Health Technology Assessment

Scoping Report

Title	Sedative-Hypnotic Drugs for the treatment of Primary Chronic Insomnia Disorder
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Technology	Sedative-Hypnotic Drugs of ATC categories N05BA (benzodiazepine derivatives), N05CD (benzodiazepine derivatives), or N05CF (Z-drugs/benzodiazepine related drugs)
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Type of Technology	Pharmaceuticals

Executive Summary

Sedative-hypnotic drugs are used to reduce tension and anxiety and induce calm (sedative effect) or to induce sleep (hypnotic effect). Following clinical guidelines and product information, these drugs should not be prescribed for longer than four weeks for primary chronic insomnia disorder. Long-term treatment with sedative-hypnotic drugs is associated with falls, car accidents, a considerable potential for misuse, addiction, an increased incidence of infections, major depression, and increased overall mortality. Despite the potential serious harms and clear guideline recommendations, the rates of long-term use of sedative-hypnotic drugs have not changed meaningfully over time. This scoping report explores the evidence base for long-term use (> one month) of sedative-hypnotic drugs of the Anatomical Therapeutic Chemical (ATC) categories N05BA (benzodiazepines derivatives in the anxiolytics group), N05CD (benzodiazepine derivatives in the hypnotics and sedatives group), or N05CF (Z-drugs/ benzodiazepine related drugs) listed in the Swiss specialities list in adult patients with primary chronic insomnia disorder.

Systematic literature searches were conducted adhering to international methodological standards. The searches were performed in PubMed (MEDLINE), Embase.com, and in other complementary databases to identify relevant efficacy, effectiveness, safety, and cost-effectiveness evidence. For the efficacy, effectiveness, and safety, nine randomised clinical trials (RCTs) were included, and no pertinent systematic reviews were found. The focus of the RCTs included is on Z-drugs. Studies on benzodiazepines or benzodiazepines derivates did not fulfil the inclusion criteria. Since nine RCTs were included, it was decided not to proceed with the systematic literature search for comparative non-randomised studies. In the systematic literature search on cost-effectiveness, only two cost-effectiveness studies were included. These studies did not provide any evidence for the Swiss setting.

In a Health Technology Assessment (HTA) phase, relevant data from the included RCTs and cost-effectiveness studies found in the systematic literature search will be critically appraised, analysed,

and synthesised. Since no cost-effectiveness studies representative for the Swiss setting were identified, a de-novo cost-effectiveness model incorporating Swiss specific costs will be developed. In addition, a budget impact may be estimated provided availability of essential data. Finally, a grey literature search on social, legal, ethical, and organisational aspects related to re-evaluating reimbursement of sedative-hypnotic medication use for primary chronic insomnia disorder will be performed.

Zusammenfassung

Sedativ-hypnotische Arzneimittel werden eingesetzt, um Anspannung und Ängste zu vermindern und Entspannung zu fördern (sedierende Wirkung) oder Schlaf zu induzieren (hypnotische Wirkung). Gemäss klinischen Leitlinien und Produktinformationen sollten diese Arzneimittel bei chronischer primärer Insomnie für maximal vier Wochen verordnet werden. Die Langzeittherapie mit sedativ-hypnotischen Arzneimitteln wurde mit Stürzen, Autounfällen, einem erheblichen Missbrauchspotenzial, Sucht, einem verstärkten Auftreten von Infektionen, schweren Depressionen sowie einer erhöhten Gesamtsterblichkeit in Zusammenhang gebracht. Trotz potenziell schwerwiegender Schäden und eindeutiger Leitlinienempfehlungen ist es im Verlauf der Zeit zu keiner wesentlichen Veränderung der Häufigkeit der Langzeitanwendung sedativ-hypnotischer Arzneimittel gekommen. Mit diesem Scoping-Report wird die Evidenzbasis für die Langzeitanwendung (> ein Monat) von sedativ-hypnotischen Arzneimitteln der anatomisch-therapeutisch-chemischen (ATC) Kategorien N05BA (Benzodiazepin-Derivate aus der Gruppe der Anxiolytika), N05CD (Benzodiazepin-Derivate in der Gruppe der Hypnotika und Sedativa) oder N05CF (Z-Drugs/Benzodiazepin-verwandte Arzneimittel), die in der Schweizer Spezialitätenliste aufgeführt sind, bei erwachsenen Patienten mit chronischer primärer Insomnie abgeklärt.

Systematische Literaturrecherchen wurden unter Einhaltung internationaler methodischer Standards durchgeführt. Diese erfolgten in PubMed (MEDLINE), Embase.com und anderen ergänzenden Datenbanken mit dem Ziel, relevante Evidenz zur Wirksamkeit, Effektivität, Sicherheit und Kosteneffektivität zu identifizieren. Im Hinblick auf die Wirksamkeit, Effektivität und Sicherheit wurden neun randomisierte klinische Studien (RCTs) eingeschlossen. Es wurden keine relevanten systematischen Reviews gefunden. Der Schwerpunkt der eingeschlossenen RCTs lag auf den Z-Drugs. Die Studien zu Benzodiazepinen oder Benzodiazepinderivaten erfüllten die Einschlusskriterien nicht. Da neun RCTs eingeschlossen wurden, wurde von der Fortsetzung der systematischen Literaturrecherche nach vergleichenden nicht-randomisierten Studien abgesehen. In die systematische Literaturrecherche zur Kosteneffektivität wurden nur zwei Kosteneffektivitätsstudien eingeschlossen. Diese Studien lieferten keine Evidenz, die für die Schweiz relevant wäre.

In der Health Technology Assessment (HTA)-Phase werden relevante Daten aus den eingeschlossenen RCTs und Kosteneffektivitätsstudien, die in der systematischen Literaturrecherche gefunden wurden, kritisch diskutiert, analysiert und synthetisiert. Da keine für den Kontext der Schweiz repräsentativen Kosteneffektivitätsstudien gefunden werden konnten, wird ein de-novo Kosteneffektivitätsmodell entwickelt, in dem die für die Schweiz spezifischen Kosten berücksichtigt werden. Sofern die

wesentlichen Daten vorliegen, kann darüber hinaus die Budgetauswirkung abgeschätzt werden. Schliesslich wird eine graue Literaturrecherche bezüglich sozialer, rechtlicher, ethischer und organisatorischer Fragen im Zusammenhang mit der Neubeurteilung der Erstattung von sedativ-hypnotischen Arzneimitteln bei chronischer primärer Insomnie durchgeführt.

Résumé

Les sédatifs-hypnotiques sont utilisés pour réduire la tension et l'anxiété et pour relaxer (effet sédatif). Selon les directives cliniques et les informations sur les produits, la durée de prescription de ces médicaments ne doit pas dépasser quatre semaines en cas d'insomnie chronique primaire. La prise prolongée de sédatifs-hypnotiques peut provoquer des chutes, des accidents de la route, un usage abusif, une dépendance, une augmentation des infections, une dépression sévère et une augmentation de la mortalité générale. Malgré les dangers pour la santé et les recommandations claires des directives cliniques, le taux d'utilisation à long terme de ces médicaments n'a pas changé de manière significative au cours des dernières années. Le présent rapport explore les données probantes relatives à l'utilisation prolongée (supérieure à un mois) de sédatifs-hypnotiques appartenant aux catégories suivantes de la classification anatomique, thérapeutique et chimique (ATC) : N05BA (dérivés des benzodiazépines appartenant au groupe des anxiolytiques), N05CD (dérivés des benzodiazépines appartenant au groupe des hypnotiques et sédatifs) et N05CF (médicaments apparentés aux benzodiazépines figurant dans la liste des spécialités pour les patients adultes présentant une insomnie chronique primaire).

Les recherches systématiques dans la littérature se sont fondées sur les normes méthodologiques internationales. Elles ont été réalisées dans PubMed (MEDLINE), Embase.com et dans d'autres bases de données complémentaires afin d'identifier les preuves pertinentes de l'efficacité, de l'innocuité et de l'économicité des sédatifs-hypnotiques. En ce qui concerne l'efficacité et l'innocuité, neuf essais cliniques randomisés (RCT pour *randomised clinical trials*) ont été inclus dans les recherches. Les résultats obtenus n'ont permis d'identifier aucune revue systématique. Les RCT portaient sur les médicaments commençant par la lettre *z*. Les études réalisées sur les benzodiazépines et leurs dérivés ne répondaient pas aux critères d'inclusion. Étant donné que neuf RCT ont été inclus, il a été décidé de ne pas poursuivre la recherche systématique d'essais comparatifs non randomisés. Dans les recherches systématiques relatives à l'économicité, seules deux études sur le sujet ont été incluses. Celles-ci n'ont pas fourni de preuves pour le contexte suisse.

Durant la phase d'évaluation des technologies de la santé (ETS ou HTA pour *health technology assessment*), les données pertinentes extraites des RCT et des études sur l'économicité identifiées dans les recherches systématiques de la littérature feront l'objet d'une évaluation critique, d'une analyse et d'une synthèse. Dans la mesure où aucune étude sur le rapport coût-efficacité représentative du contexte suisse n'a été identifiée, un modèle d'économicité *de novo* intégrant les coûts spécifiques à la Suisse sera élaboré. En outre, l'impact budgétaire pourra être estimé sous réserve de la disponibilité des données essentielles. Enfin, une recherche de la littérature grise sera effectuée pour étudier les aspects sociaux, légaux, éthiques et organisationnels liés à la réévaluation du remboursement des sédatifs-hypnotiques utilisés dans le traitement de l'insomnie chronique primaire.

Sintesi

I medicamenti sedativo-ipnotici vengono utilizzati per ridurre la tensione e l'ansia nonché per indurre la calma (effetto sedativo) o il sonno (effetto ipnotico). Secondo le linee guida cliniche e le informazioni sul prodotto, questi medicamenti non dovrebbero essere prescritti per più di quattro settimane per l'insonnia primaria cronica. Il trattamento a lungo termine con medicamenti sedativo-ipnotici è associato a cadute, incidenti automobilistici, un notevole potenziale di abuso, dipendenza, un aumento dell'incidenza di infezioni, depressione maggiore e un aumento della mortalità complessiva. Nonostante i potenziali gravi danni e le raccomandazioni chiare delle linee guida, l'impiego a lungo termine dei medicamenti sedativo-ipnotici non ha subito variazioni significative nel corso del tempo. Il presente rapporto di scoping ricerca evidenze sull'impiego a lungo termine (per più di un mese) in pazienti adulti affetti da insonnia primaria cronica dei medicamenti sedativo-ipnotici delle categorie del sistema di classificazione anatomico, terapeutico e chimico (ATC) N05BA (derivati delle benzodiazepine nel gruppo degli ansiolitici), N05CD (derivati delle benzodiazepine nel gruppo degli ipnotici e dei sedativi) o N05CF (medicamenti Z o correlati alle benzodiazepine) figuranti nell'elenco delle specialità svizzero.

Sono state condotte ricerche bibliografiche sistematiche in conformità agli standard metodologici internazionali in PubMed (MEDLINE), Embase.com e in altre banche dati complementari per identificare evidenze rilevanti di efficacia, efficienza e sicurezza, nonché di efficienza dal punto di vista dei costi. Per l'efficacia, l'efficienza e la sicurezza sono stati inclusi nove studi clinici randomizzati (SCR) e non sono state trovate revisioni sistematiche pertinenti. Gli SCR inclusi sono incentrati sui medicamenti correlati alle benzodiazepine. Gli studi sulle benzodiazepine o sui loro derivati non hanno soddisfatto i criteri di inclusione. Poiché sono stati inclusi nove SCR, si è deciso di rinunciare alla ricerca bibliografica sistematica di studi non randomizzati comparativi. Nella ricerca bibliografica sistematica sull'efficienza dal punto di vista dei costi sono stati inclusi soltanto due studi, che non hanno fornito alcuna evidenza per il setting svizzero.

In una fase di Health Technology Assessment (HTA) saranno valutati criticamente, analizzati e sintetizzati i dati rilevanti degli SCR e degli studi di efficienza dal punto di vista dei costi emersi dalla ricerca bibliografica sistematica. Poiché non sono stati identificati studi di efficienza dal punto di vista dei costi pertinenti per la Svizzera, sarà sviluppato ex novo un modello di efficienza dei costi che includa costi specifici per la Svizzera. Inoltre, potrà essere stimato l'impatto sul budget, purché siano disponibili dati essenziali. Infine sarà effettuata una ricerca bibliografica sulla letteratura grigia per quanto riguarda gli aspetti sociali, legali, etici e organizzativi legati al riesame della rimunerazione dei medicamenti sedativo-ipnotici utilizzati per il trattamento dell'insonnia primaria cronica.

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Abbreviations and acronyms

ATC	Anatomical Therapeutic Chemical
BI	Budget impact
BZ	Benzodiazepine
BZD	Benzodiazepine Derivative
BZRA	Benzodiazepine Receptor Agonist
CADTH	Canadian Agency for Drugs and Technologies
CBT-I	Cognitive Behavioural Therapy for Insomnia
CHEC	Consensus Health Economic Criteria
CL	Confidence limit
CRD	Centre for Reviews and Dissemination
DARTH	Decision Analysis in R for Technologies in Health
DDD	Defined daily doses
DSM	Diagnostic and Statistical Manual of Mental Disorders
EED	Economic Evaluation Database
EO	Economic Outcome
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public Health
GABA	Gamma-aminobutyric acid
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICDS	International Classification of Sleep Disorders
ISPOR - SMDM	International Society for Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making
LIM	Limitations for reimbursement
LYs	Life years
N.A.	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OECD	Organisation for Economic Co-operation and Development
PICO	Population, intervention, comparator, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year

RCT	Randomised controlled trial
SOL	Sleep Onset Latency
SL	Specialities List
SR	Systematic Review
TR	Text Revision
TST	Total Sleep Time
Z-drugs	Benzodiazepine related drugs
ZIN	Zorginstituut Nederland

Objective of the HTA scoping report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of long-term use of sedative-hypnotic drugs in patients with primary chronic insomnia disorder because their efficacy, effectiveness, safety, and cost-effectiveness have been questioned by the Swiss health insurance association santésuisse and a limitation/restriction of these drugs may be considered.

