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Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA 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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Executive Summary:

BACKGROUND: Sedative-hypnotic drugs are used to reduce tension and anxiety and to induce calm (sedative effect) or 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. The current total costs of these drugs have a large impact on the national healthcare budget. Despite the high costs, potential harms and clear discouraging guideline recommendations for long-term sedative-hypnotic drug treatment, the rates of sedative-hypnotic drugs use have not changed meaningfully over time.

OBJECTIVE: The aim of the HTA is to investigate the clinical efficacy, effectiveness, safety, and cost-effectiveness of intermediate (1-6 months) and long-term (≥6 months) use 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 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.

METHODS: Clinical and economic evidence was retrieved from systematic literature searches conducted in PubMed (MEDLINE) and Embase.com, as well as other sources (NHS EED and CRD). A *de novo* individual state transition cost-effectiveness model was developed to determine the cost-effectiveness of long-term use of sedative-hypnotic drugs (Z-drugs specifically due to lack of evidence for the other ATC groups of interest) to treat primary chronic insomnia disorder against no treatment, other non-pharmacological treatment, or short-term use (≤ 1 month) of sedative-hypnotic drugs applying a 10-year time horizon, and a 3% discounting of costs and effects. Although the systematic literature searches included the three ATC categories, the model was built only for N05CF (Z-drugs) due to data scarcity. Many of the effectiveness components were sourced from observational studies, as RTC outcomes sourced in the clinical effectiveness systematic literature search do not easily translate to quality-adjusted life years (QALY) and did not cover all effectiveness elements included in the cost-effectiveness model. The uncertainty around input parameters was explored in sensitivity and scenario analyses. In addition, a budget impact analysis was conducted.

RESULTS: Evidence from eight RCTs was evaluated to inform efficacy and safety outcomes of intermediate-term (1-6 months) and long-term (≥6 months) use of Z-drugs compared to placebo, no treatment, other non-pharmacological treatment for the treatment of primary chronic insomnia disorder. Only RCTs on Z-drugs were found; RCTs on benzodiazepine derivatives did not fulfil our inclusion criteria. No RCTs were found comparing intermediate- and long-term sedative-hypnotic drug use to short-term (≤1 month) use. Three RCTs compared intermediate-term use of Z-drugs with behaviour therapy. No studies were found on the efficacy of long-term use of Z-drugs compared with behaviour therapy. Three RCTs compared intermediate-term and three RCTs compared long-term use of Z-drugs with a placebo group.

Compared to placebo, use of Z-drugs seemed efficacious, while intermediate-term treatment results were inconclusive. In the RCT studies, no major safety issues, nor symptoms of tolerance to Z-drugs were observed. Withdrawal from treatment due to adverse events was found to be significantly higher

in long-term Z-drug users compared to placebo users. However, the underlying adverse events were mild, and the serious adverse events were not related to the study medication.

Results from a *de novo* economic model showed that the long-term use of Z-drugs is associated with more costs and less QALYs than short-term use of Z-drugs alone, short-term use of Z-drugs followed by cognitive behavioural therapy for insomnia (CBT-I), CBT-I alone or no treatment. The sensitivity analyses showed that the results were sensitive to the benefit derived from Z-drugs, as well as the baseline quality of life. In most scenario analyses, incremental costs and a reduction of effects with long-term use of Z-drugs were dominated as a strategy by all the comparators in our model. The PSA of each PICO yielded stable incremental costs with little variance, while incremental QALYs were more sensitive to variation in the model.

The budget impact analysis results showed that no treatment or short-term use of Z-drugs could save more than 130 million Swiss francs, while CBT-I alone or short-term use of Z-drugs in combination with CBT-I could save around 30 million Swiss francs.

Relevant ethical, legal, social, and organisational issues were informed by 20 reports, including observational studies, literature reviews, and guidelines. The included literature suggests that dependency and dosage increase are associated with Z-drug use. Long-term use of Z-drugs in the elderly may be accompanied with polypharmacy related side effects. Observational studies show that Z-drug use is associated with an increased risk of road traffic accidents and fractures.

CONCLUSION: Sparse, clinical evidence based on only two RCTs suggests that compared to placebo, long-term (≥6 months) use of Z-drugs is efficacious for the treatment of primary chronic insomnia disorders. No major safety issues, nor symptoms of tolerance to Z-drugs were observed. No RCTs on long-term use of benzodiazepine derivatives were found.

From a health economic perspective, long-term use of Z-drugs most likely increases costs and reduces effects in terms of QALYs relative to short-term use of Z-drugs alone, short-term use of Z-drugs followed by CBT-I, CBT-I alone or no treatment.

Further, literature found Z-drugs to be associated with increased risk of road traffic accidents and fractures.

Executive Summary:

AUSGANGSLAGE: Sedativ-hypnotische Medikamente werden eingesetzt, um Spannung und Angstzustände zu lindern, und haben eine beruhigende (sedative) oder einschläfernde (hypnotische) Wirkung. Gemäss klinischen Leitlinien und Produktinformationen sollten diese Medikamente im Falle einer primär chronischen Insomnie für maximal vier Wochen verschrieben werden. Die momentanen Gesamtkosten für diese Medikamente haben grosse Auswirkungen auf das nationale Gesundheitsbudget. Trotz der hohen Kosten, der möglichen Schäden und der klaren Empfehlungen der Leitlinien gegen eine Langzeitanwendung von sedativ-hypnotischen Medikamenten haben sich die Anwendungsraten sedativ-hypnotischer Medikamente über die Zeit nicht signifikant verändert.

ZIEL: Dieses HTA hat zum Ziel, die klinische Wirksamkeit, die Effektivität, die Sicherheit und die Kosteneffektivität der mittelfristigen (1–6 Monate) und der Langzeitanwendung (≥6 Monate) von in

der Schweizer Spezialitätenliste geführten sedativ-hypnotischen Medikamente der anatomisch-therapeutisch-chemischen Klassen (ATC-Codes) N05BA (Benzodiazepin-Derivate), N05CD (Benzodiazepin-Derivate) oder N05CF (Z-Drugs / Benzodiazepin-verwandte Mittel) zur Behandlung von primär chronischer Insomnie zu überprüfen. Diese Überprüfung erfolgt im Vergleich zu Placebo, keiner Therapie oder einer anderen nicht medikamentösen Behandlung oder im Vergleich zur kurzzeitigen Anwendung (≤1 Monat) von sedativ-hypnotischen Medikamenten.

