR trial:ti,kw

Notes

^aThe clinical studies limit for Embase via Elsevier was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.²⁰¹

Modifications include removal of redundant subject headings; addition of the term "comparison*" to the proximity searches with crossover, open label and equivalence/superiority terms; and removal of the animal study exclusion search terms. The "limit to humans" filter is applied to the search results in a subsequent step.

CENTRAL, Cochrane Protocols, Reviews and Trials (Cochrane Library via Wiley)

Population	No search string
Intervention	(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix"):ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium):ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as database is restricted to clinical studies in humans

APA PsycInfo (EBSCOhost)

Population	No search string
Intervention	TI(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR AB(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR TI(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR AB(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR TI("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014") OR AB("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	<i>Limit to humans</i> NOT ((DE "Animal Models" OR DE "Animals" OR DE "Animal Research" OR TI (animal model*)) NOT (DE "Human Males" OR DE "Human Females")) <i>Limit to clinical studies</i> ^a DE "Placebo" OR DE "Randomized Clinical Trials" OR DE "Randomized Con- trolled Trials" OR DE "Experiment Controls" OR DE "Clinical Trials" OR MR "CLINICAL TRIAL" OR TI ("random*" OR "sham" OR "placebo*" OR "Nonran- dom*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "qua- sirandom*" OR "pragmatic study" OR "pragmatic studies") OR AB ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-ran- dom*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR SU ("random*" OR "sham" OR "placebo*" OR "Non- random*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "qua- sirandom*" OR "pragmatic study" OR "pragmatic studies") OR KW ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-ran- dom*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR TI ((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR AB (((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR SU (((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR KW (((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR TI ((("clinical" OR "crossover" OR "cross-over" OR "multi- cent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR "comparison*"))) OR AB (((("clinical" OR "crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equiva- lence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexper- imental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR "comparison*"))) OR SU (((("clinical" OR "crossover" OR "cross-over" OR "multi- cent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR "comparison*"))) OR KW (((("clinical" OR

"crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR "comparison*")) OR TI (("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR "comparison*")) OR AB (("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR "comparison*")) OR SU (("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR "comparison*")) OR KW (("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR "comparison*")) OR TI (("pragmatic" OR "practical") N2 ("trial*")) OR AB (("pragmatic" OR "practical") N2 ("trial*")) OR SU (("pragmatic" OR "practical") N2 ("trial*")) OR KW (("pragmatic" OR "practical") N2 ("trial*")) OR TI ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*"))) OR AB ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*"))) OR SU ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*"))) OR KW ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*"))) OR TI ("phase") N5 ("study" OR "studies" OR "trial*")) OR AB ("phase") N5 ("study" OR "studies" OR "trial*")) OR SU ("phase") N5 ("study" OR "studies" OR "trial*")) OR KW ("phase") N5 ("study" OR "studies" OR "trial*")) OR TI "allocated" OR AB "allocated" OR SU "allocated" OR TI ("trial") OR KW ("trial")

Notes

^aThe clinical studies limit for APA PsycINFO via EBSCOhost was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.²⁰¹

Modifications include addition of the term "comparison*" to the proximity searches with crossover, open label and equivalence/superiority terms.

Web of Science Core Collection

Population	No search string
Intervention	TS=(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR TS=(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR TS=("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	<i>Limit to clinical studies^a, Exclude animal studies, Exclude meeting abstracts</i> (TS=(random* or sham or placebo*) OR TS=((singl* or doubl*) NEAR/1 (blind* or dumm* or mask*)) OR TS=((tripl* or trebl*) NEAR/1 (blind* or dumm* or mask*)) OR TS=(control* NEAR/3 (study or studies or trial* or group*)) OR TS=(Nonrandom* or "non random*" or non-random* or quasi-random* or quasirandom*) OR TS=(phase NEAR/6 (study or studies or trial*)) OR TS=((cross-over or cross-over) NEAR/3 (study or studies or trial* or comparison*)) OR TS=((multicent* or "multi-cent*") NEAR/3 (study or studies or trial*)) OR TI=(allocated) OR AB=(allocated) OR TS=(("open label" or "open-label") NEAR/5 (study or studies or trial* or comparison*)) OR TS=((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial* or comparison*)) OR TS=(pragmatic study or pragmatic studies) OR TS=((pragmatic or practical) NEAR/3 trial*) OR TS=((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)) OR TI=(trial) OR AK=(trial)) NOT TI=(animal* OR mouse OR mice OR rat OR rats OR pig OR pigs) AND (Meeting Abstract (Exclude – Document Types))

Notes

^aThe clinical studies limit for Web of Science Core Collection was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.²⁰¹

The filter was translated from Embase to Web of Science syntax and subject headings were removed. Modifications included addition of the term "comparison*" to the proximity searches with crossover, open label and equivalence/superiority terms. The animal study exclusion search terms were removed. A title exclusion for animal terms will be applied to the search results in a subsequent step.

Clinicaltrials.gov

Population	No search string
Intervention	valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as registry consists of clinical studies in humans.

WHO International Clinical Trials Registry Platform Search Portal

Population	No search string
Intervention	<i>Simple search, including synonyms, all trial phases</i> valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as registry consists of clinical studies in humans. Limit for interventional studies is not available.