In the scoping phase, the necessity and feasibility of conducting a full health technology assessment (HTA) on the efficacy, effectiveness, safety, and cost-effectiveness of long-term use of sedative-hypnotic drugs from the Anatomical Therapeutic Chemical (ATC) categories N05BA (benzodiazepine derivatives), N05CD (benzodiazepine derivatives), and N05CF (Z-drugs/benzodiazepine related drugs) to treat primary chronic insomnia disorder is examined and a central research question is presented based on systematic literature searches. In addition, operational key questions are formulated, in order to determine the full scope of a potential HTA report. The target population, the appropriate comparator, and the relevant health outcomes are defined.

Based on the identified evidence, the feasibility of a full HTA is assessed by the FOPH, and it will be decided whether a full HTA report is going to be commissioned for this topic or not.

1 Policy question and context

Persons with sleep problems may suffer one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and in some cases, nonrestorative or poor quality of sleep. In addition, many patients also complain of daytime symptoms, including fatigue, memory and concentration impairment, and decreased social and academic performance. Swiss surveys on sleep issues revealed the prevalence of chronic insomnia disorder amongst the Swiss population. In 2017, 6.3% (4.8% men and 7.7% women) reported moderate to severe problems falling asleep and/or sleeping through the night.[1] In an earlier survey in 2012, 8% of the Swiss population reported to have taken any sedative-hypnotic drug in the seven days preceding the survey. The use of sedative-hypnotic drugs increased significantly with age, reaching a peak in people aged 75 years and over.[2]

The prescription-only drugs with anxiolytic, sedative, muscle-relaxing, and hypnotic effects listed in the Swiss speciality list in the ATC categories N05BA (benzodiazepines derivatives), N05CD (benzodiazepine derivatives), and N05CF (Z-drugs/benzodiazepine related drugs) are reimbursed by the Swiss mandatory health insurance (with limitations for benzodiazepines[a]). Following the product information, these drugs should not be prescribed for longer than four weeks for primary chronic insomnia disorder. Long-term treatment with sedative-hypnotic drugs are associated with falls, car accidents, a considerable potential for misuse, addiction, an increased incidence of infections, major depression, and increased overall mortality.[3–5] Despite the potential serious harms and clear guideline recommendations, the rates of long-term benzodiazepine use have not changed meaningfully over time in Europe, USA, Canada, or Australia.[6]

The total costs for drugs of ATC categories N05BA, N05CD, and N05CF were 47 million Swiss francs in 2019, and have been decreasing since 2014 by around 13%.[7]

The applicant suggests that Switzerland should consider adopting policies restricting the long-term use of sedative-hypnotic drugs from the ATC categories N05BA, N05CD, and N05CF for primary chronic insomnia disorder. An example of the impact of reimbursement restriction is a study conducted in the Netherlands, after the Dutch compulsory health insurance abolished reimbursement of benzodiazepines for anxiety and sleeping disturbance in 2009, in order to avoid irregular (chronic) use of benzodiazepines. The study showed that the volume of the dispensed prescriptions and doses of benzodiazepines

[a] Further details are reported at http://www.xn--spezialittenliste-yqb.ch/ShowPreparations.aspx?searchType=SUBSTANCE

and new diagnoses for anxiety and sleeping disturbance decreased after this restriction, leading to the conclusion that there has been an overuse of benzodiazepines in the past.

The planned HTA aims to perform a focused assessment of the efficacy, effectiveness, safety, costs, cost-effectiveness, and budget impact of sedative-hypnotic drugs from the ATC categories N05BA, N05CD, and N05CF for primary chronic insomnia disorder in Switzerland.

2 Research question

In this chapter, we outline the research questions on which the systematic literature searches are based. The central research question is divided into four sub-questions. Non-pharmacological treatments and short-term use of sedative-hypnotic drugs were elected as separate comparators in order to provide comprehensive insights of risks and costs of long-term use (daily or intermitted use) of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder.

Central research question

What are the efficacy[b], effectiveness[c], and, safety[d], as well as the cost-effectiveness and budget impact of long-term drug use (> one month)[e] of treatment with sedative-hypnotic drugs of ATC categories N05BA (benzodiazepines derivatives), N05CD (benzodiazepine derivatives), or N05CF (Z-drugs/ benzodiazepine related drugs) listed in the Swiss specialities list in adult patients with primary chronic insomnia disorder?

[b] Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (i.e. internal validity).

[c] Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (i.e. external validity).

[d] Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (i.e. serious adverse events) and those that occur repetitively and the most frequent (highest rate).

[e] For the purpose of the present research, long-term use is defined as greater than one month. When referring to other studies, the definition in the corresponding study is used.

Research question for the efficacy, effectiveness, and safety systematic literature search

- What are the efficacy, effectiveness, and safety of long-term use (> one month) of the sedative-hypnotic drugs of ATC categories N05BA (benzodiazepines derivatives), N05CD (benzodiazepine derivatives), or N05CF (Z-drugs/benzodiazepine related drugs) listed in the Swiss specialties list in adult patients with primary chronic insomnia disorder compared to placebo, no treatment, or other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy)?
- What are the efficacy, effectiveness, and safety of long-term use (> one month) of the sedative-hypnotic drugs of ATC categories N05BA (benzodiazepines derivatives), N05CD (benzodiazepine derivatives), or N05CF (Z-drugs/benzodiazepine related drugs) listed in the Swiss specialities list in adult patients with primary chronic insomnia disorder compared to short-term use (≤ one month) of these sedative-hypnotic drugs?

Research question for the cost-effectiveness systematic literature search

- What are the cost-effectiveness and budget impact of long-term use (> one month) of the sedative-hypnotic drugs of ATC categories N05BA (benzodiazepine derivatives), N05CD (benzodiazepine derivatives or N05CF (Z-drugs/benzodiazepine related drugs) listed in the Swiss specialties list in adult patients with primary chronic insomnia disorder compared to placebo, no treatment, or other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy?
- What are the cost-effectiveness and budget impact of long-term use (> one month) of the sedative-hypnotic drugs of ATC categories N05BA (benzodiazepine derivativesN05CD (benzodiazepine derivatives), or N05CF (Z-drugs/benzodiazepine related drugs) listed in the Swiss specialities list in adult patients with primary chronic insomnia disorder compared to short-term use (≤ one month) of these sedative-hypnotic drugs?

3 Medical background

Insomnia is considered a disorder of hyperarousal, experienced as a state of hypervigilance during the night, and difficulty initiating and maintaining sleep.[8] For the purpose of our research questions, insomnia is limited to primary insomnia where patients do not suffer from another disorder causing insomnia.

Insomnia is consensually defined as:

(a) difficulty of falling asleep (sleep initiating insomnia), the occurrence of nocturnal awakenings with difficulties getting back to sleep (sleep maintenance insomnia), an early morning awakening (sleep off-set insomnia), or non-refreshing or non-restorative sleep, and often some combination thereof;

(b) occurring at least three times a week for at least one month; and

(c) producing clinically significant distress or impairment in social, occupational, or other important areas of daytime functioning.[8,9]

Evaluation of insomnia symptoms can be challenging due to its correlation with other comorbidities. According to the European guideline for the diagnosis and treatment of insomnia, the diagnostic procedure can include a clinical interview consisting of a sleep history (sleep habits, sleep environment, work schedules, circadian factors), the use of sleep questionnaires and sleep diaries, questions about somatic and mental health, a physical examination, and additional measures if indicated (i.e. blood tests, electrocardiogram, electroencephalogram).[10]

The most commonly used disease classification systems are the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR, DSM-5), the International Classification of Diseases (ICD-10), and the International Classification of Sleep Disorders (ICDS-2, ICSD-3).[9,11] Studies found that, for the same population, the ICD-10 yields very low numbers of diagnoses compared to the DSM IV-TR or the ICDS-2.[11] This stems from stricter definition of insomnia in the ICD-10 compared to the other categorisation frameworks.[12] Other modalities assisting in the evaluation of insomnia are wrist actigraphy, numerous insomnia rating scales recording symptoms and monitoring the response to treatment, and The Pittsburgh Sleep Quality Index, a 19-item questionnaire which measures seven domains of sleep over the prior month.[10,12]

According to the DSM-5, insomnia is considered chronic if a person has trouble falling asleep or staying asleep at least three nights per week for three months or longer. Chronic insomnia is thought to be highly prevalent, although estimates vary from less than 5% to as high as 40%.[13] In the Swiss health survey of 2017, 31% of women reported “some”, while 9.4% reported severe sleeping problems (falling asleep as well as awakening), and among men, 22.6% reported “some” and 5.3% reported severe sleeping problems.[14] Various risk factors associated with increased prevalence of chronic insomnia include older age, female gender, comorbid medical and psychiatric conditions like depression, chronic illness, or working rotating night shift.[8,12,15–17] Due to its chronicity, insomnia is associated with substantial impairments in an individual’s quality of life. Insomnia impairs cognitive and physical functioning, and is associated with a wide range of impaired daytime functions across several emotional, social, and physical domains.[16] Compared with good sleepers, patients with insomnia are more prone to accidents (home,

car, and work accidents), have higher rates of work absenteeism, diminished job performance, decreased quality of life, and increased healthcare utilisation through comorbidities (e.g. chronic obstructive pulmonary diseases, diabetes mellitus, and chronic kidney diseases).[9,10]

4 Technology

4.1 Technology description

The most commonly and effectively used drugs in the short-term treatment of insomnia (≤ one month) are benzodiazepine receptor agonists (BZRAs), which are subdivided into benzodiazepines (BZs), benzodiazepine derivatives (BZDs), and benzodiazepine related drugs (also known as 'Z-drugs'). BZRAs bind non-selectively onto the Gamma-aminobutyric acid (GABA)-A receptors to promote sleep by increasing the inhibitory effect of GABA on neuronal excitability, affecting mainly neurons located in the preoptic area and in specific hypothalamic nuclei.[18]

BZRAs have been shown to be effective in the acute treatment of insomnia. BZs are efficacious in terms of sleep onset latency (SOL) and total sleep time (TST), and they are used clinically for different types of insomnia: short-acting medications are indicated for patients with SOL, while longer-acting medications are preferable for patients with sleep maintenance insomnia.[19,20] Despite efficacy, BZs, BZDs, and Z-drugs cause important side effects such as cognitive and motor impairments, and somnolence.[19–21] In particular, long duration therapies with BZs may result in the appearance of dependency, withdrawal symptoms (e.g. rebound insomnia) and worsening of sleep parameters, such as sleep quality and sleep duration.[21]

A variety of negative side effects of BZs and Z-drugs include risk of falling, cognitive difficulties, abuse and dependence on the drug.[3] In addition to the development of addiction, physical dependence and tolerance are also areas of concern, and limit their long-term use as well.[18] International guidelines, such as those issued by the American Psychiatric Association, recommend prescription for short-term treatment no longer than four weeks only to avoid these negative consequences. Still, prevalence of long-term use is high and appear to increase with age.[3]

Table 1 shows the sedative-hypnotic drugs approved by the Swiss Agency for Therapeutic Products (Swissmedic) and listed in the Swiss specialities list in the ATC categories N05BA, N05CD, and N05CF. Not all the substances are indicated for primary chronic insomnia disorder, some are for anxiety or epilepsy only. According to the approved product information, all drugs listed in Table 1 should not be given longer than four weeks for primary chronic insomnia disorder, although potentially appropriate in certain circumstances like palliative care.

Table 1 Sedative-hypnotic drugs of ATC categories N05BA, N05CD, and N05CF listed in the Swiss specialities list

ATC Code	Active substance	DDD	Limitation in SL	Main indication in product information
Benzodiazepine derivatives				
N05BA01	diazepam	10mg	yes	Anxiety, agitation, and tension; in the form of an anxious mood or anxious behaviour, and/or functional vegetative or motor symptoms (palpitations, sweating, insomnia, tremor, nervous restlessness.)
N05BA04	oxazepam	50mg	yes	States of tension, excitement, and fear. Supplementary treatment of anxiety states in depression. Short-term treatment of sleep disorders caused by anxiety and tension
N05BA05	potassium clorazepate	20mg	yes	Anxiety states and the resulting restlessness, tension, agitation, neurovegetative and psychosomatic disorders and complaints
N05BA06	lorazepam	2.5mg	yes	Anxiety, tension, and agitation; short-term treatment of sleep disorders caused by anxiety and tension
N05BA08	bromazepam	10mg	yes	Anxiety and tension, adjuvant for anxiety in depression, nervous tension, restlessness and insomnia caused by anxiety and tension
N05BA09	clobazam	20mg	no	Anxiety and its functional manifestations and epilepsy
N05BA10	ketazolam[f]		yes	Psychic tension, agitation, restlessness, irritability, nervousness, and insomnia
N05BA11	prazepam	30mg	yes	Anxiety, tension, excitement, and restlessness
N05BA12	alprazolam	1mg	yes	Anxiety, with depression
N05BA56	lorazepam, diphenhydramin[f]		no	Insomnia and insomnia of clinically significant severity; difficulty falling asleep, frequent waking up at night)
Benzodiazepine derivatives				
N05CD01	flurazepam	30mg	no	Sleep disorders, difficulty falling asleep, frequent waking up at night or too early; sleep disorders associated with anxiety states and as a result of chronic diseases
N05CD02	nitrazepam	5mg	no	Sleep disorders, e.g. due to irritability, overstrain, anger, anxiety, worry, tension, and oppression
N05CD03	flunitrazepam	1mg	no	Short-term treatment sleep disorders, difficulty falling asleep, frequent waking up at night, waking up too early in the morning
N05CD06	lormetazepam	1mg	no	Short-term treatment of sleep disorders
N05CD07	temazepam	20mg	no	Short-term treatment of sleep disorders
N05CD08	midazolam	15mg	no	Short-term treatment of sleep disorders; sleep rhythm disturbances, difficulty falling asleep, or difficulty in falling back to sleep. Sedation in premedication before surgical or diagnostic procedures
Benzodiazepine related drugs, Z-drugs				
N05CF01	zopiclone	7.5mg	no	Short-term treatment (usually less than 10 days) of sleep disorders
N05CF02	zolpidem	10mg	no	Short- term treatment of insomnia

Abbreviations: DDD= defined daily doses, SL = Swiss specialities list

[f] No available information on DDD.