METHODEN: Aus systematischen Literaturrecherchen, die auf PubMed (MEDLINE) und Embase.com durchgeführt wurden, sowie aus anderen Quellen (NHS EED und CRD) wurde klinische und ökonomische Evidenz gewonnen. Um die Kosteneffektivität einer Langzeitanwendung von sedativ-hypnotischen Medikamenten (spezifisch von Z-Drugs, weil Evidenz für die anderen relevanten ATC-Gruppen fehlt) bei primär chronischer Insomnie im Vergleich zu keiner Therapie, einer anderen nicht medikamentösen Behandlung oder einer kurzfristigen Anwendung (≤1 Monat) von sedativ-hypnotischen Medikamenten zu ermitteln, wurde ein De-novo-Kosteneffektivitätsmodell für individuelle Zustandsübergänge entwickelt. Dabei wurde ein Zeithorizont von 10 Jahren und ein Diskontsatz von 3 % für Kosten und Nutzen verwendet. Obwohl sich die systematischen Literaturrecherchen auf alle drei ATC-Kategorien bezogen, wurde das Modell wegen mangelnder Daten nur für N05CF (Z-Drugs) erstellt. Viele der Effektivitätskomponenten stammten aus Beobachtungsstudien, da sich die Ergebnisse aus randomisierten kontrollierten Studien (RCT), die aus der systematischen Literaturrecherche zur klinischen Effektivität hervorgingen, nur schwer in qualitätsadjustierte Lebensjahre (QALY) transformieren liessen und nicht alle Effektivitätselemente des Kosteneffektivitätsmodells abdeckten. Die Unsicherheit in Bezug auf die Inputparameter wurde in Sensitivitäts- und Szenarioanalysen untersucht. Ausserdem wurde eine Budget-Impact-Analyse durchgeführt.

ERGEBNISSE: Die Evidenz aus acht RCTs wurde evaluiert, um Aussagen zu den Wirksamkeits- und Sicherheitsergebnissen einer mittelfristigen (1–6 Monate) und einer Langzeitanwendung (≥6 Monate) von Z-Drugs im Vergleich zu Placebo, keiner Therapie und einer anderen nicht medikamentösen Therapie für die Behandlung von primär chronischer Insomnie zu erhalten. Es wurden nur RCTs zu Z-Drugs gefunden. Die RCTs zu Benzodiazepin-Derivaten entsprachen nicht unseren Einschlusskriterien. Es wurden keine RCTs gefunden, die die mittelfristige und die Langzeitanwendung von sedativ-hypnotischen Medikamenten mit einer kurzzeitigen Anwendung (≤1 Monat) verglichen. Drei RCTs führten einen Vergleich der mittelfristigen Anwendung von Z-Drugs mit einer Verhaltenstherapie durch. Zur Wirksamkeit der Langzeitanwendung von Z-Drugs im Vergleich zur Verhaltenstherapie wurden keine Studien gefunden. Drei RCTs verglichen die mittelfristige Anwendung und drei RCTs die Langzeitanwendung von Z-Drugs mit einer Placebogruppe.

Im Vergleich zum Placebo schien die Anwendung von Z-Drugs wirksam zu sein, während die Ergebnisse der mittelfristigen Behandlung nicht eindeutig waren. In den RCT-Studien wurden bei Z-Drugs weder grössere Sicherheitsprobleme noch Toleranzsymptome beobachtet. Bei Anwenderinnen und Anwendern, die Z-Drugs langfristig einnahmen, wurde im Vergleich zu Personen, die ein Placebo bekamen, signifikant häufiger ein Abbruch der Behandlung infolge Nebenwirkungen beobachtet. Allerdings handelte es sich dabei um leichte Nebenwirkungen, und die schweren Nebenwirkungen waren nicht auf die Medikation im Rahmen der Studie zurückzuführen.

Ergebnisse eines *de-novo*-ökonomischen Modells haben gezeigt, dass die Langzeitanwendung von Z-Drugs mit mehr Kosten und weniger QALYs assoziiert ist als die alleinige kurzzeitige Einnahme von Z-Drugs, die kurzzeitige Einnahme von Z-Drugs gefolgt von einer kognitiven Verhaltenstherapie für Insomnie (CBT-I), eine CBT-I oder keine Therapie. Gemäss der Sensitivitätsanalysen hatten der Nutzen von Z-Drugs, aber auch die grundlegende Lebensqualität den grössten Einfluss auf die Ergebnisse. In den meisten Szenarioanalysen wurden die inkrementellen Kosten und eine Verringerung der Auswirkungen bei der Langzeitanwendung von Z-Drugs von allen Komparatoren in unserem Modell als Strategie dominiert. Die probabilistische Sensitivitätsanalyse (PSA) lieferte bei Population, Intervention, Comparator und Outcomes (PICO) jeweils stabile inkrementelle Kosten mit geringer Varianz, während inkrementelle QALYs im Modell eine höhere Sensitivität gegenüber Veränderungen aufwiesen.

Die Ergebnisse der Budget-Impact-Analyse zeigten, dass bei keiner Behandlung oder bei einer kurzzeitigen Anwendung von Z-Drugs über 130 Millionen Schweizer Franken eingespart werden könnten, gegenüber rund 30 Millionen Schweizer Franken bei einer alleinigen CBT-I oder der kurzzeitigen Verwendung von Z-Drogen in Kombination mit einer CBT-I.

Relevante ethische, rechtliche, soziale und organisatorische Fragen gingen aus 20 Berichten, einschliesslich Beobachtungsstudien, Literaturreviews und Richtlinien, hervor. Die verwendete Literatur deutet an, dass Abhängigkeit und eine Dosissteigerung mit der Verwendung von Z-Drugs assoziiert sind. Die Langzeitanwendung von Z-Drugs durch ältere Personen kann mit polypharmaziebedingten Nebenwirkungen einhergehen. Beobachtungsstudien zufolge ist die Anwendung von Z-Drugs mit einem erhöhten Risiko von Verkehrsunfällen und Knochenbrüchen assoziiert.

SCHLUSSFOLGERUNG: Spärliche klinische Evidenz, die auf nur zwei RCTs basiert, deutet an, dass im Vergleich zu Placebo eine Langzeitanwendung (≥6 Monate) von Z-Drugs wirksam zur Behandlung von primär chronischer Insomnie eingesetzt werden kann. Es wurden bei Z-Drugs weder grössere Sicherheitsprobleme noch Toleranzsymptome beobachtet. Es gibt keine RCTs zur Langzeitanwendung von Benzodiazepin-Derivaten.

Aus gesundheitsökonomischer Sicht führt eine Langzeitanwendung von Z-Drugs höchstwahrscheinlich zu höheren Kosten und geringeren QALY-Effekten im Vergleich zur alleinigen kurzzeitigen Anwendung von Z-Drugs, zur kurzzeitigen Einnahme von Z-Drugs gefolgt von einer CBT-I, zu einer CBT-I alleine oder zu keiner Behandlung.

Des Weiteren ging aus der Literatur hervor, dass die Anwendung von Z-Drugs mit einem erhöhten Risiko von Verkehrsunfällen und Knochenbrüchen assoziiert ist.

Résumé

SITUATION INITIALE : Les médicaments sédatifs hypnotiques sont utilisés dans le but de réduire la tension et l'anxiété et pour induire le calme (effet sédatif) ou le sommeil (effet hypnotique). Conformément aux directives cliniques et à la notice d'emballage, ces médicaments ne devraient pas être prescrits pendant plus de quatre semaines en cas d'insomnie chronique primaire. Le coût total actuel de ces médicaments se répercute fortement sur le budget national de la santé. Malgré les coûts

élevés, les dommages potentiels et les mises en garde claires contre l'utilisation à long terme, le taux de recours à ces médicaments n'a pas changé de manière significative au fil du temps.