B. Search strategy for economic evidence

MEDLINE (Ovid)

Population	No search string
Intervention	Valerian/ OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix").ti,ab,kw. OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium).ti,ab,kw. OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014").ti,ab,kw.
Comparator	No search string
Outcomes	exp "Costs and Cost Analysis"/ OR Economics, Pharmaceutical/ OR exp Budgets/ OR models, economic/ OR (Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*).ti,ab,kw.
Limits	<i>Limit to humans</i> not (animals not humans).sh. <i>Exclude infants</i> not (exp infant/ not (exp child/ OR exp adolescent/ OR exp adult/)) <i>Exclude conference/congress abstracts</i> limit X to (congress) → Then X not Y

Embase (Elsevier)

Population	No search string
Intervention	'valerian'/exp OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix");ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium).ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014");ti,ab,kw
Comparator	No search string
Outcomes	'economic evaluation'/exp OR 'health care cost'/exp OR 'cost'/de OR 'budget'/de OR 'budget impact'/exp OR 'budget impact analysis'/exp OR 'budget impact model'/exp OR (Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*).ti,ab,kw
Limits	<i>Limit to humans</i> NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de)) <i>Exclude infants</i> NOT ([infant]/lim NOT ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim)) <i>Exclude conference/congress abstracts</i> NOT ([conference abstract]/lim)

EconLit (EBSCOhost)

Population	No search string
Intervention	TI(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014") OR AB(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	TI(Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*) OR AB(Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*)
Limits	No limits applied as search returned 1 result as of 1 April 2025

International Network of Agencies for Health Technology Assessment (INAHTA) database

Population	No search string
Intervention	"Valerian"[mh] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[Title] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[abs] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[Keywords]
Comparator	No search string
Outcomes	No search string
Limits	No limits applied

National Health Service Economic Evaluation Database (NHS EED)

Population	No search string
Intervention	<i>Simple search in "any field"</i> (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	No limits applied

C. Valerian preparation details of included studies

Table A 1: Valerian preparation details of included studies

First author year	Daily valerian dose (mg)	Extraction solvent	Drug extraction rate	Composition	Commercial preparation name
Ahmadi 2017 ⁸⁷	530	NR	NR	More than 0.05% valerenic acid and passed the United States Pharmacopeia minimum cutoff. Each capsule of valerian had 0.554 mg of sesquiterpenic acid.	NR
Aliakbari 2018 ¹⁰⁸	NR	Methanol	NR	Total phenol and flavonoid compounds were measured to be 60.04 and 27.7 mg/ml syrup, respectively.	NR
Barton 2011 ⁸⁸	450	NR	NR	0.8% valerenic acid	NR
Chandra Shekhar 2024 ⁸⁹	200	Hydro-alcoholic	NR	Hydro-alcoholic extract of valerian root, 2% total valerenic acid in final composition (26.23% valerian, 73.27% cellulose polymer, 0.5% colloidal silicon dioxide)	Sleeproot®
Coxeter 2003 ⁹⁰	450	NR	NR	Contents standardised to 2.94 mg total Valerenic acids, 0.46 mg Valerenal and 1.23 mg Valtrates	NR
Cuellar 2009 ⁹¹	800	No extraction solvent was used.	NR	The dry root was used.	NR
Diaper 2004 ⁹²	300 and 600 ¹	Ethanol	3-6:1	70% ethanol	Sedonium®
Dimpfel 2007 ⁹³	600	Ethanol	3-6:1	70% ethanol	Nervenruh Baldrian Forte
Donath 2000 ⁹⁴	600	NR	5:1	NR	Sedonium®
Dorn 2000 ¹⁰⁷	600	NR	NR	NR	Sedonium®
Dreßing 1996 ¹²³	640	NR	4.5:1	NR	Euvegal®forte
Gammoh 2017 ¹¹⁵	320	NR	NR	NR	Cirkulin®
Gantner 2021 ¹¹⁰	NR	NR	NR	NR	NR
Gasparini 2016 ¹²⁰	NR	NR	NR	NR	NR
Hajizadeh 2023 ¹⁰⁹	530	NR	NR	NR	NR
Jacobs 2005 ⁹⁵	640	NR	NR	NR	NR
Jokar 2016 ¹¹²	1060	NR	NR	NR	NR
Kennedy 2006 ¹¹⁹	360 and 720 ²	NR	4.5:1	NR	NR
Koetter 2007 ⁹⁶	500	Methanol	5.3:1	45% methanol	NR
Leathwood 1982 ⁹⁶	400	Water/Aqueous	NR	NR	Hova®
Leathwood 1985 ⁹⁸	450 and 900 ³	Water/Aqueous	3.1:1	NR	NR
Meier 2018 ¹²¹	270	Methanol	4-6:1	Fixed herbal combination containing 4 standardized plant extracts per tablet: <i>Petasites hybridus</i> (root) – 90 mg (90 % ethanol); <i>Valeriana officinalis</i> (root) – 90 mg (45 %	NR

				methanol); <i>Passiflora incarnata</i> (herb) – 90 mg (50 % ethanol); <i>Melissa officinalis</i> (leaves) – 60 mg (20 % ethanol).	
Melzer 2009 ¹²²	270	Methanol	5-8:1	90 mg of <i>Petasites hybridus</i> (root, butterbur) extracted with 90 % ethanol; 90 mg of <i>Valeriana officinalis</i> (root, valerian) extracted with 45 % methanol; 90 mg of <i>Passiflora incarnata</i> (herb, passion-flower) extracted with 50 % ethanol; 60 mg of <i>Melissa officinalis</i> (leaves, lemon balm) extracted with 20 % ethanol.	Relaxane®
Morin 2005 ¹¹⁶	372	Methanol	5-8:1	native valerian extract prepared using 45 % methanol and hops strobile extract (<i>Humulus lupulus</i> L.) with 41.9 mg of native extract prepared using the same 45 % methanol solvent.	Sominex®
Oxman 2007 ⁹⁹	3600	NR	NR	NR	Valerina Forte®
Rodenbeck 1998 ¹¹⁷	500	NR	6:1	NR	NR
Schulz 1994 ¹⁰⁰	405	Water/Aqueous	5-6:1	NR	Valdispert®
Silva dos Santos 2023 ¹¹⁸	500	NR	NR	(at least) 0.15% valerenic acid	NR
Taavoni 2011 ¹⁰¹	1060	NR	NR	NR	NR
Taavoni 2013 ¹¹⁴	320	NR	NR	NR	NR
Taibi 2009 ¹⁰²	300	Ethanol	NR	70% ethanol, 0.8% valerenic acid	NR
Taibi 2009 ¹⁰³	600	Ethanol	NR	70% ethanol, 0.8% valerenic acid	NR
Tammadon 2021 ¹⁰⁴	530	NR	NR	NR	NR
Vorbach 1996 ¹⁰⁵	600	Ethanol	3-7:1	70% ethanol	Sedonium®
Waldschütz 2008 ¹¹¹	250	NR	NR	NR	NR
Ziegler 2002 ¹⁰⁶	600	Ethanol	3.6:1	70% ethanol	Sedonium®

Abbreviations: NR, not reported

Notes

¹ Results from study arm that received dosage of 600mg were included in the meta-analyses.