4.2 Alternative technologies

There is a variety of pharmacological treatment alternatives to BZRAs, like antihistamines, antipsychotics, antidepressants, melatonin, melatonin receptor agonists, complementary and alternative treatments (e.g. homeopathy), as well as phytotherapeutics. There are also non-pharmacological interventions to improve sleep and primary chronic insomnia disorder, like sleep hygiene or cognitive behavioural therapy for insomnia (CBT-I). Sleep hygiene refers to a list of behavioural rules designed to increase the likelihood of sleeping well. CBT-I consists of sleep hygiene instructions, stimulus control therapy, sleep restriction therapy, relaxation, and cognitive therapy.[17] A study found CBT-I in combination with pharmacotherapy to be more effective than CBT-I alone.[22] According to the European Guideline for the diagnosis and treatment of insomnia, CBT-I is recommended as first-line treatment for primary chronic insomnia in adults of any age, whilst antipsychotics, melatonin, and phytotherapeutics, as well as complementary and alternative treatments (e.g. homeopathy, acupuncture) are not recommended.[10] Swiss studies on primary chronic insomnia disorder refer to the Swissmedic drug prescription recommendations, European guideline, or international guidelines for the diagnosis and treatment of insomnia. [23,24]

5 PICO

The PICO (population-intervention-comparison-outcome) method was used to specify the questions for the systematic literature searches and is outlined in the table below.

Table 2: PICO for the systematic literature searches

P:	Adult patients with primary chronic insomnia disorder
I:	Long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss speciality list • N05BA, benzodiazepine derivatives: o diazepam o oxazepam o potassium clorazepate o lorazepam o bromazepam o clobazam o ketazolam o prazepam

	o alprazolam o lorazepam, diphenhydramine • N05CD, benzodiazepine derivatives: o flurazepam o nitrazepam o flunitrazepam o lormetazepam o temazepam o midazolam • N05CF, benzodiazepine related drugs/Z-drugs: o zopiclone o zolpidem
C:	1. Placebo; No treatment; Other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy) 2. Direct comparison with short-term use (≤ one month) of sedative-hypnotic drugs of ATC categories N05BA (benzodiazepine derivatives), N05CD (benzodiazepine derivatives), or N05CF (Z-drugs/ benzodiazepine related drugs) listed in the Swiss speciality list
O (clinical):	**Efficacy/effectiveness of benzodiazepine derivatives/Z-drugs:** a. Clinically relevant sleep improvement related to: • Sleep onset latency (i.e. amount of time between lying down to sleep and the onset of sleep); and/or • Wakefulness after sleep onset (i.e. amount of time spent awake in bed following the first attainment of sleep); and/or • Sleep duration (i.e. total amount of time spent asleep); and/or • Sleep efficiency (i.e. amount of time spent asleep as a percentage of the total time spent in bed); and/or • Perceived sleep quality; and/or • Perceived fatigue during daytime. b. Withdrawal due to lack of efficacy of benzodiazepine derivatives/Z-drugs on sleep improvement (i.e. withdrawal from the study because of disease progression or a lack of expected or desired effect related to the therapy) c. Health-Related quality of life (HRQoL) **Safety of benzodiazepine derivatives/Z-drugs:** a. Occurrence of serious adverse events (to be defined during the project) associated with the use of benzodiazepine derivatives/Z-drugs

	b. Withdrawal of treatment due to serious adverse effects of benzodiazepine derivatives/Z-drugs c. Tolerance to benzodiazepine derivatives/Z-drugs d. Development of addiction or physical dependence on benzodiazepine derivatives/Z-drugs (discontinuation symptoms are out of scope)
OE (cost-effectiveness)[g]:	**Cost-effectiveness of benzodiazepine derivatives/Z-drugs:** a. Health-care costs (total and incremental) within a specific time period b. Incremental cost-effectiveness ratio (ICER) and incremental and total costs, quality-adjusted life years (QALYs) and life years within a specific time period. **Budget impact of benzodiazepine derivatives/Z-drugs**

Abbreviations: HRQoL = Health-related Quality of Life, QALY = quality-adjusted life year, RCTs = randomised controlled trials

6 HTA key questions

For the evaluation of the long-term use of sedative-hypnotic drugs to treat primary chronic insomnia disorder the following key questions covering the central HTA domains, as designated by the European Network for Health Technology Assessment (EUnetHTA) Core Model (efficacy, effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical, and organisational aspects), are addressed:

- What is the efficacy/effectiveness of the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss speciality list to treat primary chronic insomnia disorder compared to placebo, no treatment, or other non- pharmacological treatment, or compared to the short-term use (≤ one month) of sedative-hypnotic drugs?
- Is the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder safe compared to placebo, no treatment, or other non- pharmacological treatment, or compared to the short-term use (≤ one month) of sedative-hypnotic drugs?

[g] As requested by the FOPH, the HTA will take a healthcare payer perspective. Hence, costs outside of the healthcare sector will not be included in the analysis.

- What are the costs of the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder?
- How cost-effective is the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder compared to a placebo, no treatment, or other non- pharmacological treatment, or compared to the short-term use of sedative-hypnotic drugs?
- What is the budget impact of the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder?
- Are there legal, social, or ethical issues related to the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder?
- Are there organisational issues related to the long-term use (> one month) of sedative-hypnotic drugs of ATC categories N05BA, N05CD, or N05CF listed in the Swiss specialities list to treat primary chronic insomnia disorder?

7 Methodology systematic literature search

In the scoping phase, a systematic literature search was conducted following the methodological principles of systematic reviews (SRs). A SR is a method to collect, critically appraise, and summarise the best available evidence in a transparent and systematic way using generally accepted evidence-based principles. The SR is designed to search for up-to-date and high-quality evidence, according to current standards and clinical practice. The applied methodology of SRs follows international standards, such as the Cochrane Collaboration guidelines for performing SRs, and the reporting of this scoping review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[25,26]

The SR process consists of the following fundamental steps:

1. Formulation of the research questions
2. Comprehensive information search, including defining data sources and search strategy
3. Selection procedure, applying pre-determined clear inclusion and exclusion criteria
4. Critical appraisal (quality and risk of bias assessment)
5. Data extraction

6. Data synthesis
7. Quality control

We implemented the first three fundamental SR steps in the systematic literature search during the scoping phase. The scoping phase informs the feasibility of conducting a full HTA, which includes the remaining SR steps. In the Outlook section the SR process that may be conducted for the HTA is further detailed.

In the scoping phase a stepwise systematic literature search approach was implemented:

I. Search for SRs/meta-analyses published from 2010 onwards;
II. Update search for RCTs based on the search conducted in the most relevant/recent included SRs/meta-analyses or, in case no eligible SR was identified in the first step, a systematic literature search for original RCTs from 2000 onwards;
III. In case no RCT or one only RCT is found, an additional systematic literature search will be conducted for comparative non-randomised studies.

The following sections describe in detail the search strategy for the applied systematic literature search of both the efficacy, effectiveness, and safety (Section 7.1.1) and the cost-effectiveness (Section 7.1.2) of long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder.

7.1 Databases and search strategy

7.1.1 Efficacy, effectiveness, and safety

Since many studies have been published on BZDs/Z-drugs in patients with primary chronic insomnia disorder, we implemented a stepwise approach for the efficacy, effectiveness, and safety systematic literature search. In the first step, SRs/meta-analyses of RCTs were searched. However, no pertinent SR was identified for our specific research objectives and this first step was followed by a systematic literature search for original RCTs.

Search strategy

The core of our systematic literature search was a PubMed (MEDLINE) search complemented with the database Embase.com. Since there is considerable overlap in studies included in other literature databases (such as Cochrane Library), the decision was made to search in these two main databases. The searches were built using the PICO-framework (see PICO in Table 2). Given the various outcomes of interest, it was decided to keep the search broad. Only search strings on ‘patient’ (i.e. adults with primary chronic insomnia disorder) and ‘intervention’ (i.e. long-term use of sedative hypnotic drugs on the Swiss specialities list) were applied in combination with a search string for study designs. The intervention

search string for sedative-hypnotic drugs was not limited to the duration of treatment. Furthermore, animal studies were excluded with an additional search string. In the first step (i.e. search for SRs/meta-analyses) only English language publications were included. The reason for this inclusion criterion is that good SRs will mostly be published internationally in English language as English is generally perceived to be the universal language of science. For the RCT search we searched in four languages (English, German, French, and Dutch). For these study types, it is more common that non-English languages are used to publish study results. A publication period filter was applied: 2010-2020 in the first step to search for up-to-date SRs/meta-analyses, and 2000-2020 in the second step for a broader search for original RCTs. The details of the search strategies are included in Appendix 11.1. The search for SRs/meta-analyses was conducted on 5 October 2020, and the search for RCTs on 13 October 2020. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract), was exported to Endnote version X9.3. Duplicates in Endnote were automatically identified and manually deleted.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment. In case of doubt, the study was assessed in full text.
2. Screening of full article: the articles selected during the first phase were assessed in full text. Articles were included if the reported information was relevant for the objectives and the methodological description and result section were of sufficient quality, based on the inclusion and exclusion criteria (see below).

The process of selection and inclusion and exclusion of articles was registered in Excel and an Endnote library. The exclusion criteria applied during the full-text screening phase are reported in PRISMA flow charts (Section 8.1.1). The implemented quality control during the selection process is described in a next section.

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes for articles on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder are presented in Table 3. The list of excluded studies is enclosed in Appendix 11.2.

Table 3. Inclusion and exclusion criteria for SRs/meta-analyses and RCTs

	Inclusion		**Exclusion**	
Period publication	Step 1 • 2010-5 October 2020	Step 2 • 2000-13 October 2020	Step 1 • <2010	Step 2 • <2000
Language of publication	Step 1 • English	Step 2 • English • German • French • Dutch	All other languages	
Country of study	Western countries*		All other countries	
Study design/type	Step 1 • SR/meta-analysis of RCTs	Step 2 • RCT • Open-label extension studies (i.e. of an RCT included with our systematic literature search)	• Comparative non-randomised studies (e.g. cohort studies, case-control studies) • Case reports • Non-pertinent publication types (e.g. expert opinion, letter to editor, editorial, comment) • Abstract	
			Step 1 • Narrative review, without transparent and systematic reporting of the study results • Less recent SR, covering the same RCTs/outcomes of interest as the included most recent SR • Primary studies (e.g. original RCT or modelling study)	Step 2 • SR/meta-analysis
Study quality	• Sufficient methodological quality and coherent reporting of the results		• Insufficient methodological quality or incoherent reporting of the results (e.g. not reported whether baseline values were comparable between the groups, unexplained errors in patient flow)	
Study population	• Patients ≥18 years • Study with focus on a general population with primary chronic insomnia disorder (e.g., according to DSM-5, ICD-10, or ICSD-3) • Patients who use benzodiazepine derivatives/Z-drugs for primary chronic insomnia disorder as primary reason		• Patients <18 years • Patients who use benzodiazepine derivatives/Z-drugs for any other reason than primarily for chronic insomnia disorder (e.g. anxiety, psychiatric disorders, epileptic disorder) • Patients who use benzodiazepine derivatives/Z-drugs for treatment of drug addiction • Palliative care	
Study intervention	• Benzodiazepine derivatives/Z-drugs listed in the Swiss specialities list†¥ • Treatment duration >1 month		• Benzodiazepine derivatives/Z-drugs not listed in the Swiss specialities list†¥ • Benzodiazepine derivatives/ Z-drugs with treatment duration ≤1 month (to be determined in further detail after data extraction of the included RCTs) or unclear treatment duration	

		• All medical interventions other than benzodiazepines/benzodiazepine derivatives/Z-drugs listed in the Swiss specialities list
Study comparison	• Placebo • No treatment • Other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy) • Direct comparison with short-term use (≤1 month; to be determined in further detail after data extraction of the included RCTs) of benzodiazepine derivatives/Z-drugs†	• Benzodiazepine derivatives/Z-drugs vs. other benzodiazepine derivatives/Z-drugs with same treatment duration • Comparison of different doses of benzodiazepine derivatives/Z-drugs • Benzodiazepine derivatives/Z-drugs vs. other drugs • No comparison
Study outcomes	See PICO table†	• Other outcomes

Keys: PICO = Population-Intervention-Comparator-Outcome, RCT = randomised controlled trial, SR = systematic review. * Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf); † See PICO in Table 2. ¥All articles reporting on benzodiazepine derivatives/Z-drugs as intervention were included during the title and abstract screening. In the full-text selection phase, only the articles reporting on the benzodiazepine derivatives/Z-drugs listed in the Swiss specialities list were included.

Quality control

The following quality control measures were applied during the systematic literature search:

- Search strategy

  We developed a search strategy outlining the parameters of the systematic literature search, with the proposed search strategies and sources for the SRs. A medical information specialist was consulted during the development of the search strategies. Quality checks were implemented, and the search strategy was checked by a second researcher. Separate search strategies were made for the efficacy/effectiveness/safety systematic literature search and the cost-effectiveness/budget impact systematic literature search.