OBJECTIF : L'objectif de l'ETS consiste à étudier l'efficacité clinique (théorique et pratique), la sécurité et le rapport coût-efficacité de l'utilisation à moyen (1 à 6 mois) et à long terme (≥ 6 mois) de médicaments sédatifs-hypnotiques des catégories ATC N05BA (dérivés de benzodiazépine), N05CD (dérivés de benzodiazépine) ou N05CF (médicaments Z / médicaments apparentés aux benzodiazépines) figurant sur la liste des spécialités pour traiter l'insomnie chronique primaire par rapport à un placebo, à l'absence de traitement ou à un autre traitement non pharmacologique, ou par rapport à l'utilisation à court terme (≤ 1 mois) de médicaments sédatifs-hypnotiques.

MÉTHODES : Des recherches systématiques menées dans la littérature spécialisée telle que PubMed (MEDLINE) et Embase.com, ainsi que dans d'autres sources (NHS EED et CRD) ont permis d'amener des preuves cliniques et économiques. Un modèle *de novo* de coût-efficacité de transition d'état individuel a été développé pour déterminer le rapport coût-efficacité de l'utilisation à long terme de médicaments sédatifs-hypnotiques (médicaments Z spécifiquement en raison de l'absence de preuves pour les autres groupes ATC d'intérêt) pour traiter l'insomnie chronique primaire par rapport à l'absence de traitement, à un autre traitement non pharmacologique ou à l'utilisation à court terme (≤ 1 mois) de médicaments sédatifs-hypnotiques avec un horizon temporel de dix ans et une actualisation de 3 % des coûts et des effets. Bien que les recherches systématiques aient porté sur les trois catégories ATC, le modèle n'a été établi que pour N05CF (médicaments Z) en raison de l'insuffisance des données. Nombre d'éléments d'efficacité ont été tirés d'études d'observation ; les résultats des essais randomisés contrôlés (ERC) tirés des recherches systématiques dans la littérature spécialisée sur l'efficacité clinique ne se traduisent pas aisément en gain d'années de vie pondérées par la qualité (QALYG) et ne couvrent pas tous les éléments d'efficacité inclus dans le modèle coût-efficacité. Des analyses de sensibilité et de scénarios ont porté sur l'incertitude entourant les paramètres d'entrée. En outre, l'impact budgétaire a fait l'objet d'une analyse.

RÉSULTATS : Les données probantes de huit ERC ont été évaluées afin de clarifier les résultats en termes d'efficacité et de sécurité de l'utilisation à moyen terme (1 à 6 mois) et à long terme (≥ 6 mois) des médicaments Z par rapport à des placebos, à l'absence de traitement et à un autre traitement non pharmacologique pour le traitement de l'insomnie chronique primaire. Seuls des ERC sur les médicaments Z ont été identifiés. Les ERC sur les dérivés de benzodiazépine ne satisfaisaient pas à nos critères d'inclusion. Aucun ERC comparant le recours aux médicaments sédatifs-hypnotiques à moyen et à long terme au recours à court terme (≤ 1 mois) n'a été trouvé. Trois ERC ont comparé l'utilisation à moyen terme de médicaments Z à la thérapie comportementale. Aucune étude n'a été identifiée comparant l'efficacité à long terme des médicaments Z à la thérapie comportementale. Trois ERC ont comparé l'utilisation à moyen terme et trois ERC, l'utilisation à long terme des médicaments Z avec un groupe placebo.

En comparaison avec le placebo, l'utilisation des médicaments Z semble efficace, tandis que les résultats de traitements à moyen terme ne sont pas concluants. Lors des ERC, aucun problème majeur de sécurité ni aucun symptôme de tolérance aux médicaments Z n'ont été observés. On a constaté que l'abandon du traitement en raison d'effets indésirables était significativement plus élevé chez les

personnes recourant à des médicaments Z à long terme que chez les personnes utilisant un placebo. Néanmoins, les effets indésirables sous-jacents étaient légers et les effets indésirables graves n'étaient pas liés au médicament étudié.

Les résultats d'un modèle économique *de novo* ont montré que l'utilisation à long terme de médicaments Z entraînait plus de coûts et moins de QALYG que l'utilisation à court terme de médicaments Z uniquement, l'utilisation à court terme de médicaments Z suivie d'une thérapie cognitivo-comportementale pour l'insomnie (TCC-I), la TCC-I seule ou aucun traitement. Les analyses de sensibilité ont montré que les résultats étaient sensibles au bénéfice tiré des médicaments Z, ainsi qu'à la qualité de vie de base. Dans la plupart des analyses de scénarios, les coûts différentiels et la baisse des effets de l'utilisation à long terme des médicaments Z ont été dépassés, en tant que stratégie, par tous les comparateurs de notre modèle. Les ASP de chaque PICO ont indiqué des coûts différentiels stables avec peu d'écarts, tandis que les QALYG incrémentielles étaient plus sensibles à la variation dans le modèle.

Les résultats de l'analyse de l'impact budgétaire ont montré que l'absence de traitement ou l'utilisation à court terme de médicaments Z pourrait permettre d'économiser plus de 130 millions francs Suisse, tandis que la TCC-I seule ou l'utilisation à court terme de médicaments Z en association avec la TCC-I pourrait permettre d'économiser environ 30 millions francs Suisse.

Les aspects éthiques, juridiques, sociaux et organisationnels pertinents ont été mis en évidence par 20 rapports, dont des études d'observation, des analyses documentaires et des lignes directrices. La littérature incluse suggère que la dépendance et l'augmentation de la dose sont associées à l'utilisation des médicaments Z. L'utilisation à long terme de médicaments Z chez les personnes âgées peut s'accompagner d'effets secondaires liés à la polypharmacie. Des études d'observation montrent que l'utilisation de médicaments Z est associée à un risque accru de fractures et d'accidents de la route.

CONCLUSION : Des preuves cliniques éparses et basées uniquement sur deux ERC suggèrent que, en comparaison avec un placebo, le recours à long terme (≥ 6 mois) de médicaments Z est efficace pour traiter l'insomnie chronique primaire. Aucun problème majeur de sécurité ni aucun symptôme de tolérance aux médicaments Z n'ont été observés. Aucun ERC sur l'utilisation à long terme des dérivés des benzodiazépines n'a été identifié.

Du point de vue de l'économie de la santé, l'utilisation à long terme des médicaments Z augmente très probablement les coûts et réduit les effets en termes de QALYG par rapport à l'utilisation à court terme des médicaments Z seuls, à l'utilisation à court terme des médicaments Z suivis d'une TCC-I, à la TCC-I seule ou à l'absence de traitement.

Enfin, la littérature spécialisée indique que l'utilisation de médicaments Z est associée à un risque accru de fractures et d'accidents de la route.

Sintesi

SITUAZIONE INIZIALE: i medicamenti sedativo-ipnotici vengono utilizzati per ridurre i livelli di tensione e di ansia e per indurre la calma (effetto sedativo) o il sonno (effetto ipnotico). Secondo le linee guida cliniche e le informazioni di prodotto, questi farmaci non dovrebbero essere prescritti per durate

superiori a quattro settimane per l'indicazione dell'insonnia cronica primaria. I costi totali attuali comportati da questi medicamenti producono un impatto economico incisivo sul bilancio sanitario nazionale. Nonostante fattori quali i costi elevati, i potenziali effetti negativi e le raccomandazioni chiaramente disincentivanti per una terapia a lungo termine con farmaci sedativo-ipnotici espresse nelle linee guida, i tassi di utilizzo per questi preparati non hanno evidenziato variazioni significative nel corso del tempo.