² Results from study arm that received dosage of 360mg were included in the descriptive tables.

³ Results from study arm that received dosage of 450mg were included in the meta-analyses.

D. Risk of bias assessment

Table A 2: Risk of bias for PICO 1

Study ID	Outcome	D1	D2	D3	D4	D5	Overall
Dimpfel 2007	night awakenings	!	+	+	+	!	!
Diaper, 2004	night awakenings	!	+	+	+	!	!
Jacobs, 2005	night awakenings	+	+	-	+	!	-
Taibi, 2009	night awakenings	+	+	+	+	!	!
Taibi, 2009	night awakenings	+	+	+	+	!	!
Oxman, 2007	night awakenings	+	+	+	+	+	+
Aliakbari F, Rafieian M, 2018	PSQI total score	!	!	+	-	!	-
Ahmadi 2017	psqi total score	-	+	-	+	!	-
Shekhar, 2024	psqi total score	!	!	+	+	!	!
Cuellar, 2009	PSQI total score	+	+	!	+	!	!
Tammadon, 2021	PSQI total score	!	+	+	+	!	!
Taavoni, 2011	PSQI total score	!	+	+	+	!	!
Aliakbari F, Rafieian M, 2018	sleep duration	!	!	+	-	!	-
Dimpfel 2007	sleep duration	!	+	+	+	!	!
Shekhar, 2024	sleep duration	!	!	+	+	!	!
Coxeter, 2003	sleep duration	+	+	-	+	!	-
Cuellar, 2009	sleep duration	+	+	!	+	!	!
Diaper, 2004	sleep duration	!	+	+	+	!	!
Donath, 2000	sleep duration	!	+	+	+	!	!
Leathwood, 1985	sleep duration	!	+	+	+	!	!
Taibi, 2009	sleep duration	+	+	+	+	!	!
Schulz, 1994	sleep duration	!	+	+	+	!	!
Oxman, 2007	sleep duration	+	+	+	+	+	+
Dimpfel 2007	sleep efficiency	!	+	+	+	!	!
Shekhar, 2024	sleep efficiency	!	!	+	+	!	!
Cuellar, 2009	sleep efficiency	+	+	!	+	!	!
Diaper, 2004	sleep efficiency	!	+	+	+	!	!
Donath, 2000	sleep efficiency	!	+	+	+	!	!
Taibi, 2009	sleep efficiency	+	+	+	+	!	!
Taibi, 2009	sleep efficiency	+	+	+	+	!	!
Schulz, 1994	sleep efficiency	!	+	+	+	!	!
Aliakbari F, Rafieian M, 2018	sleep latency	!	!	+	-	!	-
Dimpfel 2007	sleep latency	!	+	+	+	!	!
Shekhar, 2024	sleep latency	!	!	+	+	!	!

Coxeter, 2003	sleep latency						
Cuellar, 2009	sleep latency						
Diaper, 2004	sleep latency						
Donath, 2000	sleep latency						
Jacobs, 2005	sleep latency						
Koetter, 2007	sleep latency						
Leathwood, 1985	sleep latency						
Taibi, 2009	sleep latency						
Taibi, 2009	sleep latency						
Schulz, 1994	sleep latency						
Oxman, 2007	sleep latency						
Vorbach, 1996	sleep quality						
Coxeter, 2003	sleep quality						
Cuellar, 2009	sleep quality						
Diaper, 2004	sleep quality						
Donath, 2000	sleep quality						
Dorn, 2000	sleep quality						
Jacobs, 2005	sleep quality						
Leathwood, 1982	sleep quality						
Taibi, 2009	sleep quality						
Oxman, 2007	sleep quality						
Ziegler, 2002	sleep_quality						
Coxeter, 2003	total adverse events						
Donath, 2000	total adverse events						
Dorn, 2001	total adverse events						
Koetter, 2007	total adverse events						
D1	Randomisation process						
D2	Deviations from the intended interventions						
D3	Missing outcome data						
D4	Measurement of the outcome						
D5	Selection of the reported result						

Low risk
 Some concerns
 High risk

Table A 3: Risk of bias for PICO 2

<u>Study ID</u>	<u>Outcome</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Rodenbeck, 1998	night awakenings	!	+	-	+	!	-
Gammoh, 2017	night awakenings	!	+	-	+	!	-
Taavoni, 2014	PSQI total score	!	+	+	+	!	!
Rodenbeck, 1998	sleep duration	!	+	-	+	!	-
Gammoh, 2017	sleep duration	!	+	-	+	!	-
Morin, 2005	sleep duration	-	+	-	+	!	-
Rodenbeck, 1998	sleep efficiency	!	+	-	+	!	-
Morin, 2005	sleep efficiency	-	+	-	+	!	-
Dreissing, 1996	sleep latency	+	+	+	+	!	!
Rodenbeck, 1998	sleep latency	!	+	-	+	!	-
Koetter, 2007	sleep latency	!	+	+	+	!	!
Gammoh, 2017	sleep latency	!	+	-	+	!	-
Morin, 2005	sleep latency	-	+	-	+	!	-
Dreissing, 1996	sleep quality	+	+	+	+	!	!
Leathwood, 1982	sleep quality	!	+	+	+	!	!
Gammoh, 2017	sleep quality	!	+	-	+	!	-
Morin, 2005	total adverse effects	-	+	-	+	!	-
Koetter, 2007	total adverse events	!	+	+	+	!	!
D1	Randomisation process	+	Low risk				
D2	Deviations from the intended interventions	!	Some concerns				
D3	Missing outcome data	-	High risk				
D4	Measurement of the outcome						
D5	Selection of the reported result						