  The supplementary search technique citation chasing (i.e. backward by finding other studies cited within the included articles) was applied in addition to the database searches. Additional studies were enclosed in the selection process.

- Selection process

  The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher. Both researchers categorised the titles as 'include for full-text assessment', 'exclude for full-text assessment', or 'doubt'. If there

were differences between the two researchers regarding more than 2% of the articles selected as 'include for full-text assessment', another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 2% discrepancy at 50% of the duplicate selection, the screening of title and abstracts would have been done fully in duplicate by two independent researchers. If the two reviewers disagreed on the relevance of a study, this was discussed. If the differences remained after discussion, the study was assessed in full text. During screening there was less than 2% discrepancy between the two researchers.

The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers. The results were compared and discussed early in the process. If there were differences between the two researchers with regard to more than 5% of the articles screened in duplicate, another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 5% discrepancy at 50% of the duplicate selection, the screening of full-text articles would have been done fully in duplicate by two independent researchers. The remaining full-text selection was done by one researcher in close collaboration with a second reviewer; any doubts were discussed in detail. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

7.1.2 Cost-effectiveness

Search strategy

Similar to the efficacy, effectiveness, and safety systematic literature search, a systematic literature search for cost-effectiveness studies was conducted in PubMed (MEDLINE) and Embase.com databases using the PICO-framework. In addition to PubMed (MEDLINE) and Embase.com, a search on the NHS EED and HTA database of the Centre for Reviews and Dissemination (CRD) database was conducted. NHS EED includes economic evaluations of health and social care interventions. The HTA database includes completed and ongoing health technology assessments from around the world. The HTA database is a valuable source for identifying grey literature, as much of the information it contains is only available directly from individual funding agencies, such as the Swiss Federal Office of Public Health (FOPH), National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), and Dutch Healthcare Institute (ZIN)

In PubMed (MEDLINE) and Embase.com, the search terms of the efficacy, effectiveness, and safety literature search were combined with cost-effectiveness search terms to find economic evaluations. The

search terms for economic evaluations were developed together with a medical information specialist and were also used in the previous project on primary prevention of cardiovascular disease using statins by the authors together with the FOPH. The search terms for the CRD databases are a combination of search terms related to sleep or insomnia and benzodiazepines (Appendix 11.3). The database output, including all indexed fields per hit (e.g. title, authors, abstract), was exported to Endnote version X9. These hits were unduplicated during the project.

Selection procedure

From the articles retrieved from PubMed (MEDLINE), Embase.com, NHS EED and HTA database of CRD, the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract:

   The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the HTA objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment.

2. Screening of full article:

   The full-text articles, selected in the first step, were assessed based on the inclusion and exclusion criteria as defined in the scoping protocol. Articles were included if they fulfilled the inclusion criteria and excluded when they did not.

The process of selection and inclusion and exclusion of articles was registered in Excel and in an End-note library by one of the reviewers. This method provides transparency regarding all selection steps and assures reproducibility. PRISMA flow chart are presented in Figure 3, showing the numbers of studies screened by title and abstract, assessed in full-text, and included with the systematic literature search.

Inclusion and Exclusion criteria

The list of inclusion and exclusion criteria are presented in Table 4. An overview of search terms applied for the cost-effectiveness systematic literature search are listed in Appendix 11.3.

Table 4. Inclusion and exclusion criteria for the cost-effectiveness systematic literature search

	Inclusion	**Exclusion**
Period publication	No restriction on publication period was applied	
Language of publication	• English • German • French • Dutch	All other languages
Country of study	• Western countries*	All other countries
Study design/type	Economic evaluations • Cost-utility • Cost-effectiveness • Cost-minimization • Cost-benefit • Costing studies (including budget impact analyses) • Resource use measurement	
Study quality		
Study population	• Patients ≥18 years • Study with focus on a general population with primary chronic insomnia disorder (e.g., according to DSM-5, ICD-10, or ICSD-3) • Patients who use benzodiazepine derivatives/Z-drugs for primary chronic insomnia disorder as primary reason	• Patients <18 years • Patients who use benzodiazepine derivatives/Z-drugs for any other reason than primarily for chronic insomnia disorder (e.g. anxiety, psychiatric disorders, epileptic disorder) • Patients who use benzodiazepine derivatives/Z-drugs for treatment of drug addiction • Palliative care
Study intervention	• Benzodiazepine derivatives/Z-drugs listed in the Swiss specialities list† • Treatment duration >1 month (During the project, the exact length of long-term use will be determined in further detail)	• Benzodiazepine derivatives /Z-drugs with treatment duration ≤1 month (During the project, the exact length of short-term use will be determined in further detail) • All other interventions

Study comparison	• Placebo • No treatment • Other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy) • Direct comparison with short-term use (≤1 month; During the project, the exact length of short-term use will be determined in further detail) of benzodiazepine derivatives/Z-drugs†	• Benzodiazepine derivatives/Z-drugs vs. other benzodiazepine derivatives/Z-drugs with same treatment duration • Comparison of different doses of benzodiazepine derivatives/Z-drugs • Benzodiazepine derivatives/Z-drugs vs. other drugs • No comparison
Study outcomes	See PICO table†	Other outcomes

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf); † See PICO in Table 2.

Quality control

The same quality control measures as in the efficacy, effectiveness, and safety systematic literature search were applied in the cost-effectiveness systematic literature search.

Legal, social, ethical, and organisational domain search strategy

The search results of the efficacy, effectiveness, and safety search and the cost-effectiveness literature searches were screened for legal, social, ethical, and organisational aspects of our research questions. Potentially relevant studies were identified, and the full texts will be reviewed in the HTA phase. Further, grey literature searches will be conducted in the HTA phase.

8 Synthesis of evidence base

8.1 Evidence base pertaining to efficacy, effectiveness, and safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness, and its safety.

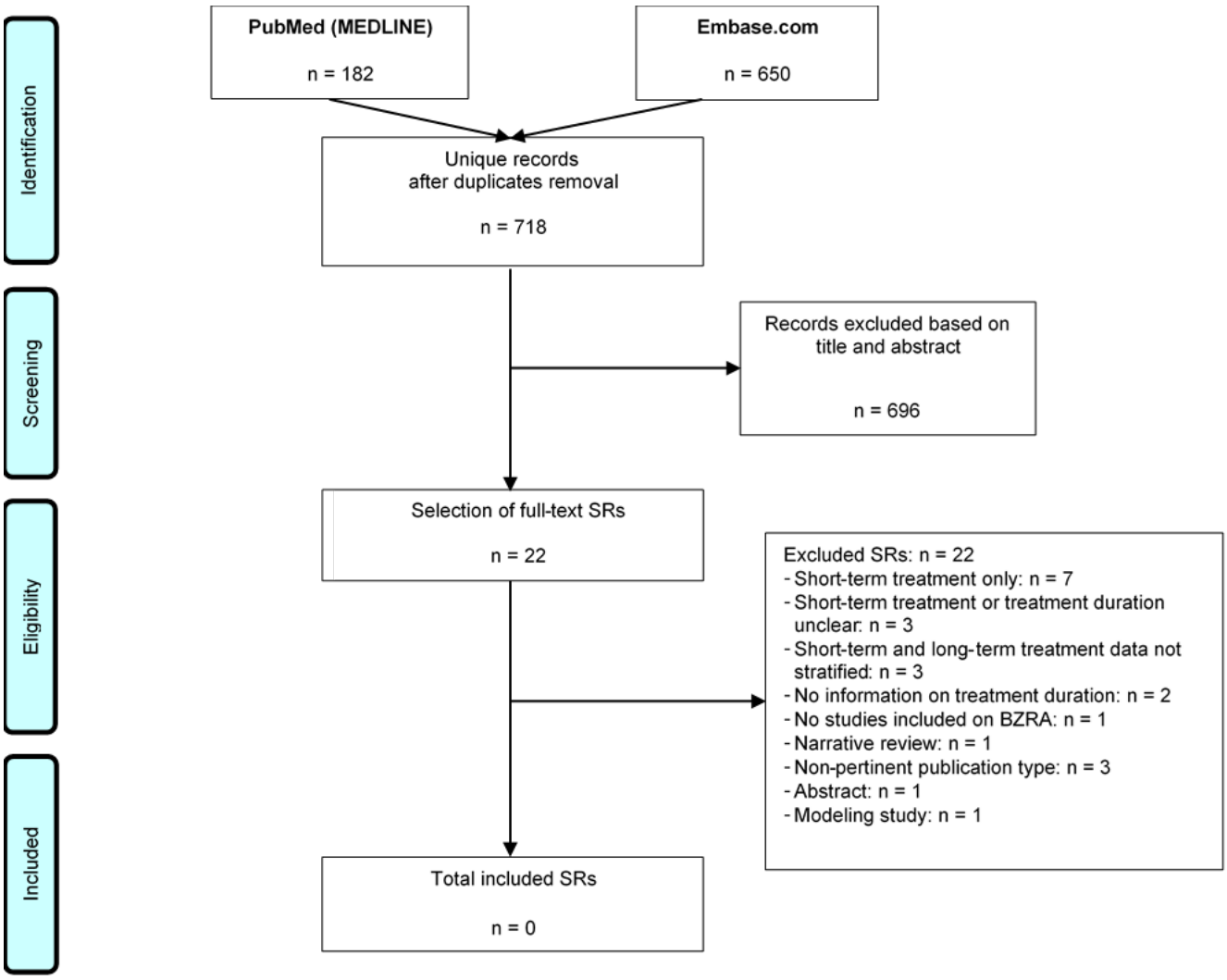
- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalization, or cause prolongation of existing hospitalization (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

8.1.1 PRISMA flow charts for efficacy, effectiveness, and safety systematic literature searches

Systematic literature search for systematic reviews

In total, 718 unique records were identified in PubMed (MEDLINE) and Embase.com on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder for the study design SR/meta-analysis. Of those, 696 records were excluded based on their title and abstract, resulting in 22 SRs/meta-analyses selected to be screened in full text. After applying the inclusion and exclusion criteria, no SR nor meta-analysis was finally included. The main reasons for exclusion were short-term treatment only (n=7 studies), followed by short-term treatment or treatment duration unclear (n=3 studies), and short-term and long-term treatment data not stratified (n=3 studies). A complete overview of the reasons for exclusion is shown in the PRISMA flow chart (Figure 1). An overview of the reasons for exclusion per excluded SR is detailed in Appendix 11.2.

Figure 1. PRISMA flowchart of the efficacy, effectiveness, and safety systematic literature search for systematic reviews on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder



Abbreviations: BZRA = benzodiazepine and Z-drugs, SRs = systematic reviews

Systematic literature search for RCTs

In total, 2'003 unique records were identified in PubMed (MEDLINE) and Embase.com on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder for the study design RCT. Of those, 1'937 records were excluded based on their title and abstract, resulting in 66 RCTs selected to be screened in full text. After applying the inclusion and exclusion criteria, nine RCTs were finally included:

1. Krystal AD, Erman M, Zammit GK, et al. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with

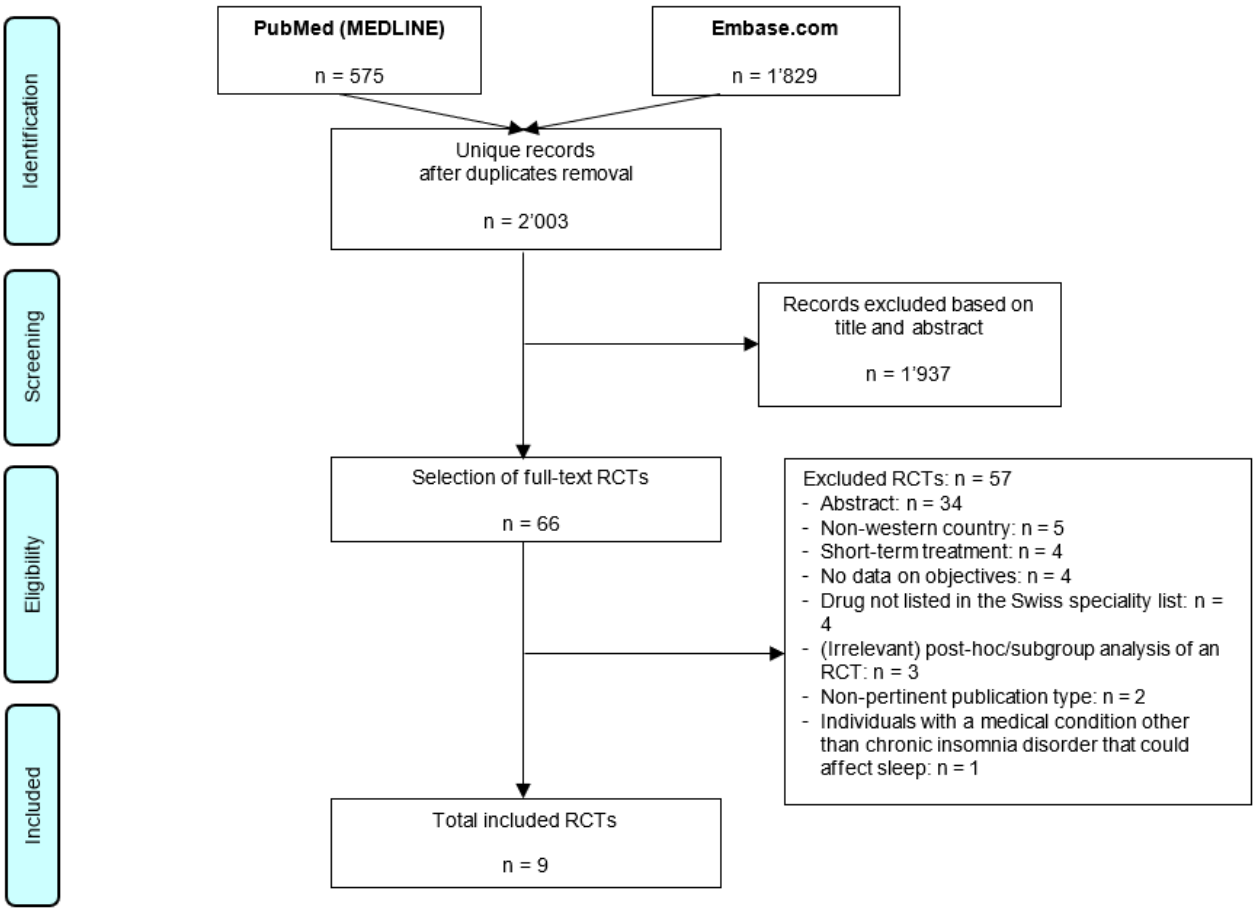
chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sleep 2008;31(1):79-90.