OBIETTIVO: l'obiettivo del presente Health Technology Assessment (HTA) è quello di indagare su efficacia, utilità, sicurezza e rapporto costi-utilità per l'uso a medio termine (1-6 mesi) e a lungo termine (≥6 mesi) dei medicamenti sedativo-ipnotici delle categorie ATC denominate N05BA (derivati delle benzodiazepine del gruppo Ansiolitici), N05CD (derivati delle benzodiazepine del gruppo Ipnotici e sedativi) o N05CF (medicamenti Z / correlati alle benzodiazepine) inseriti nell'elenco svizzero delle specialità per la terapia dell'insonnia cronica primaria, effettuandone un confronto con il placebo, l'assenza di trattamento, altre terapie non farmacologiche, ovvero con l'impiego a breve termine (≤ un mese) degli stessi medicamenti sedativo-ipnotici.

METODI: le evidenze cliniche ed economiche sono state ricavate da ricerche bibliografiche sistematiche condotte in PubMed (MEDLINE) ed Embase.com, nonché attingendo ad altre fonti (NHS EED e CRD). Un modello *de novo* di transizione di stato a livello individuale sull'efficacia dei costi è stato sviluppato al fine di determinare l'efficacia dei costi dell'uso a lungo termine dei medicamenti sedativo-ipnotici (segnatamente medicamenti Z a causa della carenza di elementi di evidenza per gli altri gruppi di interesse ATC) per la terapia dell'insonnia cronica primaria nel raffronto con l'assenza di trattamento, con altre terapie non farmacologiche o con l'impiego a breve termine (≤ 1 mese) di medicamenti sedativo-ipnotici, applicando un orizzonte temporale di dieci anni e uno sconto del 3% su costi ed effetti. Sebbene le ricerche bibliografiche sistematiche abbiano incluso le tre categorie ATC, il modello è stato creato soltanto per quella N05CF (medicamenti Z) a causa della scarsità di dati. Molte delle componenti di utilità sono state reperite da studi osservazionali, in quanto i risultati degli studi RTC individuati nella ricerca bibliografica sistematica di utilità clinica non si traducono facilmente in anni di vita ponderati per la qualità (QALY) e non coprivano l'intero spettro degli elementi di utilità inclusi nel modello costi-utilità. L'incertezza circa i parametri di input è stata esaminata mediante analisi di sensibilità e di scenario. È stata inoltre condotta un'analisi di impatto sul bilancio.

RISULTATI: le evidenze di otto studi controllati randomizzati (RCT) sono state valutate per acquisire informazioni in merito all'efficacia e ai risultati di sicurezza dell'uso a medio termine (1-6 mesi) e a lungo termine (≥6 mesi) dei medicamenti Z rispetto sia al placebo, sia all'assenza di trattamento o ad altre terapie non farmacologiche per la cura dell'insonnia cronica primaria. Sono stati reperiti soltanto RCT su medicamenti Z; gli RCT sui derivati delle benzodiazepine non hanno invece soddisfatto i nostri criteri di inclusione. Non è stato individuato alcun RCT in cui viene effettuato un raffronto tra l'uso a medio e lungo termine dei farmaci sedativo-ipnotici con quello a breve termine (≤1 mese). Tre RCT hanno confrontato l'impiego a medio termine dei farmaci Z con la terapia comportamentale. Non è stato individuato alcuno studio sull'efficacia dell'uso a lungo termine dei farmaci Z rispetto alla terapia comportamentale. Tre RCT hanno confrontato l'uso a medio termine dei medicamenti Z con un gruppo placebo e tre altri RCT hanno fatto lo stesso per l'impiego a lungo termine.

Rispetto al placebo, l'uso dei medicamenti Z è apparso efficace, mentre i risultati di trattamento a medio termine sono stati inconclusivi. Negli studi RCT non sono stati osservati né problematiche rilevanti di sicurezza, né sintomi di tolleranza ai medicamenti Z. L'interruzione del trattamento a causa di eventi avversi è stata individuata come significativamente più elevata negli utilizzatori a lungo termine di medicamenti Z rispetto al gruppo placebo. Gli eventi avversi sottostanti sono stati tuttavia di lieve entità, mentre quelli di grave entità non apparivano correlati al farmaco oggetto dello studio.

I risultati di un modello economico *de novo* hanno mostrato che l'uso a lungo termine di medicamenti Z è associato a costi maggiori e a un numero minore di QALY rispetto sia all'impiego a breve termine di farmaci Z da soli, sia all'uso a breve termine di farmaci Z seguito da terapia cognitivo-comportamentale per l'insonnia (CBT-I), alla sola CBT-I o all'assenza di trattamenti. Le analisi di sensibilità hanno mostrato che i risultati, così come la qualità di vita di base, erano sensibili ai vantaggi derivanti dai medicamenti Z. Nella maggior parte delle analisi di scenario, i costi incrementali e una riduzione degli effetti dati dall'uso a lungo termine dei medicamenti Z sono stati dominati come strategia rispetto a tutti i fattori di comparazione presenti nel nostro modello. Le analisi di sensibilità probabilistiche (PSA) di ogni modello PICO hanno indicato costi incrementali stabili a fronte di una bassa varianza, mentre i QALY incrementali hanno evidenziato una maggiore sensibilità alla variazione nel modello.

I risultati dell'analisi sull'impatto prodotto sul bilancio hanno mostrato che l'assenza di terapia o l'uso a breve termine di medicamenti Z potrebbero consentire risparmi per oltre CHF 130 milioni, mentre i minori costi ammonterebbero a circa CHF 30 milioni in caso di attuazione di terapie cognitivo-comportamentali, sia da sole che in combinazione con l'uso a breve termine di medicamenti Z.

Questioni rilevanti di ordine etico, legale, sociale e organizzativo sono state sollevate da 20 rapporti, tra cui studi osservazionali, rassegne bibliografiche e linee guida. La bibliografia inclusa indica che all'uso dei medicamenti Z sono associati fenomeni di dipendenza e di incremento del dosaggio. L'uso a lungo termine di farmaci Z nelle persone anziane può essere accompagnato da effetti collaterali correlati a polifarmacoterapia. Gli studi osservazionali evidenziano che l'uso di medicamenti Z è associato a un rischio aumentato di incidenti automobilistici e di fratture ossee.

CONCLUSIONE: sparute evidenze cliniche basate soltanto su due RCT indicano che, rispetto al placebo, l'uso a lungo termine (≥6 mesi) di medicamenti Z è efficace per la terapia dell'insonnia cronica primaria. Non sono stati osservati né problematiche rilevanti di sicurezza, né sintomi di tolleranza ai medicamenti Z. Non è stato trovato alcun RCT sull'impiego a lungo termine dei derivati delle benzodiazepine.

Da una prospettiva di economia sanitaria, l'assunzione a lungo termine di medicamenti Z accresce con tutta probabilità i costi e riduce gli effetti in termini di QALY rispetto all'impiego a breve termine di farmaci Z, sia come monoterapia che seguiti da CBT-I, nonché rispetto alla sola CBT-I o all'assenza di trattamento.