Table A 4: Risk of Bias for PICO 3

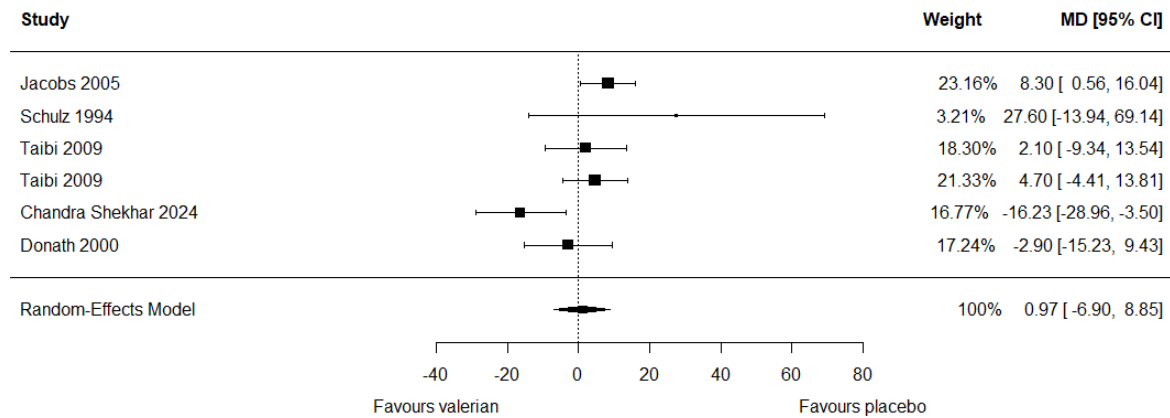
<u>Study ID</u>	<u>Outcome</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Gammoh, 2017	anxiety	!	+	-	+	!	-
Silva dos Santos, 2023	specific adverse events	!	+	+	+	!	!
Kennedy, 2006	State	!	+	-	+	!	-
Kennedy, 2006	Trait	!	+	-	+	!	-
D1	Randomisation process	+	Low risk				
D2	Deviations from the intended interventions	!	Some concerns				
D3	Missing outcome data	-	High risk				
D4	Measurement of the outcome						
D5	Selection of the reported result						

Table A 5: Risk of Bias for PICO 4

<u>Study ID</u>	<u>Outcome</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Melzer, 2009	anxiety	+	+	!	+	!	!
Meier, 2017	STAI-state	+	+	+	!	!	!
Meier, 2017	total adverse events	+	+	+	!	!	!
Melzer, 2009	total adverse events	+	+	!	+	!	!
D1	Randomisation process	+	Low risk				
D2	Deviations from the intended interventions	!	Some concerns				
D3	Missing outcome data	-	High risk				
D4	Measurement of the outcome						
D5	Selection of the reported result						

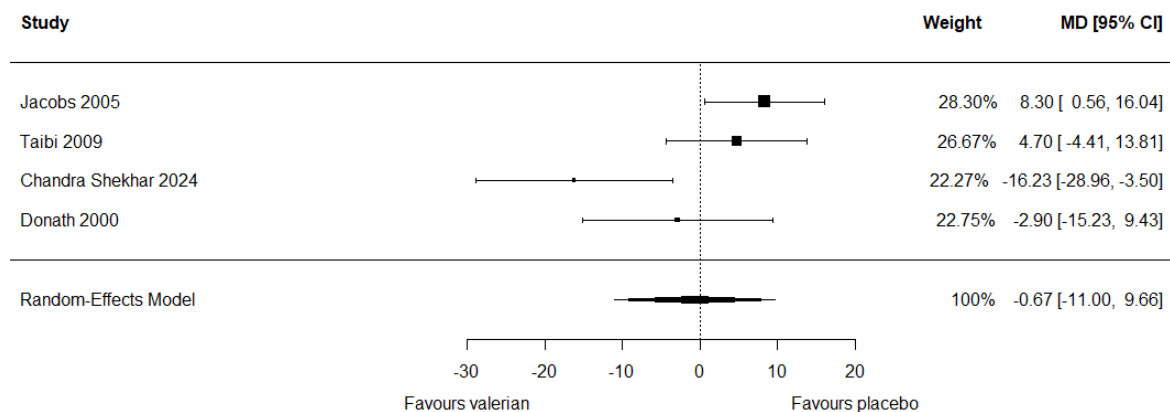
E. Results subgroup-analyses

Figure A 1 Forest-plot of subgroup meta-analysis on sleep latency comparing valerian versus placebo, follow up ≥ 7 days



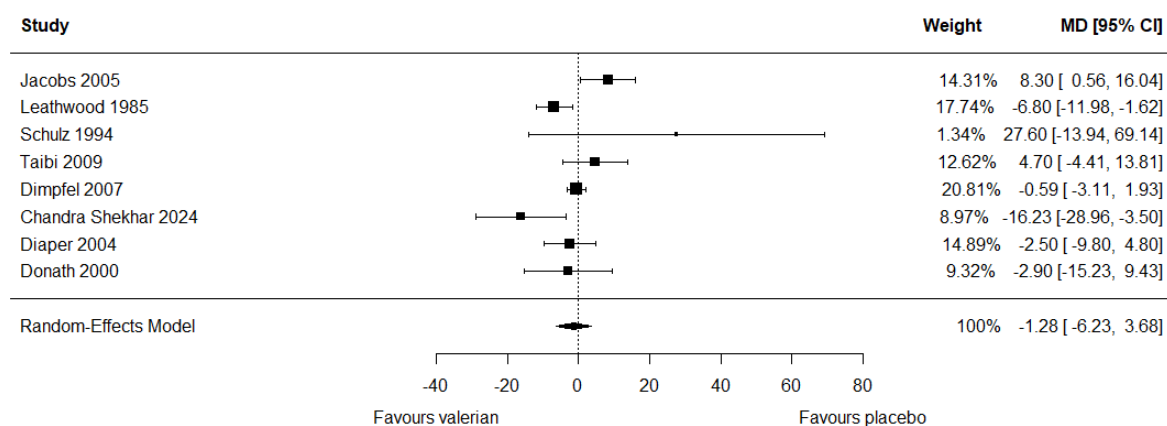
Abbreviations: CI, confidence interval; MD, mean difference