2. Morin CM, Edinger JD, Beaulieu-Bonneau S, et al. Effectiveness of Sequential Psychological and Medication Therapies for Insomnia Disorder: A Randomized Clinical Trial. JAMA Psychiatry 2020.
3. Omvik S, Sivertsen B, Pallesen S, et al. Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with Zopiclone. Behav Res Ther 2008;46(5):623-41.
4. Perlis ML, McCall WV, Krystal AD, et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. J Clin Psychiatry 2004;65(8):1128-37.
5. Randall S, Roehrs TA, Roth T. Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. Sleep 2012;35(11):1551-7.
6. Roehrs TA, Randall S, Harris E, et al. MSLT in primary insomnia: stability and relation to nocturnal sleep. Sleep 2011;34(12):1647-52.
7. Sivertsen B, Omvik S, Pallesen S, et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. Jama 2006;295(24):2851-8.
8. Walsh JK. Zolpidem "as needed" for the treatment of primary insomnia: a double-blind, placebo-controlled study. Sleep Med Rev 2002;6 Suppl 1:S7-10; discussion S10-1, S31-3.
9. Walsh JK, Roth T, Randazzo A, et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. Sleep 2000;23(8):1087-96.

Only studies on Z-drugs were found. Studies on benzodiazepines or benzodiazepines derivates did not fulfil the inclusion/exclusion criteria’s and were therefore not included.

The main reasons for exclusion were abstracts only (n=34 studies), followed by studies performed in non-western countries (n=5 studies), no data on objectives (n=4 studies), and (irrelevant) post-hoc/subgroup analysis of an RCT (n=4 studies). An overview of the reasons for exclusion is enclosed in the PRISMA flow chart (Figure 2). A complete overview of the reasons for exclusion by each excluded RCT is enclosed in Appendix 11.2.

Figure 2. PRISMA flowchart of the efficacy, effectiveness, and safety systematic literature search for RCTs on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder



Abbreviations: RCT = randomized control trial

Systematic literature search for comparative non-randomised studies

Since the systematic literature search for RCTs included nine RCTs, it was decided not to proceed with the systematic literature search for comparative non-randomised studies.

8.2 Evidence base pertaining to costs and cost-effectiveness and budget impact

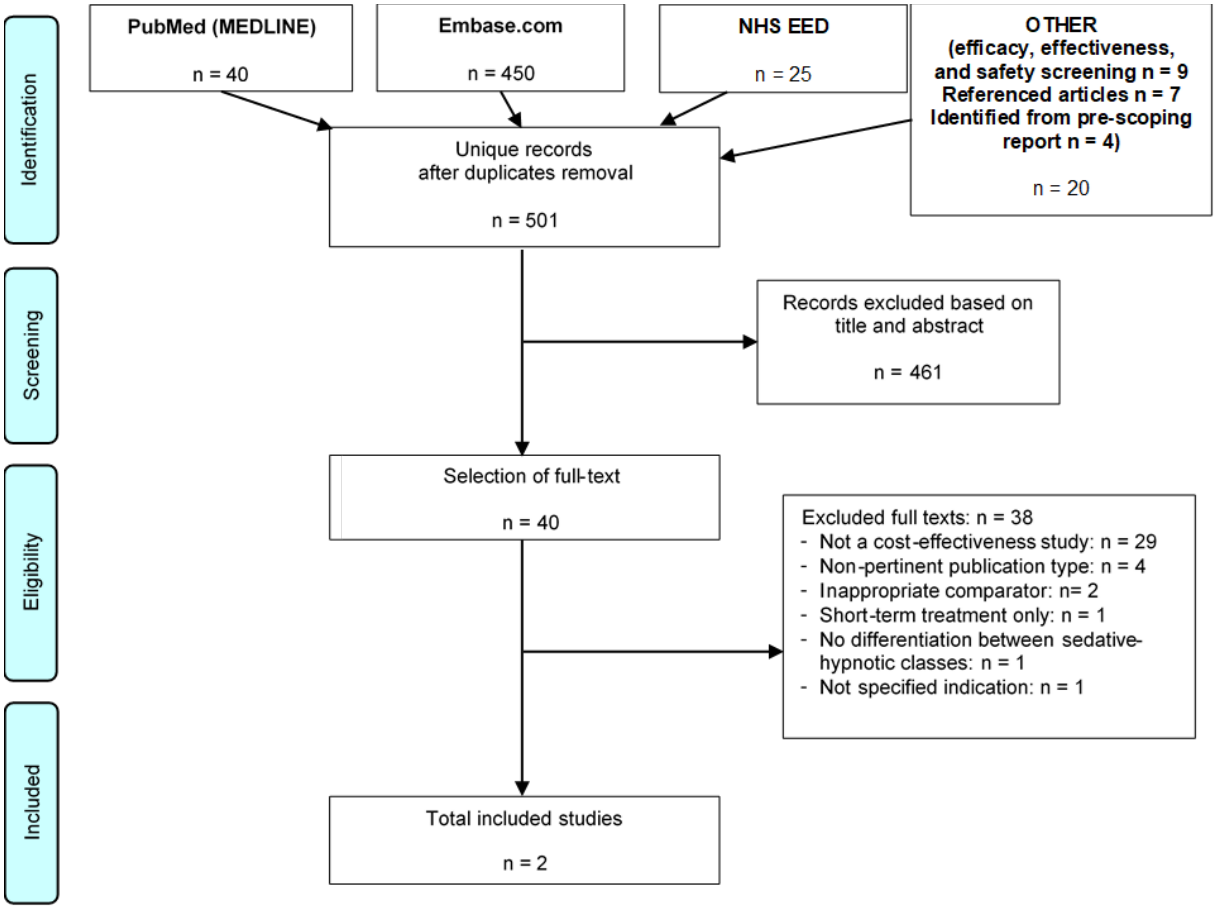
8.2.1 PRISMA flow chart for cost-effectiveness search

In total, 501 unique records were identified in PubMed (MEDLINE) and Embase.com, as well as the NHS EED and other sources, on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder for the cost-effectiveness search. Of those, 461 records were excluded based on their title and abstract, yielding 40 studies to be screened in full text. After applying the inclusion and exclusion criteria, 38 studies were excluded, leaving the following two studies included:

1. Morgan, K., Dixon, S., Mathers, N., Thompson, J., & Tomeny, M. (2003). Psychological treatment for insomnia in the management of long-term hypnotic drug use: a pragmatic randomised controlled trial. The British journal of general practice: the journal of the Royal College of General Practitioners, 53(497), 923–928.
2. Moriarty F, Cahir C, Bennett K, et al. Economic impact of potentially inappropriate prescribing and related adverse events in older people: A cost-utility analysis using Markov models. BMJ Open 2019;9:1–9. doi:10.1136/bmjopen-2018-021832

The main reasons for exclusion were that the studies were not cost-effectiveness studies (n = 29) followed by non-pertinent publication type (n = 4), inappropriate comparator (n = 2), short-term treatment only (n = 1), no specified indication (n = 1) and no differentiation between sedative-hypnotic classes (n = 1). An overview of the reasons for exclusion is shown in the PRISMA flow chart (Figure 3) and a full overview of the reasons for exclusion by each excluded study is detailed in Appendix 11.4.

Figure 3. PRISMA flowchart of the cost-effectiveness systematic literature search on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder



Abbreviations: NHS EED = National Health Service Economic Evaluation Database

9 Outlook

To answer the HTA key questions of the FOPH, an HTA specific for the Swiss context is necessary. This chapter describes the methodological steps to be taken for the HTA.

9.1 Efficacy, effectiveness, and safety

From the systematic literature search, nine RCTs on the efficacy and safety of long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder were included. To critically appraise, analyse, and synthesise the pertinent clinical evidence on the outcomes of interest a rigorous SR methodology will be applied, adhering to the international methodological standards of Cochrane and the PRISMA reporting guidelines. The methodology will be outlined in a separate HTA protocol. Briefly, the risk of bias of the RCTs included on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder will be assessed based on the key risk of bias criteria used in the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[27] Data from the included RCTs will be extracted, including the study characteristics, treatment duration, and pre-specified outcomes of interest (i.e. clinically relevant sleep improvement, withdrawal due to lack of efficacy of BZDs/Z-drugs on sleep improvement, HRQoL, occurrence of serious adverse events, withdrawal of treatment due to serious adverse effects, tolerance to BZDs/Z-drugs, and development of addiction or physical dependence on BZDs/Z-drugs). After data-extraction of the treatment duration applied in the included RCTs, the threshold value for short-term use versus long-term use of sedative hypnotic drugs will be discussed with the FOPH and clinical experts and might be reconsidered. In clinical guidelines a threshold of four weeks is used for the short-term use of sedative-hypnotic drugs for the treatment primary chronic insomnia disorder, however it is not clear whether long-term treatment starts from four weeks on. For example, RCTs with a treatment duration of six weeks only, might be better in line with short-term than long-term use of sedative-hypnotic drugs. Based on the heterogeneity and number of studies per outcome, it will be explored for which outcomes it is possible to calculate pooled estimates and implement a GRADE assessment for the level of evidence. Outcomes for which it is not possible to calculate pooled estimates and implement a GRADE assessment will be presented narratively in summary tables/figures and accompanying text, to provide insight into the direction of the treatment effects found in the clinical literature. Since nine RCTs are included with the systematic literature search for RCTs, it was decided not to proceed with the systematic literature search for comparative non-randomised studies.

9.2 Cost-effectiveness

The evidence base for the cost-effectiveness systematic literature search included only two economic evaluations of long-term use of sedative-hypnotic drugs to treat primary chronic insomnia disorder against cognitive behaviour therapy in a UK setting [28] and no benzodiazepines use in an Irish setting [29], respectively. The identified studies will be subjected to a critical appraisal using the Consensus Health Economic Criteria (CHEC). The CHEC is a 19-item checklist with clear questions about the economic evaluation that gives insight into the general quality of the study.[30,31] In addition to the CHEC, sedative-hypnotic-specific modelling questions will be added (e.g. which adverse events are considered) to evaluate the quality of the model for the purpose of estimating the cost-effectiveness of the sedative-hypnotic drugs.

The identified studies do not provide sufficient evidence on the cost-effectiveness of long-term use of sedative-hypnotic drugs to treat primary chronic insomnia disorder against placebo, no treatment, other non-drug treatment, nor short-term use of sedative-hypnotic drugs treatment in the Swiss context.The lack of studies in the Swiss context as well as the lack of studies considering adverse events (such as falls) associated with long-term use of sedative hypnotic drugs, suggests that developing a de novo economic model that incorporates the most recent efficacy, effectiveness, and safety, and (where possible) Switzerland-specific costs and utility evidence is appropriate. The next chapter explains our general approach to health economic modelling that will be further detailed in the HTA report.

9.3 Approach to health economic modelling

This chapter describes the steps for developing a de novo-health economic model, including conceptual model development, selecting the appropriate model type, main characteristics of the health economic model, informing model input parameters, the cost-effectiveness and budget impact analyses.

9.3.1 Conceptual health economic model development

The decision problem and the PICO that were described in this report will be used as a starting point for the development of the conceptual health economic model. A conceptual model is essential to identify necessary inputs of the model, and therefore helps to structure further research and data collection efforts. The conceptual model addresses the key parameters that drive both costs and health effects as well as their relation.

According to the International Society for Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making (ISPOR-SMDM) good modelling research practice[32], a careful review of existing health economic models, if available, is a prerequisite when developing the underlying conceptual

model. For this purpose, findings in the studies identified during the cost-effectiveness search, especially Moriarty et al., will be reviewed and considered as starting points for the development of the conceptual health economic model.[29] The draft conceptual model will be discussed with a clinical expert to ensure that the model structure reflects clinical practice.

9.3.2 Selection of the model type

The design of the conceptual model drives the choices between different model types (e.g. a decision tree, cohort level Markov model or patient level simulation model). A *decision tree* is suitable for decision problems with a short and fixed time horizon without events that can happen multiple times during the model time horizon. For longer time horizons, when timing of events and/or when recurring events need to be considered, a *cohort level Markov model* is more suitable. If it is important to consider a patient's history, a *patient level simulation model* can be considered appropriate as this type of model can incorporate recurrence of events and "remember patient history" without leading to excessive number of health states. However, patient level simulation models are also more demanding in terms of data requirements. That is why the translation of the conceptual model to a specific type of health economic model also strongly depends on the available evidence. Crucial, in this aspect, is therefore the availability of data that will be extracted in the HTA phase from the systematic literature searches that were described in this report.