Dalla bibliografia è inoltre emerso che i medicamenti Z sono associati a un rischio aumentato di incidenti automobilistici e di fratture ossee.

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Abbreviations and acronyms

ATC	Anatomical Therapeutic Chemical
BI	Budget Impact
BFS	Bundesamt für Statistik
BZ	Benzodiazepines
BZD	Benzodiazepine derivatives
BZRA	Benzodiazepine receptor agonists (BZ, BZD, and Z-drugs)
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEA	Cost-Effectiveness Analysis
CBT-I	cognitive behavioural therapy for insomnia
CHEC	Consensus Health Economic Criteria
CHF	Swiss Franc
COPD	Chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
DARTH	Decision Analysis in R for Technologies in Health
DRG	Diagnosis Related Groups
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESS	Epworth Sleepiness Scale
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public health
GABA	Gamma-aminobutyric acid
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICSD	International Classification of Sleep Disorders
ICER	Incremental cost-effectiveness ratio
LY	Life years
MAIS	Maximum Abbreviated Injury Score
MCID	Minimal clinically important difference
NA	Not applicable
NICE	National Institute for Health and Care Excellence

NHS EED	National Health Service Economic Evaluation Database
OECD	Organisation for Economic Co-operation and Development
OOP	Out-Of-Pocket
OR	Odds ratio
OWSA	One Way Sensitivity Analysis
PICO (EO)	Population, intervention, comparator, outcome, (economic outcomes)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probability Sensitivity Analysis
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality-adjusted life year
RTA	Road traffic accident
RCT	Randomized controlled trials
SD	Standard Deviation
SE	Sleep efficiency
SF-36	Short form health survey-36 items
SL	Swiss speciality list
SOL	Sleep onset latency
TST	Total sleep time
VAS	Visual Analog Scale
Z-drugs	Benzodiazepine related drugs
ZIN	Zorginstituut Nederland (Dutch Healthcare Institute)

Objective of the HTA report

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

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 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 was examined and a central research question was presented based on systematic literature searches. In addition, operational key questions were formulated, in order to determine the full scope of a potential HTA. The target population, the appropriate comparator, and the relevant health outcomes were defined.

Based on the identified evidence in the scoping phase, the feasibility of a full HTA was assessed by the FOPH, and a full HTA report was commissioned for this topic, which is presented here.

1 Policy question and context

Each HTA topic entails a policy and a research question. In healthcare, a **policy question** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology.

This HTA report addresses the following policy question brought forward by the applicant:
Can long-term use of sedative-hypnotic drugs for primary chronic insomnia disorder be restricted?

Persons with sleep problems may suffer one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and 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. To distinguish chronic insomnia disorder not caused by other disorders, the focus of this research is on chronic insomnia disorder as the primary indication. Thus, excluding chronic insomnia disorder as a secondary indication.
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 discouraging guideline recommendations, the rates of long-term use of benzodiazepine derivatives use have not changed meaningfully over time in Europe, USA, Canada, or Australia.[6]
In Switzerland, the total costs for drugs of ATC categories N05BA, N05CD, and N05CF had a downward trend since 2014 to 2019, yet still amounted to 47 million Swiss francs in 2019.[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 in 2009 which assessed the impact of abolishing reimbursement of benzodiazepines for anxiety and sleeping disturbance in the Dutch compulsory health insurance in order to avoid irregular

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

(chronic) use of benzodiazepines. The study showed that the volume of the dispensed prescriptions and doses of benzodiazepines and new diagnoses for anxiety and sleeping disturbance decreased after this restriction, leading to the conclusion that there had been an overuse of benzodiazepines in the past. [8,9] The HTA aims to perform a focused assessment of the efficacy, effectiveness, safety, 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

To answer a policy question, the research question has to be defined and answered first. The **research question** is an answerable inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow.

This HTA report addresses the following research question:

What are the efficacy, effectiveness, and safety, as well as the cost-effectiveness and budget impact of long-term drug use (defined as greater than one month) 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 speciality 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) or compared to short-term use (defined as smaller than or equal to 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.[10] 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 offset 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.[10,11]

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, and actigraphy).[12] Other modalities assisting in the evaluation of insomnia are polysomnography, 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 and sleep diaries.[12,13]

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 (ICSD-2, ICSD-3).[11,14] The definition of chronic insomnia disorder differ between the disease classification systems. 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. Studies found that, for the same population, the ICD-10 yields very low numbers of diagnoses compared to the DSM IV-TR or the ICSD-2.[14] This stems from the stricter definition of insomnia in the ICD-10 compared to the other categorisation frameworks.[13]

Chronic insomnia is thought to be highly prevalent. While prevalence data on insomnia diagnoses from epidemiological studies are rare, a study reviewing prevalence of insomnia found estimates around the world varied from less than 5% (according to the DSM-IV) to as high as 40% (in studies assessing insomnia symptoms).[15] 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.[16] Various risk factors associated with increased prevalence of chronic insomnia include older age, female gender, comorbid medical and psychiatric disorders like depression, chronic illness, or working rotating night shift.[10,13,17–19] 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.[18] 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).[11,12]

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 are oral drugs that 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 other specific hypothalamic nuclei. BZD bind non-selectively at the benzodiazepine binding sides (alpha, beta and gamma subunits) of the GABA receptor, while the Z-drugs have different selective affinities to the BZD-binding side subunits of the GABA-receptor.[20]

BZRAs have been shown to be effective in the acute treatment of insomnia. BZRAs 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.[21,22] Despite efficacy, BZs, BZDs, and Z-drugs may cause important side effects such as cognitive and motor impairments, and somnolence.[21–23] In particular, long duration therapies with BZs may result in the appearance of tolerance, dependency, withdrawal symptoms (e.g. rebound insomnia) and worsening of sleep parameters, such as sleep quality and sleep duration, which can be treated acutely only with an increase in BZs dosage.[23]

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 of Z-drug as well.[20] 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.

Table 1 shows the sedative-hypnotic drugs approved by the Swiss Agency for Therapeutic Products (Swissmedic) and listed in the Swiss speciality 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 for primary chronic insomnia disorder listed in Table 1 should not be given longer than four weeks, although physicians can deem it potentially appropriate in certain circumstances, like acute states of severe psychiatric disorders and palliative care. In these cases, chronic insomnia disorder would likely represent a secondary, not the primary, disorder.