Figure A 2 Forest-plot of subgroup meta-analysis on sleep latency comparing valerian versus placebo, follow up ≥ 14 days



Abbreviations: CI, confidence interval; MD, mean difference

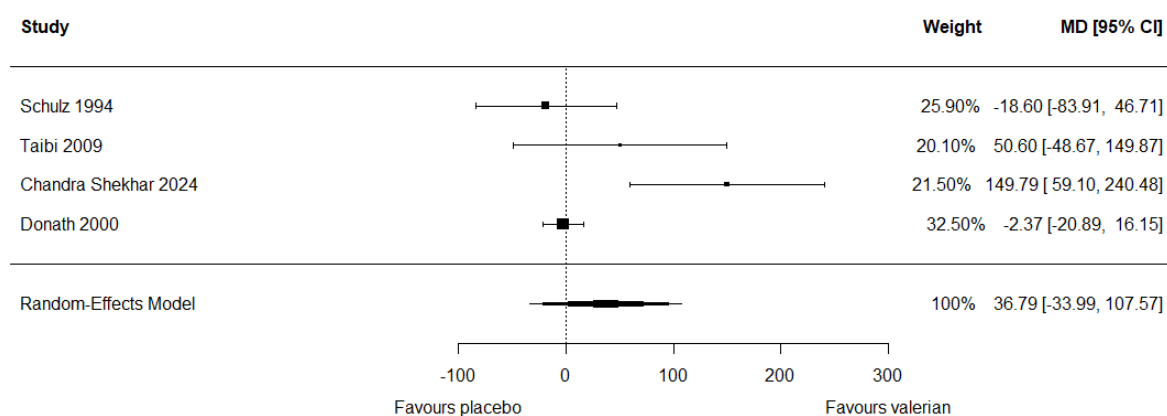
Figure A 3 Forest-plot of subgroup meta-analysis on sleep latency comparing valerian versus placebo, without comorbidities



Abbreviations: CI, confidence interval; MD, mean difference

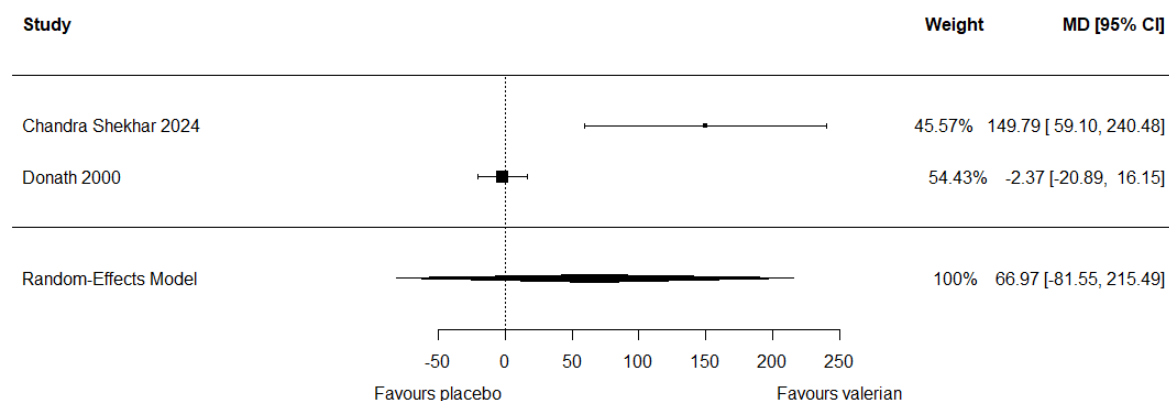
Notes: *Leathwood 1985, Dimpfel 2007 and Diaper 2004 had follow-up < 7 days*

Figure A 4 Forest-plot of subgroup meta-analysis on sleep duration comparing valerian versus placebo, follow up ≥ 7 days



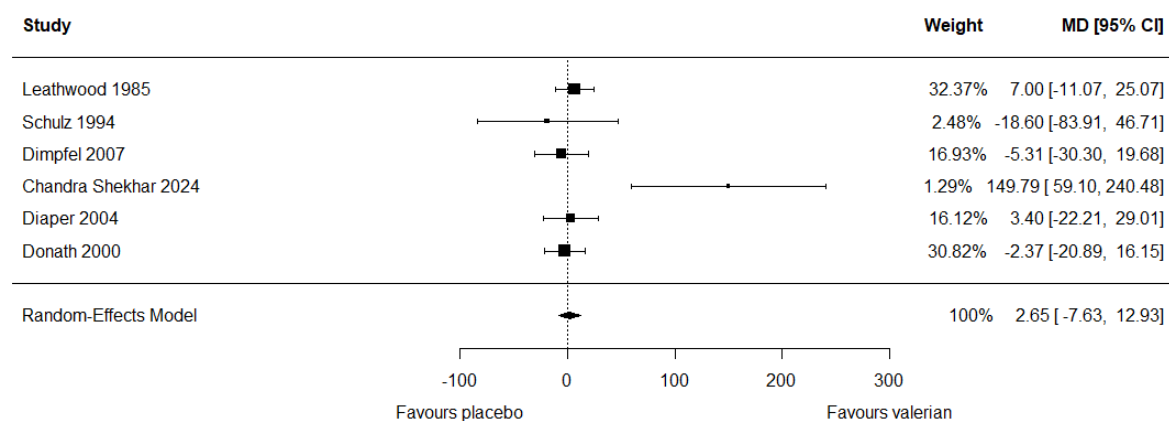
Abbreviations: CI, confidence interval; MD, mean difference