9.3.3 Main characteristics of the health economic model

- **Setting:** The analysis will be performed for the Swiss healthcare setting. This means that where possible and relevant, input parameters will be based on data from Switzerland, e.g., Swiss lifetables for background mortality and Swiss sources for healthcare costs.
- **Perspective:** The analysis will be performed from a healthcare payer perspective. This means that only direct healthcare costs will be included. Societal costs, such as informal care and productivity costs, will not be included.
- **Time horizon:** The preferred time horizon of the base-case analysis is lifetime. A lifetime horizon will depend on the feasibility and availability of data. Shorter time horizons will be considered in scenario analyses, if relevant.
- **Discount rate:** In the base-case analysis, costs and effects will be discounted at 3.0%. In scenario analyses, the impact of not discounting or using a discount rate of 5.0% will be explored.
- **Health outcomes:** Health outcomes will be reported in life years (LYs) and quality-adjusted life years (QALYs).
- **Currency, price data, and conversion:** Costs will be reported in Swiss Franc (CHF) adjusted for inflation to current price levels using inflation rates from the Swiss Federal Statistical Office, which will be accessed from the Organisation for Economic Co-operation and Development (OECD) website (https://data.oecd.org).

9.3.4 Model input parameters

The model input parameters on clinical outcomes will be informed mainly from the results of the data extraction of the systematic literature search of efficacy, effectiveness and safety. Clinical expert opinion will be used whenever data is unavailable from the literature.

If no Swiss-specific data on costs, resource use and utilities are identified in the systematic literature searches for efficacy, effectiveness and safety and cost-effectiveness described in this report, additional searches may be performed. First, searches on medical databases may be performed in collaboration with the FOPH to determine medication use, healthcare resource use, and unit costs. In addition, systematic literature searches may be performed by adding a search filter for costs and resource use and/or utilities to the clinical search strings used in the systematic literature searches described in this report. The search filter for costs, resource use and utilities can be based on the search string that was developed by Canadian Agency for Drugs and Technologies in Health (CADTH) for PubMed (MEDLINE) and Embase.com (Appendix 11.5).[h] Search terms that were already included in the preliminary search for cost-effectiveness analyses will be omitted to avoid overlapping studies. The search strings regarding sedative-hypnotic drugs and the comparators outlined in the PICO will not be added in this search because studies reporting utilities in patients with primary chronic insomnia disorder who are not on any of these treatments can also be relevant. If the required data cannot be identified from the medical database and systematic literature searches, assumptions will be made based on data from other comparable countries and/or expert opinion.

9.3.5 Health economic model and cost-effectiveness analysis

Following the conceptual model development and data collection, the health economic model can be populated with the obtained parameters. The model will be programmed in statistical programming language R based on the modelling framework developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup. [33–35] Parametric uncertainty will be explored through one-way and probabilistic sensitivity analyses and structural uncertainty will be explored in several scenario analyses. Subgroup analyses will be performed where possible to differentiate cost-effectiveness by population or disease/indication area.

[h] https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco

9.3.6 Budget impact analysis

In addition to the cost-effectiveness model, a budget impact (BI) model will be developed to calculate the projected population-level overall costs of sedative-hypnotic drugs in patients with primary chronic insomnia disorder. The BI model will be built as an extension to the cost-effectiveness model, described above. Hence, the core model characteristics for the BI model will be dependent on the cost-effectiveness model. The time horizon of the BI model will be restricted to 5 years. For the BI model, data is required about the current use of sedative-hypnotic drugs in patients with primary chronic insomnia disorder in Switzerland. If this data is not available, assumptions will be made based on data from other comparable countries and/or expert opinion.

9.4 Legal, social, ethical, and organisational aspects

In the HTA phase, we will review the full texts of studies identified for legal, social, ethical, and organisational aspects encountered during the efficacy, effectiveness, and safety and cost-effectiveness systematic literature searches. In addition, we will further search for grey literature on these HTA domains on relevant websites. The results of the main legal, social, ethical, and organisational aspects will be reported in the HTA report.

10 References

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11 Appendices

11.1 Appendix 11.1 Search strategy for efficacy, effectiveness, and safety systematic literature search

Table I. Search strategy for the efficacy, effectiveness, and safety systematic literature search for systematic reviews and RCTs: PubMed (MEDLINE)

	SRs/meta-analyses	**RCTs**
Population: primary chronic insomnia disorder	"sleep wake disorders"[Mesh] OR sleep*[tiab] OR wake*[tiab] OR awake*[tiab] OR insomnia[tiab] OR DIMS[tiab]	sleep wake disorders"[Mesh] OR sleep disorder*[tiab] OR sleep problem*[tiab] OR sleep disturbance*[tiab] OR sleepless*[tiab] OR sleep-wake disorder*[tiab] OR sleep-wake disorder*[tiab] OR disorders of initiating and maintaining sleep[tiab] OR DIMS[tiab] OR insomnia[tiab]
Intervention: sedative-hypnotics	"benzodiazepines"[Mesh] OR benzodiazepine[tiab] OR benzodiazepines[tiab] OR diazepam[tiab] OR oxazepam[tiab] OR potassium clorazepate[tiab] OR lorazepam[tiab] OR bromazepam[tiab] OR clobazam[tiab] OR ketazolam[tiab] OR prazepam[tiab] OR alprazolam[tiab] OR lorazepam, diphenhydramin[tiab] OR "benzodiazepines/analogs and derivatives"[Mesh] OR flurazepam[tiab] OR nitrazepam[tiab] OR flunitrazepam[tiab] OR lormetazepam[tiab] OR temazepam[tiab] OR midazolam[tiab] OR z-drugs[tiab] OR zopiclone[tiab] OR zolpidem[tiab]	
Comparison	No search string	
Outcomes	No search string	
Limits	*Study design*	
	((systematic*[tiab] OR comprehensive*[tiab]) AND (bibliographic*[tiab] OR literature[tiab] OR review*[tiab])) OR literature review*[tiab] OR meta-analysis[pt] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab]	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR RCT[tiab] OR RCTs[tiab] OR random*[tiab] OR controlled[tiab] OR control-treated[tiab] OR placebo[tiab] OR "cross-over studies"[Mesh] OR "single-blind method"[Mesh] OR single-blind*[tiab] OR singleblind*[tiab] OR single-masked[tiab] OR "double-blind method"[Mesh] OR double-blind*[tiab] OR doubleblind*[tiab] OR double-masked[tiab] OR triple-blind*[tiab] OR tripleblind*[tiab] OR triple-masked[tiab]) NOT ("systematic review"[pt] OR review[ti] OR "meta-analysis"[pt] OR meta-analysis[ti])
	Publication period	
	2010 - October 5, 2020	2000 - October 13, 2020
	Language	
	English	English, German, French, Dutch

Table II. Search strategy for the efficacy, effectiveness, and safety systematic literature search for systematic reviews and RCTs: Embase.com

	SRs/meta-analyses	RCTs
Population: primary chronic insomnia disorder	'sleep disorder'/exp OR sleep*:ti,ab OR wake*:ti,ab OR awake*:ti,ab OR insomnia:ti,ab OR DIMS:ti,ab	'insomnia'/exp OR "sleep disorder*":ti,ab OR "sleep problem*":ti,ab OR "sleep disturbance*":ti,ab OR sleepless*:ti,ab OR "sleep-wake disorder*":ti,ab OR "sleepwake disorder*":ti,ab OR "disorders of initiating and maintaining sleep":ti,ab OR DIMS:ti,ab OR insomnia:ti,ab
Intervention: sedative-hypnotics	“benzodiazepines“[Mesh] OR benzodiazepine[tiab] OR benzodiazepines[tiab] OR diazepam[tiab] OR oxazepam[tiab] OR potassium clorazepate[tiab] OR lorazepam[tiab] OR bromazepam[tiab] OR clobazam[tiab] OR ketazolam[tiab] OR prazepam[tiab] OR alprazolam[tiab] OR lorazepam, diphenhydramin[tiab] OR "benzodiazepines/analogs and derivatives"[Mesh] OR flurazepam[tiab] OR nitrazepam[tiab] OR flunitrazepam[tiab] OR lormetazepam[tiab] OR temazepam[tiab] OR midazolam[tiab] OR z-drugs[tiab] OR zopiclone[tiab] OR zolpidem[tiab]	
Comparison	No search string	
Outcomes	No search string	
Limits	*Study design*	
	(((systematic*:ti,ab OR comprehensive*:ti,ab) AND (bibliographic*:ti,ab OR literature:ti,ab OR re-view*:ti,ab)) OR "literature review*":ti,ab OR 'meta analysis'/exp OR meta-analys*:ti,ab OR meta-analyz*:ti,ab OR meta-analyt*:ti,ab OR metaanalys*:ti,ab OR metaanalyz*:ti,ab OR metaanalyt*:ti,ab)	('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR RCT:ti,ab OR RCTs:ti,ab OR random*:ti,ab OR controlled:ti,ab OR control-treated:ti,ab OR placebo:ti,ab OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR single-blind*:ti,ab OR singleblind*:ti,ab OR single-masked:ti,ab OR 'double blind procedure'/exp OR double-blind*:ti,ab OR double-blind*:ti,ab OR double-masked:ti,ab OR 'triple blind procedure'/exp OR triple-blind*:ti,ab OR tripleblind*:ti,ab OR triple-masked:ti,ab) NOT ('systematic review'/exp OR review:ti OR 'meta analysis'/exp OR meta-analysis:ti)
	Publication period	
	2010 - October 5, 2020	2000 - October 13, 2020
	Language	
	English	English, German, French, Dutch

11.2 Appendix 11.2 Excluded studies during full-text selection efficacy, effectiveness, and safety search

Table III. Excluded studies found with the systematic literature search for systematic reviews on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder

Reference	Reason for exclusion
Alessi C, Vitiello MV. Insomnia (primary) in older people. BMJ clinical evidence 2011;2011 [published Online First: 2011/10/28]	Short-term and long-term treatment data not stratified
Brasure M, MacDonald R, Fuchs E, et al. AHRQ Comparative Effectiveness Reviews. Management of Insomnia Disorder 2015	Non-pertinent publication type (book/report)
Brower KJ. Assessment and treatment of insomnia in adult patients with alcohol use disorders. Alcohol (Fayetteville, NY) 2015;49(4):417-27. doi: 10.1016/j.alcohol.2014.12.003 [published Online First: 2015/05/11]	Narrative review
Gerlach LB, Wiechers IR, Maust DT. Prescription Benzodiazepine Use Among Older Adults: A Critical Review. Harv Rev Psychiatry 2018;26(5):264-73. doi: 10.1097/hrp.0000000000000190 [published Online First: 2018/09/07]	No information on treatment duration
Greene N, Greene M. Evaluation of treatment patterns and clinical trials published on patients diagnosed with insomnia: A literature update. Value in Health 2013;16(7):A722-A23. doi: 10.1016/j.jval.2013.08.2254	Abstract
Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: Meta-analysis of data submitted to the Food and Drug Administration. BMJ (Online) 2013;346(7889) doi: 10.1136/bmj.e8343	Short-term and long-term treatment data not stratified
Kanji S, Mera A, Hutton B, et al. Pharmacological interventions to improve sleep in hospitalised adults: A systematic review. BMJ Open 2016;6(7) doi: 10.1136/bmjopen-2016-012108	Short-term treatment
Kolla BP, Mansukhani MP, Schneekloth T. Pharmacological treatment of insomnia in alcohol recovery: a systematic review. Alcohol and alcoholism (Oxford, Oxfordshire) 2011;46(5):578-85. doi: 10.1093/alcalc/agr073 [published Online First: 2011/07/01]	Short-term treatment
Kong F, Liu G, Xu J. Pharmacological agents for improving sleep quality at high altitude: a systematic review and meta-analysis of randomized controlled trials. Sleep Medicine 2018;51:105-14. doi: 10.1016/j.sleep.2018.06.017	Short-term treatment or treatment duration unclear
Liira J, Verbeek JH, Costa G, et al. Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. Cochrane Database of Systematic Reviews 2014;2014(8) doi: 10.1002/14651858.CD009776.pub2	Short-term treatment
Lu XM, Zhu JP, Zhou XM. The effect of benzodiazepines on insomnia in patients with chronic obstructive pulmonary disease: A meta-analysis of treatment efficacy and safety. International Journal of COPD 2016;11(1):675-85. doi: 10.2147/COPD.S98082	Short-term treatment
Machado FV, Louzada LL, Cross NE, et al. More than a quarter century of the most prescribed sleeping pill: Systematic review of	Short-term treatment

zolpidem use by older adults. Exp Gerontol 2020;136:110962. doi: 10.1016/j.exger.2020.110962 [published Online First: 2020/05/04]	
McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in Alzheimer's disease. Cochrane Database of Systematic Reviews 2014;2014(3) doi: 10.1002/14651858.CD009178.pub2	No studies included on benzodiazepines or Z-drugs
Reynolds AC, Marshall NS, Hill CL, et al. Systematic review of the efficacy of commonly prescribed pharmacological treatments for primary treatment of sleep disturbance in patients with diagnosed autoimmune disease. Sleep Medicine Reviews 2020;49 doi: 10.1016/j.smrv.2019.101232	Short-term treatment
Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. Journal of Sleep Research 2017;26(6):675-700. doi: 10.1111/jsr.12594	Non-pertinent publication type (guideline)
Samara MT, Huhn M, Chiocchia V, et al. Efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly: a systematic review and network meta-analysis. Acta Psychiatrica Scandinavica 2020;142(1):6-17. doi: 10.1111/acps.13201	Short-term treatment or treatment duration unclear
Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American academy of sleep medicine clinical practice guideline. Journal of Clinical Sleep Medicine 2017;13(2):307-49. doi: 10.5664/jcsm.6470	Non-pertinent publication type (guideline)
Schroeck JL, Ford J, Conway EL, et al. Review of Safety and Efficacy of Sleep Medicines in Older Adults. Clinical Therapeutics 2016;38(11):2340-72. doi: 10.1016/j.clinthera.2016.09.010	No information on treatment duration
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. European Journal of Clinical Pharmacology 2020;76(3):363-81. doi: 10.1007/s00228-019-02812-z	Short-term treatment
Winkler A, Auer C, Doering BK, et al. Drug treatment of primary insomnia: A meta-analysis of polysomnographic randomized controlled trials. CNS Drugs 2014;28(9):799-816. doi: 10.1007/s40263-014-0198-7	Short-term and long-term treatment data not stratified
Zhang XJ, Li QY, Wang Y, et al. The effect of non-benzodiazepine hypnotics on sleep quality and severity in patients with OSA: a meta-analysis. Sleep and Breathing 2014:1-9. doi: 10.1007/s11325-014-0943-7	Short-term treatment or treatment duration unclear
Zheng X, He Y, Yin F, et al. Pharmacological interventions for the treatment of insomnia: quantitative comparison of drug efficacy. Sleep Medicine 2020;72:41-49. doi: 10.1016/j.sleep.2020.03.022	Modelling study