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

ATC Code	Active substance	DDD*	Limitation in SL	Main indication in product information	Indicated to treat sleep disorder or insomnia in the 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.)	Yes
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	Yes
N05BA05	potassium clorazepate	20mg	yes	Anxiety states and the resulting restlessness, tension, agitation, neurovegetative and psychosomatic disorders and complaints	No
N05BA06	lorazepam	2.5mg	yes	Anxiety, tension, and agitation; short-term treatment of sleep disorders caused by anxiety and tension	No
N05BA08	bromazepam	10mg	yes	Anxiety and tension, adjuvant for anxiety in depression, nervous tension, restlessness and insomnia caused by anxiety and tension	Yes
N05BA09	clobazam	20mg	no	Anxiety and its functional manifestations and epilepsy	No
N05BA10	ketazolam[b]		yes	Psychic tension, agitation, restlessness, irritability, nervousness, and insomnia	Yes
N05BA11	prazepam	30mg	yes	Anxiety, tension, excitement, and restlessness	No
N05BA12	alprazolam	1mg	yes	Anxiety, with depression	No
N05BA56	lorazepam, diphenhydramin[b]		no	Insomnia and insomnia of clinically significant severity; difficulty falling asleep, frequent waking up at night)	Yes
Benzodiazepine derivatives					
N05CD01	flurazepam	30mg	no	Sleep disorders, difficulty falling asleep, frequent waking up at night, waking up too early; sleep disorders associated with anxiety states and as a result of chronic diseases	Yes
N05CD02	nitrazepam	5mg	no	Sleep disorders, e.g. due to irritability, overstrain, anger, anxiety, worry, tension, and oppression	Yes
N05CD03	flunitrazepam	1mg	no	Short-term treatment sleep disorders, difficulty falling asleep, frequent waking up at night, waking up too early in the morning	Yes
N05CD06	lormetazepam	1mg	no	Short-term treatment of sleep disorders	Yes
N05CD07	temazepam	20mg	no	Short-term treatment of sleep disorders	Yes
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	Yes
Benzodiazepine related drugs, Z-drugs					
N05CF01	zopiclone	7.5mg	no	Short-term treatment (usually less than 10 days) of sleep disorders	Yes
N05CF02	zolpidem	10mg	no	Short- term treatment of insomnia	Yes
*The DDD listed are general recommendation, not specific indication related DDD.					

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

BZRAs have several contraindications, including BZRAs sensitivity, neuromuscular disease (e.g. myasthenia gravis), narrow-angle glaucoma, respiratory depression (COPD, respiratory failure), Parkinson's disease, porphyria, sleep apnoea, children and adolescents less than 18 years old, pregnancy, and breast-feeding. [24]

[b] No available information on DDD.

4.2 Alternative technologies

There is a variety of pharmacological treatment alternatives to BZRAs, like antihistamines, anti-psychotics, 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, such as maintaining a regular sleep routine, avoid daytime naps, and have a quiet, comfortable bedroom. CBT-I consists of sleep hygiene instructions, stimulus control therapy, sleep restriction therapy, relaxation, and cognitive therapy.[19] 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 and acupuncture) are not recommended.[12]

4.3 Regulatory status / provider

The Swiss licensed BZRAs are diazepam, oxazepam, potassium clorazepate, lorazepam, bromazepam, clobazam, ketazolam, prazepam, alprazolam, lorazepam, flurazepam, nitrazepam, flunitrazepam, lormetazepam, temazepam, midazolam, zopiclone, and zolpidem (Table 1). They must be prescribed by a physician, usually the general practitioner (GP). Currently, sedative-hypnotic drugs are reimbursed without any restrictions (if used in their licensed indication) in Switzerland.

In other European countries, the reimbursement of sedative-hypnotic drugs has been restricted or discouraged with financial incentives. For example, in the Netherlands benzodiazepines were delisted from the Dutch reimbursement list in 2009. [25] While in France, the French National Ministry of Health tried to motivate GPs to reduce the proportion of patients on long-term use of benzodiazepines and patients of 65 years or older who were prescribed long half-life benzodiazepines with a pay-for-performance initiative that could result in an extra payment of up to 490 euros per year for GPs. [26]

5 Population, Intervention, Comparator, Outcome (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: ◦ diazepam ◦ oxazepam ◦ potassium clorazepate ◦ lorazepam ◦ bromazepam ◦ clobazam ◦ ketazolam ◦ prazepam ◦ alprazolam ◦ lorazepam, diphenhydramine • N05CD, benzodiazepine derivatives: ◦ flurazepam ◦ nitrazepam ◦ flunitrazepam ◦ lormetazepam ◦ temazepam ◦ midazolam • N05CF, benzodiazepine related drugs/Z-drugs: ◦ zopiclone ◦ zolpidem
C:	1. Placebo; No treatment; 2. Other non- pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy) 3. 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 (as defined in the included studies) 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)[c]:	**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**

[c] 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.

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, cost-effectiveness, budget impact, ethical, legal, social, 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 speciality 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?
- 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 speciality 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 speciality list to treat primary chronic insomnia disorder?
- Are there **ethical, legal, or social issues** related to 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?
- 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 speciality list to treat primary chronic insomnia disorder?

7 Efficacy, effectiveness, and safety

Summary statement efficacy, effectiveness, and safety

In this HTA, eight RCTs (low risk of bias n=2; moderate/unclear risk of bias n=5; high risk of bias n=1) were included on the efficacy and safety of the intermediate-term (1-6 months) and long-term (≥6 months) use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder. Only RCTs on the ATC category N05CF (Z-drugs) were included, RCTs on sedative-hypnotic drugs of ATC categories N05BA (benzodiazepine derivatives) and N05CD (benzodiazepine derivatives) listed in the Swiss speciality list did not fulfil our inclusion criteria. No RCTs were found with short-term (≤1 month) use of sedative-hypnotic drugs as direct comparator to long-term use.

Efficacy of Z-drugs versus behaviour therapy

No studies were found on the efficacy of long-term (≥6 months) use of Z-drugs compared with behaviour therapy and most efficacy outcomes for intermediate-term (1-6 months) use of Z-drugs for primary chronic insomnia disorder were inconclusive (Table 3). Therefore, no conclusion can be drawn on the efficacy of Z-drugs compared with behaviour therapy.

Efficacy of Z-drugs versus placebo

Compared to placebo, long-term use (≥6 months) of Z-drugs seemed efficacious while results for intermediate (1-6 months) use of Z-drugs were inconclusive. Seven efficacy outcomes were unanimously significant in favour of long-term use of Z-drugs, although this was based on only two RCTs (Table 3).

Safety of Z-drugs

No major safety issues of Z-drugs were reported and no tolerance to Z-drugs was observed in the efficacy studies. In these studies no statistical tests were performed to detect treatment differences of safety. Withdrawal from treatment due to adverse events was found to be significantly higher in long-term Z-drug users compared to placebo users. However, the underlying adverse events were mild and the serious adverse events were not related to the study medication.