Figure A 5 Forest-plot of subgroup meta-analysis on sleep duration comparing valerian versus placebo, follow up ≥ 14 days



Abbreviations: CI, confidence interval; MD, mean difference

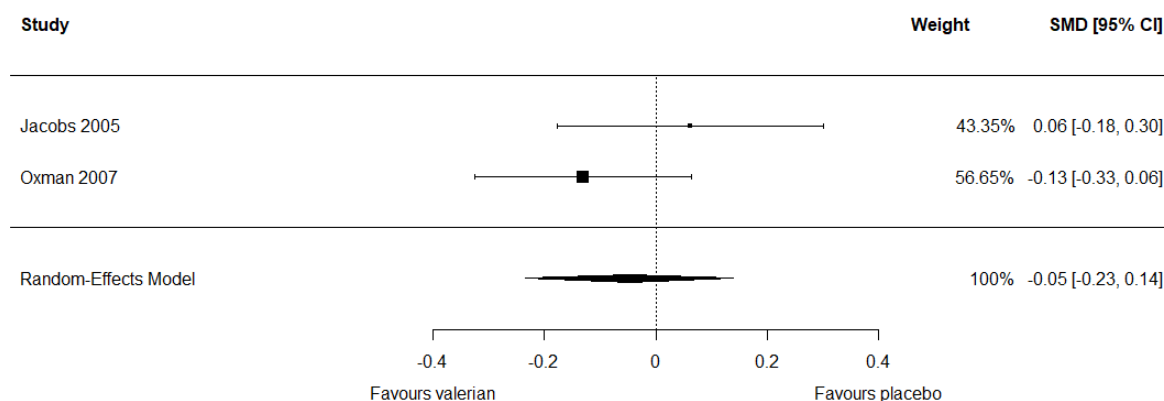
Figure A 6 Forest-plot of subgroup meta-analysis on sleep duration comparing valerian versus placebo, without comorbidities



Abbreviations: CI, confidence interval; MD, mean difference

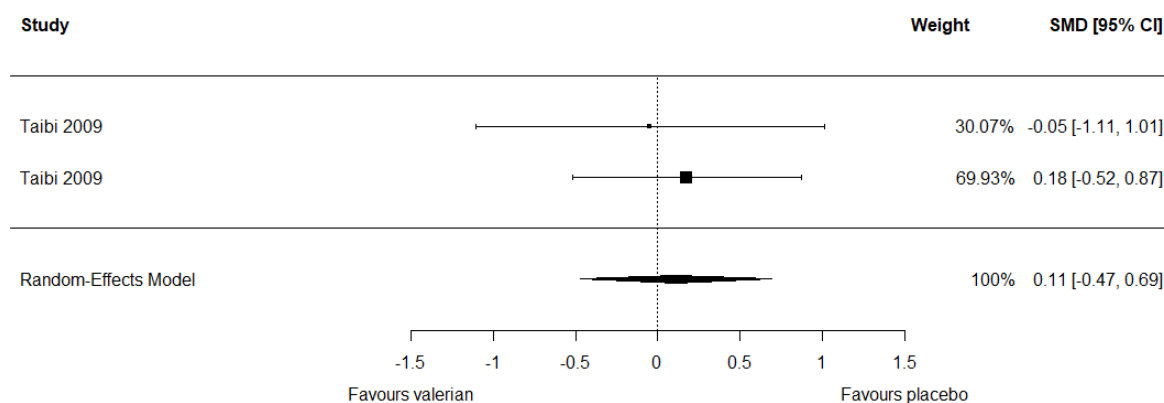
Notes: Leathwood 1985, Dimpfel 2007 and Diaper 2004 had follow-up < 7 days

Figure A 7 Forest-plot of subgroup meta-analysis on sleep quality comparing valerian versus placebo change from baseline scores, without comorbidities



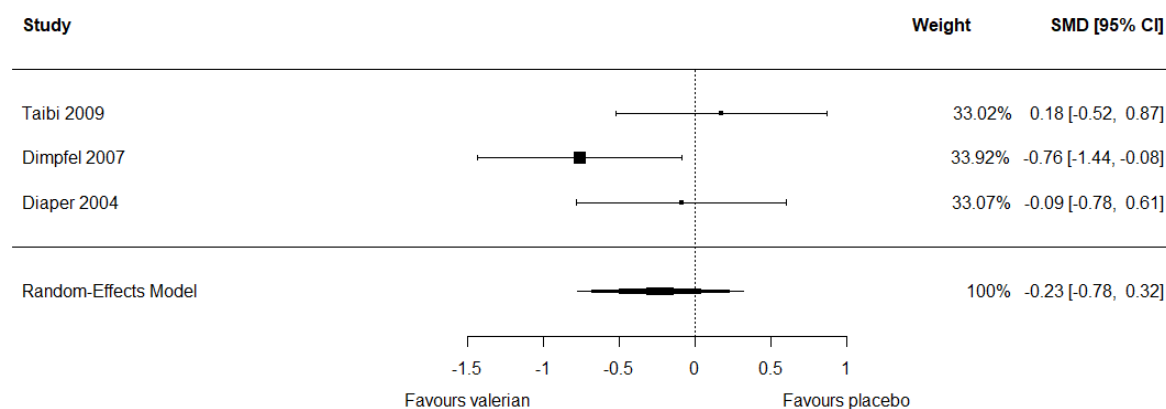
Abbreviations: CI, confidence interval; SMD, standardised mean difference

Figure A 8 Forest-plot of subgroup meta-analysis on night awakenings comparing valerian versus placebo post-intervention, follow up ≥ 7 days