Table IV. Excluded studies found with the systematic literature search for RCTs on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder

Reference	Reason for exclusion
Ancoli-Israel S, Richardson GS, Mangano RM, et al. Long-term use of sedative hypnotics in older patients with insomnia. Sleep Med 2005;6(2):107-13. doi: 10.1016/j.sleep.2004.10.015 [published Online First: 2005/02/18]	Drug not listed in the Swiss specialities list (Zaleplon)
Beaulieu-Bonneau S, Edinger JD, Ivers H, et al. Weekly changes in sleep and insomnia symptoms during acute treatment of persistent insomnia with behavioural or pharmacological therapy. Journal of Sleep Research 2018;27:166-67. doi: 10.1111/jsr.12751	Abstract
Dasgupta R, Randall S, Roehrs T, et al. Greater total sleep time is associated with lower pre-sleep salivary cortisol during chronic zolpidem use. Sleep 2011;34:A174.	Abstract
Dauvilliers Y, Zammit G, Fietze I, et al. Daridorexant, a New Dual Orexin Receptor Antagonist to Treat Insomnia Disorder. Ann Neurol 2020;87(3):347-56. doi: 10.1002/ana.25680 [published Online First: 2020/01/19]	No data on objectives
Edinger J, Morin C, Beaulieu-Bonneau S, et al. Sequenced therapies for patients with chronic insomnia disorder: findings derived from sleep diary data. Sleep Medicine 2019;64:S101. doi: 10.1016/j.sleep.2019.11.278	Abstract
Erman M, Guiraud A, Joish VN, et al. Zolpidem extended-release 12.5 mg associated with improvements in work performance in a 6-month randomized, placebo-controlled trial. Sleep 2008;31(10):1371-8. [published Online First: 2008/10/16]	(Irrelevant) post-hoc/subgroup analysis of an RCT included in the systematic literature search
Fung CH, Martin JL, Josephson K, et al. Predictors of sleeping medication use and impact of cognitive behavioral therapy for insomnia on sleeping medication use among older adults with chronic insomnia. Sleep 2016;39:A350-A51.	Abstract
Hasler BP, Buysse DJ, Germain A. Morningness-eveningness changes in response to behavioral sleep treatment are associated with changes in positive affect and sleep quality. Sleep 2013;36:A230-A31.	Abstract
Hermans LWA, Regis M, Fonseca P, et al. Assessing sleep-wake survival dynamics in relation to sleep quality in a placebo-controlled pharmacological intervention study with people with insomnia and healthy controls. Psychopharmacology (Berl) 2020 doi: 10.1007/s00213-020-05660-3 [published Online First: 2020/09/18]	Short-term treatment (1 night)
Jan YW, Yang CM, Huang SH, et al. Treatment effect of cognitive-behavior therapy for insomnia combined with usual medication. Sleep and Biological Rhythms 2019;17(3):311-21. doi: 10.1007/s41105-019-00218-z	Non-western country (Taiwan)
Koshorek G, Verkler J, Withrow D, et al. Are people with severe insomnia able to discontinue hypnotics after chronic use? Sleep	Abstract

2019;42:A153-A54. doi: 10.1093/sleep/zsz067.377	
Koshorek G, Withrow D, Roth T, et al. Inability to discontinue chronic hypnotic use. Sleep 2018;41:A158.	Abstract
Krystal A, Ancoli-Israel S, McCall W, et al. A 12-week study of eszopiclone in elderly out-patients with primary insomnia: Effects of treatment discontinuation. European Neuropsychopharmacology 2008;18(S4):S517-S18.	Abstract
Krystal A, Cooper J, Schaefer K, et al. Weight changes in patients with primary insomnia following long-term eszopiclone treatment. Sleep 2009;32:A280-A81.	Abstract
Kuo TF, Stowers P, Tortora L, et al. Sodium oxybate and zolpidem in the treatment of chronic insomnia: A randomized, double-blind, double-dummy, placebo-controlled, 3-ARM, parallel-group study. Sleep 2009;32:A273.	Abstract
McCall WV, Benca RM, Rosenquist PB, et al. Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT): A Randomized Clinical Trial. Am J Psychiatry 2019;176(11):957-65. doi: 10.1176/appi.ajp.2019.19030267 [published Online First: 2019/09/21]	Individuals with a medical condition other than chronic insomnia disorder that could affect sleep (major depressive disorder)
Moline M, Murphy P, Pinner K, et al. Effect of lemborexant on sleep architecture in older adults with insomnia disorder. Sleep 2019;42:A150. doi: 10.1093/sleep/zsz067.368	Abstract
Moline M, Pinner K, Cheng J, et al. Effect of lemborexant compared with placebo and zolpidem extended release on sleep architecture in older adults with insomnia disorder. Sleep Medicine 2019;64:S437. doi: 10.1016/j.sleep.2019.11.1227	Abstract
Morin C, Edinger J, Krystal A, et al. How best to sequence cognitive behavioural therapy and medication when treating chronic insomnia with and without psychiatric comorbidity? Journal of Sleep Research 2018;27:56-57. doi: 10.1111/jsr.12751	Abstract
Morin CM, Bastien CH, Brink D, et al. Adverse effects of temazepam in older adults with chronic insomnia. Hum Psychopharmacol 2003;18(1):75-82. doi: 10.1002/hup.454 [published Online First: 2003/01/18]	(Irrelevant) post-hoc/subgroup analysis of an RCT published before 2000 (i.e. not in our search period)
Morin CM, Edinger JD, Krystal AD, et al. Sequenced therapies for comorbid and primary insomnia: Preliminary findings of a randomized controlled trial. Sleep 2015;38:A225.	Abstract
Morin CM, Edinger JD, Krystal AD, et al. Sequential therapies for comorbid and primary insomnia: A randomized controlled trial. Sleep 2017;40:A127.	Abstract
Pan Y, Luo J, Zhang HL. Study on the effect of acupuncture at Sìshéncōng (EX-HN 1) and Bǎihuì (GV 20) on the serum amino acids neurotransmitters of insomnia patients. World Journal of Acupuncture - Moxibustion 2017;27(1):23-27. doi: 10.1016/S1003-5257(17)30095-8	Non-western country (China)

Pchelina PV, Tabidze AA, Poluekotov MG. A Comparative Study of the Efficacy of Cognitive Behavioral Therapy and Zopiclone in Chronic Insomnia. Neuroscience and Behavioral Physiology 2019;49(1):38-44. doi: 10.1007/s11055-018-0688-z	Non-western country (Russia)
Pimlott NJG. Pharmacologic or behavioural therapy for elderly people's insomnia: Which is better? Canadian Family Physician 2000;46(JUL.):1430-32.	Non-pertinent publication type
Randall S, Roehrs T, Harris E, et al. Chronic use of zolpidem is not associated with loss of efficacy. Sleep 2010;33:A221.	Abstract
Randall S, Roehrs T, Maan R, et al. Chronic hypnotic use: Risk of rebound insomnia. Sleep 2009;32:A34.	Abstract
Randall S, Roehrs T, Roth T. Age effects on zolpidem efficacy. Sleep 2012;35:A220.	Abstract
Randall S, Roehrs T, Roth T. Chronic zolpidem: Correlation of subjective and objective efficacy measures and daytime function. Sleep 2012;35:A219.	Abstract
Riemann D, Voderholzer U, Cohrs S, et al. Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. Pharmacopsychiatry 2002;35(5):165-74. doi: 10.1055/s-2002-34119 [published Online First: 2002/09/19]	Short-term treatment (28 days)
Roehrs T, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to dose escalation: A prospective placebo controlled study. Sleep 2010;33:A200.	Abstract
Roehrs T, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not produce withdrawal symptoms on drug discontinuation: A prospective placebo controlled study. Sleep 2011;34:A178.	Abstract
Roehrs T, Randall S, Roth T. Chronic hypnotic self-administration and hyperarousal in insomnia. Sleep 2012;35:A219.	Abstract
Roehrs T, Roth T. Effects of gender on zolpidem efficacy and safety. Sleep 2014;37:A172.	Abstract
Roehrs T, Roth T. Ethnicity and zolpidem sleep effects in insomnia. Sleep 2014;37:A183.	Abstract
Roehrs T, Roth T. Gender effects on zolpidem efficacy and safety. Drug and Alcohol Dependence 2015;156:e191. doi: 10.1016/j.drugalcdep.2015.07.514	Abstract
Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to dose escalation: a prospective placebo-controlled study. Sleep 2011;34(2):207-12. doi: 10.1093/sleep/34.2.207 [published Online First: 2011/02/03]	No data on objectives
Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. J Psychopharmacol 2012;26(8):1088-95. doi: 10.1177/0269881111424455 [published Online First: 2011/10/19]	No data on objectives

Roehrs TA, Roth T. Gender Differences in the Efficacy and Safety of Chronic Nightly Zolpidem. J Clin Sleep Med 2016;12(3):319-25. doi: 10.5664/jcsm.5574 [published Online First: 2015/10/09]	(Irrelevant) post-hoc/subgroup analysis of an RCT included in the systematic literature search
Roehrs TA, Roth T. Hyperarousal in insomnia and hypnotic dose escalation. Sleep Med 2016;23:16-20. doi: 10.1016/j.sleep.2016.06.008 [published Online First: 2016/10/04]	No data on objectives
Rosenberg R, Filippov G, LoPresti A, et al. SAFETY OF LEMBOREXANT IN ELDERLY SUBJECTS WITH INSOMNIA: RESULTS FROM A PHASE 3 STUDY (SUNRISE 1). American Journal of Geriatric Psychiatry 2019;27(3):S155-S56. doi: 10.1016/j.jagp.2019.01.109	Abstract
Rosenberg R, Murphy P, Chou C, et al. Comparison of lemborexant with zolpidem extended release and placebo: topline results from a phase 3 study in subjects 55 years and older with insomnia. Journal of Sleep Research 2018;27:165. doi: 10.1111/jsr.12751	Abstract
Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. JAMA Netw Open 2019;2(12):e1918254. doi: 10.1001/jamanetworkopen.2019.18254 [published Online First: 2019/12/28]	Short-term treatment (30 days)
Scharf MB, Black J, Hull S, et al. Long-term nightly treatment with indiplon in adults with primary insomnia: results of a double-blind, placebo-controlled, 3-month study. Sleep 2007;30(6):743-52. doi: 10.1093/sleep/30.6.743 [published Online First: 2007/06/22]	Drug not listed in the Swiss specialities list (Indiplon)
Schmidt L, Zarra J. Long-term efficacy and safety of zolpidem extended-release 12.5mg administered for 6 months in old patients with chronic primary insomnia. European Neuropsychopharmacology 2011;21:S254. doi: 10.1016/S0924-977X(11)70393-5	Abstract
Sivertsen B. Cognitive therapy superior to zopiclone for insomnia. Journal of Family Practice 2006;55(10):845.	Non-pertinent publication type
Walsh JK, Vogel GW, Scharf M, et al. A five week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Med 2000;1(1):41-49. doi: 10.1016/s1389-9457(99)00006-4 [published Online First: 2000/03/25]	Drug not listed in the Swiss specialities list (Zaleplon)
Wilson SJ, Rich AS, Rich NC, et al. Evaluation of actigraphy and automated telephoned questionnaires to assess hypnotic effects in insomnia. Int Clin Psychopharmacol 2004;19(2):77-84. doi: 10.1097/00004850-200403000-00004 [published Online First: 2004/04/13]	Short-term treatment (2 weeks)
Withrow D, Koshorek G, Roth T, et al. Self-reported sleep during discontinuation of chronic hypnotic use. Sleep 2018;41:A158.	Abstract
Wu R, Bao J, Zhang C, et al. Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. Psychotherapy and Psychosomatics 2006;75(4):220-28.	Non-western country (China)

Zammit G, Mayleben D, Kumar D, et al. Efficacy of lemborexant vs zolpidem extended release and placebo in elderly subjects with insomnia: Results from sunrise 1. Journal of the American Geriatrics Society 2019;67:S51-S52. doi: 10.1111/jgs.15898	Abstract
Zammit G, Mayleben D, Kumar D, et al. EFFICACY OF LEMBOREXANT COMPARED WITH ZOLPIDEM EXTENDED RELEASE AND PLACEBO IN ELDERLY SUBJECTS WITH INSOMNIA: RESULTS FROM A PHASE 3 STUDY (SUNRISE 1). American Journal of Geriatric Psychiatry 2019;27(3):S154-S55. doi: 10.1016/j.jagp.2019.01.108	Abstract
Zammit G, Rosenberg R, Mayleben D, et al. Lemborexant versus zolpidem extended release on morning postural stability in older adults. Journal of Managed Care and Specialty Pharmacy 2019;25:S67.	Abstract
Zammit GK, McNabb LJ, Caron J, et al. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. Curr Med Res Opin 2004;20(12):1979-91. doi: 10.1185/174234304x15174 [published Online First: 2005/02/11]	Drug not listed in the Swiss specialities list (Eszopiclone)
Zarra J, Schmidt L. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, in old patients with chronic primary insomnia: A randomized, doubleblind, placebo-controlled, parallel-group, multicenter study. European Psychiatry 2011;26 doi: 10.1016/S0924-9338(11)73271-0	Abstract
Zarra J, Schmidt L. Long-term efficacyand safety of zolpidem extended-release 12.5 mg administered for six months in older patients with chronic primary insomnia: Multicenter study. Alzheimer's and Dementia 2012;8(4):P586-P87. doi: 10.1016/j.jalz.2012.05.1597	Abstract
Zhou QH, Wang HL, Zhou XL, et al. Efficacy and safety of suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomised, double-blind, double-dummy, placebo-controlled trial. BMJ Open 2017;7(4):e014280. doi: 10.1136/bmjopen-2016-014280 [published Online First: 2017/04/06]	Non-western country (China)