Table 3. Overview of the evidence on the efficacy and safety of the long-term use of Z-drugs for the treatment of primary chronic insomnia disorder

Outcomes	Z-drugs versus CBT-I / BT-I						Z-drugs versus placebo					
	Intermediate treatment duration (1-6 months)			Long treatment duration (≥ 6 months)			Intermediate treatment duration (1-6 months)			Long treatment duration (≥ 6 months)		
	Number of RCTs with significant results in favour of:		Not significant	Number of RCTs with significant results in favour of:		Not significant	Number of RCTs with significant results in favour of:		Not significant	Number of RCTs with significant results in favour of:		Not significant
	Z-drugs	CBT-I / BT-I		Z-drugs	CBT-I / BT-I		Z-drugs	Placebo		Z-drugs	Placebo	
Night-time sleep outcome TST: ● Objective ● Subjective	- -	- -	n=1[27] n=2[27, 28]	No RCTs found			- n=1[29]	- -	n=1[27] n=2[27, 30]	n=1[31] n=1[32]	- -	- -
Night-time sleep outcome sleep efficiency: ● Objective ● Subjective	- -	- -	n=1[27] n=1[27]				- -	- -	n=1[27] n=1[27]	n=1[31] -	- -	- -
Night-time sleep outcome WASO: ● Objective ● Subjective	- -	- -	- n=1[28]				- -	- -	- n=1[29]	n=1[31] n=1[32]	- -	- -
Night-time sleep outcome QoS: ● Objective ● Subjective	- -	- -	- -				- -	- -	- -	- n=1[32]	- -	- -
Night-time sleep outcome sleep latency: ● Objective ● Subjective	- -	- n=1[28]	- -				- -	- -	- n=2[29, 30]	n=1[31] n=1[32]	- -	- -
Night-time sleep outcome total wake time: ● Objective ● Subjective	- -	n=1[27] -	- n=1[27]				- -	- -	n=1[27] n=1[27]	- -	- -	- -
Night-time sleep outcome NAW: ● Objective ● Subjective	- -	- -	- -				- n=1[29]	- -	- -	- n=1[32]	- -	- -
Daytime sleepiness outcome sleepiness: ● Objective ● Subjective	- n=1[3] [3]	- -	- -				- -	- -	- -	- n=1[32]	- -	n=1[34] n=1[32]
Daytime sleepiness outcome concentration: ● Objective ● Subjective	- -	- -	- -				- -	- -	- -	- n=1[32]	- -	- -
Treatment response rate	-	-	n=1[28]				-	-	-	-	-	-
Insomnia remission rate	-	-	n=1[28]				-	-	-	-	-	-
Clinical significance of treatment effects	-	n=1[27]	-				-	-	-	-	-	-
Withdrawal due to lack of efficacy	-	-	-				-	-	n=1[30]	-	-	n=1[32]
QoL[a]	-	-	n=1[33]				-	-	n=1[30]	-	-	-

Keys: BT-I = behaviour therapy – insomnia, CBT-I = cognitive behavioural therapy – insomnia, n = number, NAW = number of awakenings, RCT = randomised controlled trial, TST = total sleep time, QoL = quality of life, QoS = quality of sleep, WASO = wake after sleep onset. [a] QoL measures reported in reference[33]: physical and mental component summary of the 36-item short-form health survey (SF-36) and the quality of life inventory; in reference[30]: 10 QoL domains of the SF-36.

7.1 Methodology efficacy, effectiveness, and safety

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 systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[35,36]

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

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:

I. Search for SRs/meta-analyses published from 2010 onwards;
II. Since no pertinent SR was identified in the first step for our specific research objectives, no update search could be done for RCTs based on the search conducted in the included Instead, the first step was followed by a systematic literature search for original RCTs from 2000 onwards;
III. In case no RCT or one only RCT was found, an additional systematic literature search would have been conducted for comparative non-randomised studies. Since multiple RCTs were included, this third step was not implemented.

The following sections describe the SR methodology of the efficacy, effectiveness, and safety of long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder as applied to this HTA.

7.1.1 Databases and search strategy

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

speciality 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. 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 the Appendix 15.1. 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 X20.1. 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 results 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 7.2.2). 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 4. The list of excluded studies is enclosed in the Appendix 15.2.

Table 4. Inclusion and exclusion criteria for SRs/meta-analyses and RCTs

	Inclusion		**Exclusion**	
Period publication	Step 1: SRs • 2010-5 October 2020	Step 2: RCTs • 2000-13 October 2020	Step 1: SRs • <2010	Step 2: RCTs • <2000
Language of publication	Step 1: SRs • English	Step 2: RCTs • English • German • French • Dutch	All other languages	
Country of study	Western countries*		All other countries	
Study design/type	Step 1: SRs • SR/meta-analysis of RCTs	Step 2: RCTs • 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: SRs • 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: RCTs • SR/meta-analysis
Study quality	• Sufficient methodological quality and coherent reporting of the results (e.g. data reported in text and tables are coherent without unexplainable errors and interpretation of the study results is not hampered)		• 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 speciality list†¥ • Treatment duration >1 month		• Benzodiazepine derivatives/Z-drugs not listed in the Swiss speciality list†¥ • Benzodiazepine derivatives/Z-drugs with treatment duration ≤1 month 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) 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 speciality 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.

- Data extraction and synthesis
  The critical appraisal of included studies was done in duplicate. In case of discrepancy a third researcher was consulted to reach consensus. The data extraction spreadsheet was fully checked with the original articles by a second researcher. The data synthesis files and evidence profiles/summary tables were fully reviewed by a second researcher.

7.1.2 Assessment of quality of evidence

Based on the key risk of bias criteria used in the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, the risk of bias of the study designs of the included RCTs was assessed.[37] These key study limitations or risk of bias of RCTs include:

- Lack of allocation concealment (i.e. those enrolling patients are aware of the study arm or period to which the next enrolled patient will be allocated, e.g. based on birth date or chart number)
- Lack of blinding (i.e. patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated)
- Incomplete accounting of patients and outcome events:
  - Loss to follow-up (i.e. the implications of particular rates of loss to follow-up vary widely and is dependent on the relation between loss to follow-up and number of events; the higher the proportion lost to follow-up in relation to intervention and control arm event rates, and differences between intervention and control arm, the greater the threat of bias)
  - Intention to treat (i.e. failure to adhere to the intention-to-treat principle)
- Selective outcome reporting (i.e. incomplete or absent reporting of some outcomes and not others on the basis of the results)
- Other limitations (e.g. use of unvalidated outcome measures; carryover effects in crossover trial)

Each risk of bias criterion of the included RCTs was rated as low risk of bias, moderate or unclear (i.e. not reported in the article) risk of bias, or high risk of bias. Based on the crucial limitations for one or more of these criteria, the risk of bias of the study design within the whole study was rated in one of the three categories: low risk of bias, moderate risk of bias, or high risk of bias. For outcomes for which it was possible to calculate pooled estimates, a GRADE assessment for the level of the quality or certainty of the evidence on outcome level was implemented. Within GRADE, the risk of bias of the study design is one of the features on which the certainty of the evidence is assessed (see below). The risk of bias was assessed by two independent researchers. In case of discrepancy a third researcher was consulted to reach consensus.

The GRADE approach is a system for rating the certainty of a body of evidence in SRs, which for a specific outcome is rated across studies instead of a quality assessment of individual studies.[33] The certainty of the evidence was assessed by looking at the following features of the evidence found for each outcome:

- **Study limitations (risk of bias)** – the 'internal validity' of the evidence
- **Inconsistency** – the heterogeneity or variability in the estimates of treatment effect across studies
- **Indirectness** – the degree of differences between the population, intervention, comparator for the intervention, and outcome of interest across studies
- **Imprecision (random error)** – the extent to which confidence in the effect estimate is adequate to support a particular decision
- **Publication bias/other considerations – the degree of selective publication of studies**

The certainty of the evidence was classified as high, moderate, low, or very low:

- **High** – further research is very unlikely to change our confidence in the estimate of effect
- **Moderate** – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **Low** – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Very low** – any estimate of effect is very uncertain

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

Relevant data from the included RCTs was extracted in a data-extraction spreadsheet in Microsoft Excel. Based on this data-extraction sheet, the data was further summarised and presented in this HTA report in study characteristics tables, summary tables, and accompanying text. Separate summary tables were made for the different outcomes of interest and a pre-defined stratification was implemented as described below. The summary tables present the key features (i.e. risk of bias, intervention used including dose and duration, comparator including duration, and sample size) and main outcomes of the included studies. Additional information on how to interpret the baseline values and the direction of the treatment effects is added with footnotes below the summary tables. If articles presented an outcome in a figure only (without quantification) and there was no difference at baseline between the study arms, the direction and significance of the effect of sedative hypnotic-drugs was summarised in text and tables.