Abbreviations: CI, confidence interval; SMD, standardised mean difference

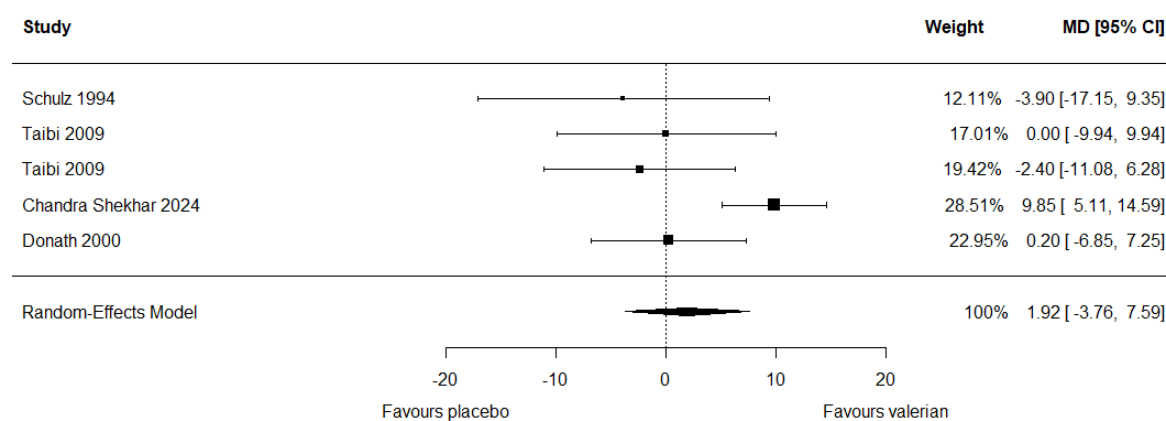
Figure A 9 Forest-plot of subgroup meta-analysis on night awakenings comparing valerian versus placebo post-intervention, without comorbidities



Abbreviations: CI, confidence interval; SMD, standardised mean difference

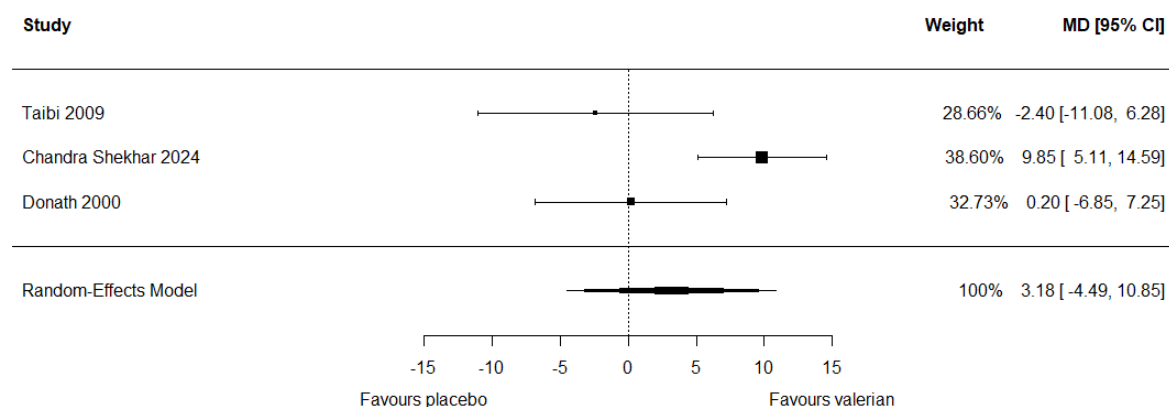
Notes: *Dimpfel 2007 and Diaper 2004 had follow-up < 7 days*

Figure A 10 Forest-plot of subgroup meta-analysis on sleep efficiency comparing valerian versus placebo, follow up ≥ 7 days



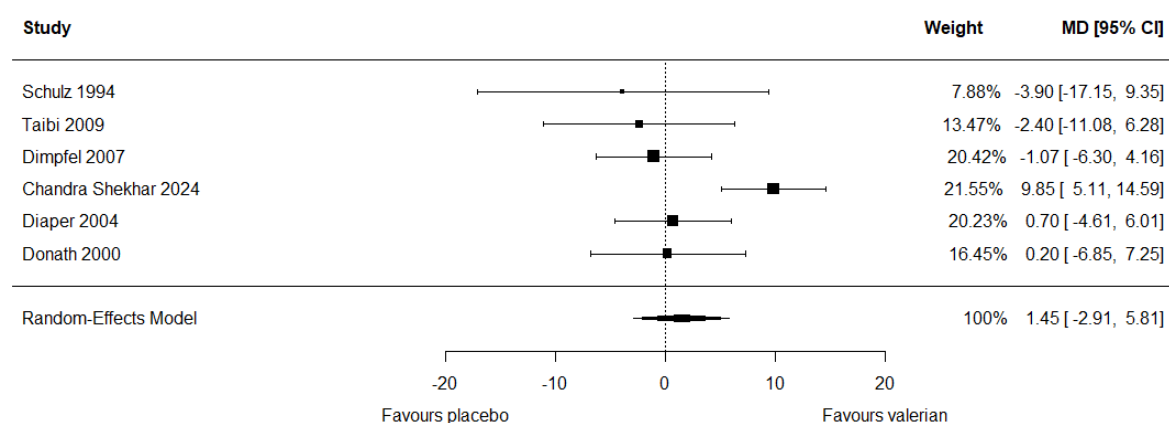
Abbreviations: CI, confidence interval; MD, mean difference

Figure A 11 Forest-plot of subgroup meta-analysis on sleep efficiency comparing valerian versus placebo, follow up ≥ 14 days