11.3 Appendix 11.3 Search strategy for cost-effectiveness systematic literature search

Table V. Search strategy for the cost-effectiveness systematic literature search: PubMed (MEDLINE)

Population: primary chronic insomnia disorder	"sleep wake disorders"[Mesh] OR sleep*[tiab] OR wake*[tiab] OR awake*[tiab] OR insomnia[tiab] OR DIMS[tiab]
Intervention: sedative-hypnotics	"benzodiazepines"[Mesh] OR benzodiazepine[tiab] OR benzodiazepines[tiab] OR diazepam[tiab] OR oxazepam[tiab] OR potassium clorazepate[tiab] OR lorazepam[tiab] OR bromazepam[tiab] OR clobazam[tiab] OR ketazolam[tiab] OR prazepam[tiab] OR alprazolam[tiab] OR lorazepam, diphenhydramin[tiab] OR "benzodiazepines/analogs and derivatives"[Mesh] OR flurazepam[tiab] OR nitrazepam[tiab] OR flunitrazepam[tiab] OR lormetazepam[tiab] OR temazepam[tiab] OR midazolam[tiab] OR z-drugs[tiab] OR zopiclone[tiab] OR zolpidem[tiab]
Comparison	No search string
Outcomes	No search string
Cost-effectiveness	"Technology Assessment, Biomedical"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "technology assessment" [tiab] OR "economic evaluation" [tiab] OR "economic value" [tiab] OR "cost-benefit" [tiab] OR "cost-effective" [tiab] OR "cost-effectiveness" [tiab] OR "cost-utility" [tiab] OR "cost-consequence" [tiab] OR "quality-adjusted life year" [tiab] OR "QALY" [tiab]
	Language: English, German, French, Dutch

Table VI. Search strategy for the cost-effectiveness systematic literature search: Embase.com and NHS EED

Population: primary chronic insomnia disorder	'sleep disorder'/exp OR sleep*:ti,ab OR wake*:ti,ab OR awake*:ti,ab OR insomnia:ti,ab OR DIMS:ti,ab
Intervention: sedative-hypnotics	'benzodiazepine'/exp OR benzodiazepine:ti,ab OR benzodiazepines:ti,ab OR diazepam:ti,ab OR oxazepam:ti,ab OR "potassium clorazepate":ti,ab OR lorazepam:ti,ab OR bromazepam:ti,ab OR clobazam:ti,ab OR ketazolam:ti,ab OR prazepam:ti,ab OR alprazolam:ti,ab OR "lorazepam, diphenhydramin":ti,ab OR 'benzodiazepine derivative'/exp OR flurazepam:ti,ab OR nitrazepam:ti,ab OR flunitrazepam:ti,ab OR lormetazepam:ti,ab OR temazepam:ti,ab OR midazolam:ti,ab OR z-drugs:ti,ab OR zopiclone:ti,ab OR zolpidem:ti,ab
Comparison	No search string
Outcomes	No search string
Cost-effectiveness	'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assess-

	ment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti
	Language: English, German, French, Dutch

11.4 Appendix 11.4 Excluded studies during full-text selection cost-effectiveness search

Table VII. Excluded studies found with the systematic literature search for economic evaluations on long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia

Reference	Reason for exclusion
Baldwin D. (2005). Short-term treatment with hypnotic drugs for insomnia: going beyond the evidence. *Journal of psychopharmacology (Oxford, England)*, *19*(2), 134–135. https://doi.org/10.1177/0269881105051991	Short-term treatment
Belleville, G., Guay, C., Guay, B., & Morin, C. M. (2007). Hypnotic taper with or without self-help treatment of insomnia: a randomized clinical trial. *Journal of consulting and clinical psychology*, *75*(2), 325–335. https://doi.org/10.1037/0022-006X.75.2.325	Not a cost-effectiveness study
Botteman M. (2009). Health economics of insomnia therapy: implications for policy. *Sleep medicine*, *10 Suppl 1*, S22–S25. https://doi.org/10.1016/j.sleep.2009.07.001	Not a cost-effectiveness study
Dang, A., Garg, A., & Rataboli, P. V. (2011). Role of zolpidem in the management of insomnia. *CNS neuroscience & therapeutics*, *17*(5), 387–397. https://doi.org/10.1111/j.1755-5949.2010.00158.x	Not a cost-effectiveness study
Fiorentino, L., & Ancoli-Israel, S. (2007). Sleep dysfunction in patients with cancer. *Current treatment options in neurology*, *9*(5), 337–346.	Not a cost-effectiveness study
A Gray (Senior Lecturer) (2005) Insomnia in the elderly—Is an evidence-based approach possible?, South African Family Practice, 47:3, 31-36, DOI: 10.1080/20786204.2005.10873197 To link to this article: https://doi.org/10.1080/20786204.2005.10873197	Not a cost-effectiveness study
Gründer, G. & Aldenhoff, J. & Bergmann, Frank & Eckermann, G. & Maier, W. & Möller, H.-J & Fritze, J.. (2009). Opinion of the German Society for Psychiatry, Psychotherapy and Neurology on the recommendations of the Drug Commission of the German Doctors Association on prescribing benzodiazepine-containing hypnotics, September 11, 2008. 16. 79-80.	Non-pertinent publication type, an opinion piece post meeting.
Gupta M, Agarwal M. Understanding medication errors in the elderly. N Z Med J. 2013 Nov	Not a cost-effectiveness study

1;126(1385):62-70. PMID: 24217592.	
Harrington, J. J., & Avidan, A. Y. (2005). Treatment of sleep disorders in elderly patients. *Current treatment options in neurology*, *7*(5), 339–352. https://doi.org/10.1007/s11940-005-0027-x	Not a cost-effectiveness study
Holbrook A. M. (2004). Treating insomnia. *BMJ (Clinical research ed.)*, *329*(7476), 1198–1199. https://doi.org/10.1136/bmj.329.7476.1198	Not a cost-effectiveness study
Lyons, J. S., Larson, D. B., & Hromco, J. (1992). Clinical and economic evaluation of benzodiazepines: a value analysis. *PharmacoEconomics*, *2*(5), 397–407. https://doi.org/10.2165/00019053-199202050-00007	Not a cost-effectiveness study
Martin, S. A., Aikens, J. E., & Chervin, R. D. (2004). Toward cost-effectiveness analysis in the diagnosis and treatment of insomnia. *Sleep medicine reviews*, *8*(1), 63–72. https://doi.org/10.1016/j.smrv.2003.08.001	Not a cost-effectiveness study
McKinstry, B., Wilson, P., & Espie, C. (2008). Non-pharmacological management of chronic insomnia in primary care. *The British journal of general practice: the journal of the Royal College of General Practitioners*, *58*(547), 79–80. https://doi.org/10.3399/bjgp08X264018	Non-pertinent publication type, editorial.
Metge, C., Grymonpre, R., Dahl, M., & Yogendran, M. (2005). Pharmaceutical use among older adults: using administrative data to examine medication-related issues. *Canadian journal on aging = La revue canadienne du vieillissement*, *24 Suppl 1*, 81–95. https://doi.org/10.1353/cja.2005.0052	Not a cost-effectiveness study
Modlin, T. (2002). Sleep disorders and hypnosis: To cope or cure? *Sleep and Hypnosis, 4*(1), 39–46	Not a cost-effectiveness study
Morin, C., Wooten, V., (1996). Psychological and pharmacological approaches to treating insomnia: Critical issues in assessing their separate and combined effects. Clinical Psychology Review, 16 (6) 521-542. https://doi.org/10.1016/0272-7358(96)00027-X.	Not a cost-effectiveness study
Naccache, F., & Vorspan, F. (2018). Stratégies de sevrage de benzodiazépines en ambulatoire. Revue de la littérature [Benzodiazepine cessation in ambulatory practice. A review]. *Presse medicale (Paris, France: (1983)*, *47*(10), 899–912. https://doi.org/10.1016/j.lpm.2018.10.007	Not a cost-effectiveness study
Navarro, R., Mitrzyk, B. M., & Bramley, T. J. (2007). Chronic insomnia treatment and Medicare Part D: implications for managed care organizations. *The*	Not a cost-effectiveness study

American journal of managed care, *13*(5 Suppl), S121–S124.	
Rasu, R., Balkrishnan, R., Shenolikar, R., & Nahata, M. (2005, December 1). Treatment of insomnia: a review and update. *Expert Review of Pharmacoeconomics & Outcomes Research*. https://doi.org/10.1586/14737167.5.6.733	Not a cost-effectiveness study
Reese, J. P., Stiasny-Kolster, K., Oertel, W. H., & Dodel, R. C. (2007). Health-related quality of life and economic burden in patients with restless legs syndrome. *Expert review of pharmacoeconomics & outcomes research*, *7*(5), 503–521. https://doi.org/10.1586/14737167.7.5.503	Not a cost-effectiveness study
Singh, D. (2012). PHS40 An Example of Irrational Decision Making in the Elderly: Why are Pharmacological Therapies Preferentially Reimbursed Over Non-Pharmacological Therapies for Insomnia? Value in Health, 15(7), A525	Non-pertinent publication type, poster's abstract
Sivertsen, B., & Nordhus, I. H. (2007). Management of insomnia in older adults. *The British journal of psychiatry : the journal of mental science*, *190*, 285–286. https://doi.org/10.1192/bjp.bp.106.031278	Not a cost-effectiveness study
Tannenbaum, C., Singh, D., & Diaby, V. (2014). Cost-effectiveness of insomnia treatment strategies when falls are considered: B102. *Journal of the American Geriatrics Society*, *62*.	Non-pertinent publication type, poster's abstract
Taylor, S. R., & Weiss, J. S. (2009). Review of insomnia pharmacotherapy options for the elderly: implications for managed care. *Population health management*, *12*(6), 317–323. https://doi.org/10.1089/pop.2008.0047	Not a cost-effectiveness study
Yeung, W. F., Chung, K. F., Poon, M. M. K., Ho, F. Y. Y., Zhang, S. P., Zhang, Z. J., ... & Wong, V. T. (2012). Chinese herbal medicine for insomnia: a systematic review of randomized controlled trials. *Sleep medicine reviews*, *16*(6), 497-507.	Not a cost-effectiveness study
Mitchell, M. D., Gehrman, P., Perlis, M., & Umscheid, C. A. (2012). Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC family practice*, *13*(1), 40.	Not a cost-effectiveness study
Hirst, A., & Sloan, R. (2001). Benzodiazepines and related drugs for insomnia in palliative care. *Cochrane Database of Systematic Reviews*, (4).	Not a cost-effectiveness study
Tannenbaum, C., Diaby, V., Singh, D., Perreault, S., Luc, M., & Vasiliadis, H. M. (2015). Sedative-hypnotic medicines and falls in community-dwelling older adults: a cost-effectiveness (decision-tree)	No differentiation between sedative-hypnotics classes

analysis from a US Medicare perspective. *Drugs & Aging*, *32*(4), 305-314.	
Bain, K. T. (2006). Management of chronic insomnia in elderly persons. *The American journal of geriatric pharmacotherapy*, *4*(2), 168-192.	Not a cost-effectiveness study
Hajak, G. (2006). New paradigms in the pharmacological treatment of insomnia. *Sleep Medicine*, *7*, S20-S26.	Not a cost-effectiveness study
Menzin, J., Lang, K. M., Levy, P., & Levy, E. (2001). A general model of the effects of sleep medications on the risk and cost of motor vehicle accidents and its application to France. *PharmacoEconomics*, *19*(1), 69–78. https://doi.org/10.2165/00019053-200119010-00005	Not a cost-effectiveness study
Morin C. M. (2003). Measuring outcomes in randomized clinical trials of insomnia treatments. *Sleep medicine reviews*, *7*(3), 263–279. https://doi.org/10.1053/smrv.2002.0274	Not a cost-effectiveness study
Roehrs, T., Verster, J. C., Koshorek, G., Withrow, D., & Roth, T. (2018). How representative are insomnia clinical trials?. *Sleep medicine*, *51*, 118–123. https://doi.org/10.1016/j.sleep.2018.06.003	Not a cost-effectiveness study
Shaw, J., Murphy, A. L., Turner, J. P., Gardner, D. M., Silvius, J. L., Bouck, Z., Gordon, D., & Tannenbaum, C. (2019). Policies for Deprescribing: An International Scan of Intended and Unintended Outcomes of Limiting Sedative-Hypnotic Use in Community-Dwelling Older Adults. *Healthcare policy = Politiques de sante*, *14*(4), 39–51. https://doi.org/10.12927/hcpol.2019.25857	Not a cost-effectiveness study

11.5 Appendix 11.5 Search terms for health-related quality of life and utilities and resource use and costs from the Canadian Agency for Drugs and Technologies in Health (CADTH).

Health related quality of life and utilities	"Quality of Life"[Mesh] OR “Value of Life”[tiab] OR “Quality of Life”[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR eq5d[tiab] OR “eq 5d”[tiab]
Resource use and costs	((economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “eco-nomic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”) OR (“healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance) OR ((cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)) OR (economic* OR pharmacoeconomic* OR price* OR pricing) OR ((healthcare OR “health care”) AND (utilization OR utilisation)) OR (cost* AND (treat* OR therap*)) OR ((direct OR indirect) AND cost*) OR (“resource use” OR “resource utilization" OR “resource utilisation”) OR (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”))