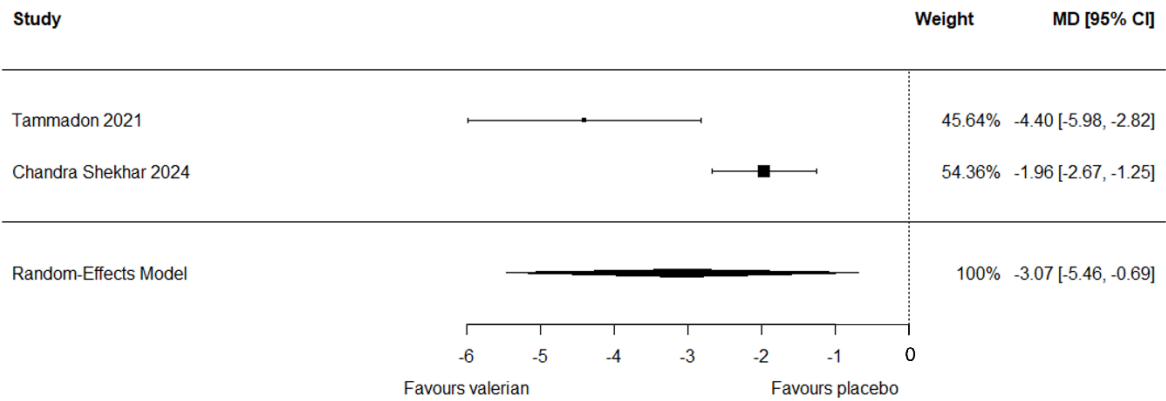
Abbreviations: CI, confidence interval; MD, mean difference

Figure A 12 Forest-plot of subgroup meta-analysis on sleep efficiency comparing valerian versus placebo, without comorbidities



Abbreviations: CI, confidence interval; MD, mean difference
 Notes: Dimpfel 2007 and Diaper 2004 had follow-up < 7 days

Figure A 13 Forest-plot of subgroup meta-analysis on PSQI total score comparing valerian versus placebo, without comorbidities



Abbreviations: CI, confidence interval; MD, mean difference

F. Input parameters for budget impact analysis

Table A 6: Relative risks of switching to benzodiazepines after policy change

Valerian-containing medicines	Relative risks by brand
Dormiplant	1.32
Hova	1.34
Redormin	1.32
Relaxane	1.32
Sedonium	1.32

Table A 7: Increased probability of switching by indication

	Dormiplant	Hova	Redormin	Relaxane	Sedonium	Total
Insomnia symptoms	0.50%	0.24%	6.39%	0.00%	0.07%	7.20%
Mental stress symptoms	0.36%	0.26%	0.00%	6.56%	0.00%	7.18%

Note: No increased switching to benzodiazepines was considered for symptoms of test anxiety.

Table A 8: Parameters and distributions for sensitivity analysis

Parameter name	Base case	SD	alpha	beta	Lower value	Higher value
Population size in year 1	8'962'258	448112.9	na	na	8'083'973	9'840'543
Population growth per year	0.01		na	na	0%	2%
Population aged 6 to 11 years old	550277	27513.85	na	na	496'351	604'203
Population aged 12 to 17 years old	538248	26912.4	na	na	485501	590995
Population aged 18 to 65 years old	5722922	286146.1	na	na	5162086	6283758
Population aged 12 to 65 years old	6261170	313058.5	na	na	5647587	6874753
Population aged over 65	1629483	81474.15	na	na	1469797	1789169
Prevalence of insomnia symptoms	0.25	0.025	74.75	224.25	0.20	0.30
Prevalence of mental stress symptoms	0.27	0.025	84.88	229.48	0.22	0.32
Prevalence of test anxiety symptoms	0.22	0.025	60.18	213.38	0.17	0.27
Indication split Dormiplant	0.83	0.06	28.99	5.94	0.69	0.93
Indication split Hova	0.76	0.09	17.47	5.42	0.57	0.91
Indication split Relaxane	0.26	0.05	18.22	51.70	0.17	0.37
Number of prescriptions Dormiplant	26224	1311	na	na	23'654	28'794
Number of prescriptions Hova	12083	604	na	na	10'898	13'267
Number of prescriptions Redormin	376377	18819	na	na	339'493	413'261
Number of prescriptions Relaxane	376377	18819	na	na	339'493	413'261
Number of prescriptions Sedonium	3134	157	na	na	2'827	3'441
Odds ratio of switching to psychotropic drugs due to policy effect	1.46	na	na	na	1.39	1.52
Probability of switching to psychotropic drugs from Dormiplant	0.22	0.04	19.20	66.94	0.14	0.32
Probability of switching to psychotropic drugs from Hova	0.20	0.04	15.45	63.05	0.12	0.29
Probability of switching to psychotropic drugs from Redormin	0.22	0.04	19.14	66.88	0.14	0.32
Probability of switching to psychotropic drugs from Relaxane	0.22	0.04	19.04	66.79	0.14	0.31
Probability of switching to psychotropic drugs from Sedonium	0.24	0.04	21.46	68.74	0.16	0.33
Number of patients on Dormiplant from SWICA data	783	39	na	na	707	860
Number of patients on Hova from SWICA data	450	23	na	na	406	494
Number of patients on Redormin from SWICA data	8266	413	na	na	7456	9076
Number of patients on Relaxane from SWICA data	9378	469	na	na	8459	10297
Number of patients on Sedonium from SWICA data	87	4	na	na	78	95
Price Dormiplant, 50 pieces	17.45	na	na	na	13.96	20.94
Price Dormiplant, 100 pieces	30.75	na	na	na	24.6	36.9
Price Hova, 30 pieces	10.60	na	na	na	8.48	12.72
Price Hova, 60 pieces	18.65	na	na	na	14.92	22.38
Price Redormin 250mg, 20 pieces	8.55	na	na	na	6.84	10.26
Price Redormin 250mg, 60 pieces	22.10	na	na	na	17.68	26.52
Price Redormin 500mg, 10 pieces	8.55	na	na	na	6.84	10.26
Price Redormin 500mg, 30 pieces	22.10	na	na	na	17.68	26.52
Price Relaxane, 20 pieces	11.25	na	na	na	9	13.5
Price Relaxane, 60 pieces	28.85	na	na	na	23.08	34.62
Price Sedonium, 25 pieces	9.90	na	na	na	7.92	11.88
Price Sedonium, 50 pieces	18.25	na	na	na	14.6	21.9