Data stratification

Different levels of heterogeneity in comparator, treatment duration, and outcome measure were observed for the included RTCs. The options for clinically relevant data merging/stratification were discussed with clinical experts, based on the variety of the data reported in the included RCTs. The clinical experts were blinded for the study results. The study results were stratified on multiple levels:

1. Intervention
    a. Benzodiazepines derivates of ATC category N05BA listed in the Swiss speciality list
    b. Benzodiazepine derivatives of ATC category N05CD listed in the Swiss speciality list
    c. Z-drugs of ATC category N05CF listed in the Swiss speciality list

    All categories are reported here for a complete overview of the intervention categories, only RCTs on Z-drugs fulfilled our inclusion criteria and were included in the SR.
2. Comparator: the results of two different comparisons are stratified to make data-merging possible.
    a. Z-drugs versus cognitive behaviour therapy-insomnia (CBT-I)/behaviour therapy-insomnia (BT-I)
    b. Z-drugs versus placebo
3. Treatment duration: within the included RCTs on long-term use (≥1 month), we additionally distinguish between patients on treatment to six months (intermediate-term treatment duration) and patients on treatment for six months or longer (long-term treatment duration).
    a. Patients on intermediate-term treatment duration (1-6 months)
    b. Patients on long-term term treatment duration (≥6 months)
4. Outcomes measure: sleep outcomes were measured subjectively (e.g. questionnaire filled out by the patients) and objectively (e.g. valid test like polysomnogram [PSG]). How sleep outcomes are measured might affect the results, for example patients' self-reported sleep time has been shown to deviate from findings based on PSG, ranging from underestimations to overestimations. [38]
    a. Subjective measured sleep outcomes
    b. Objective measured sleep outcomes

Data synthesis

Based on the summary tables, it was determined for which outcomes it was possible to calculate pooled estimates and implement a GRADE assessment for the certainty of the evidence on outcome level (see Section 7.1.2). Pooled estimates were calculated and a GRADE assessment for the certainty of the evidence on outcome level was made, when 1) two or more studies report on the same outcome and assessed in the same way and 2) sufficient data is reported in the studies.

This could be done for one outcome: withdrawal from treatment due to adverse events on two stratification levels (i.e. comparator and treatment duration). Pooling of data was done with the number of patients provided in the articles included for the safety analysis and an unadjusted risk ratio (RR) was calculated. Considering the heterogeneity in the data, a random-effects model (DerSimonian & Laird[39]) was performed. All analyses were conducted using the MetaXL (www.epigear.com) add-in for Microsoft Excel. The evidence was summarised in GRADE evidence profiles. Evidence profiles include information about the body of evidence (i.e. number of studies including references, study design), the quality

assessment (i.e. risk of bias, inconsistency, indirectness, imprecision, publication bias/other considerations), number of patients in the intervention and control group, effect, and a grade for the quality of evidence.

7.2 Results efficacy, effectiveness, and safety

7.2.1 Evidence base pertaining to efficacy, effectiveness, and safety

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

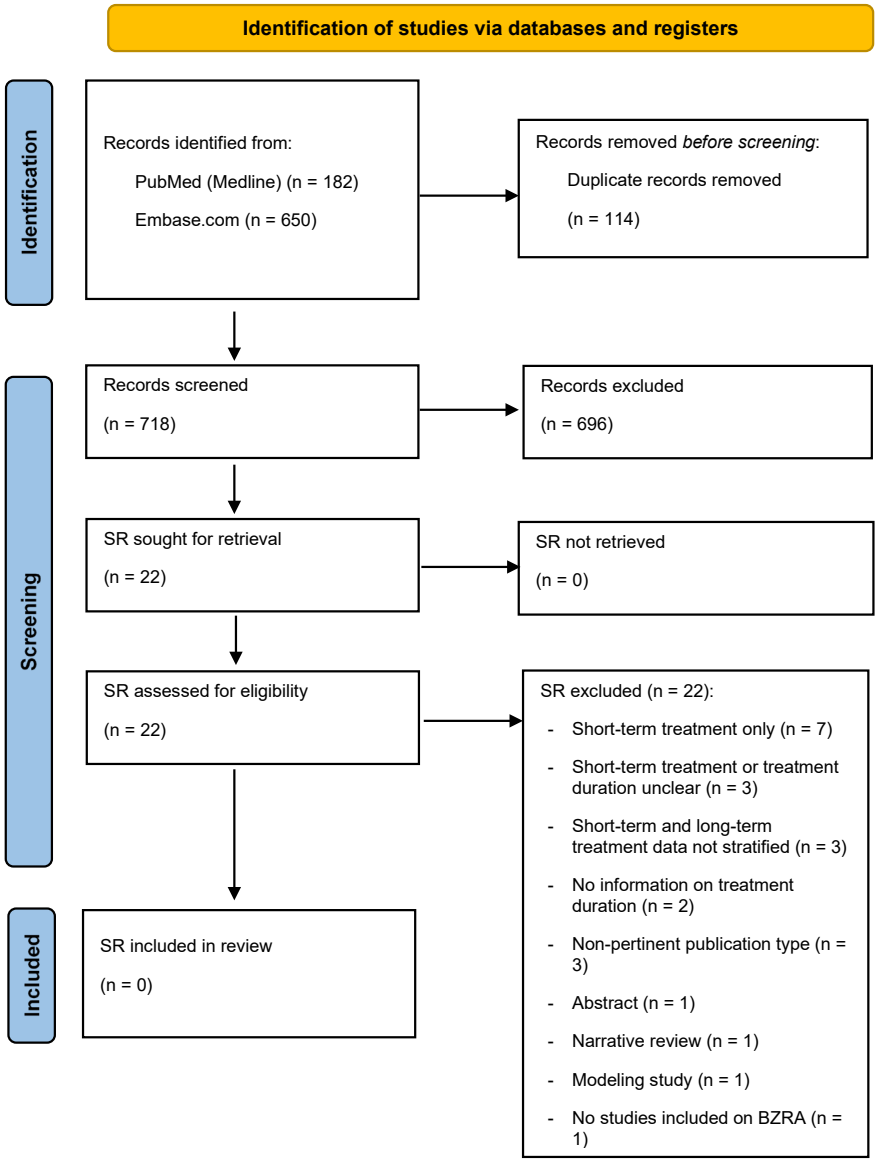
- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in 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 hospitalisation, or cause prolongation of existing hospitalisation (SAEs).

7.2.2 PRISMA flow diagram

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 15.2.

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



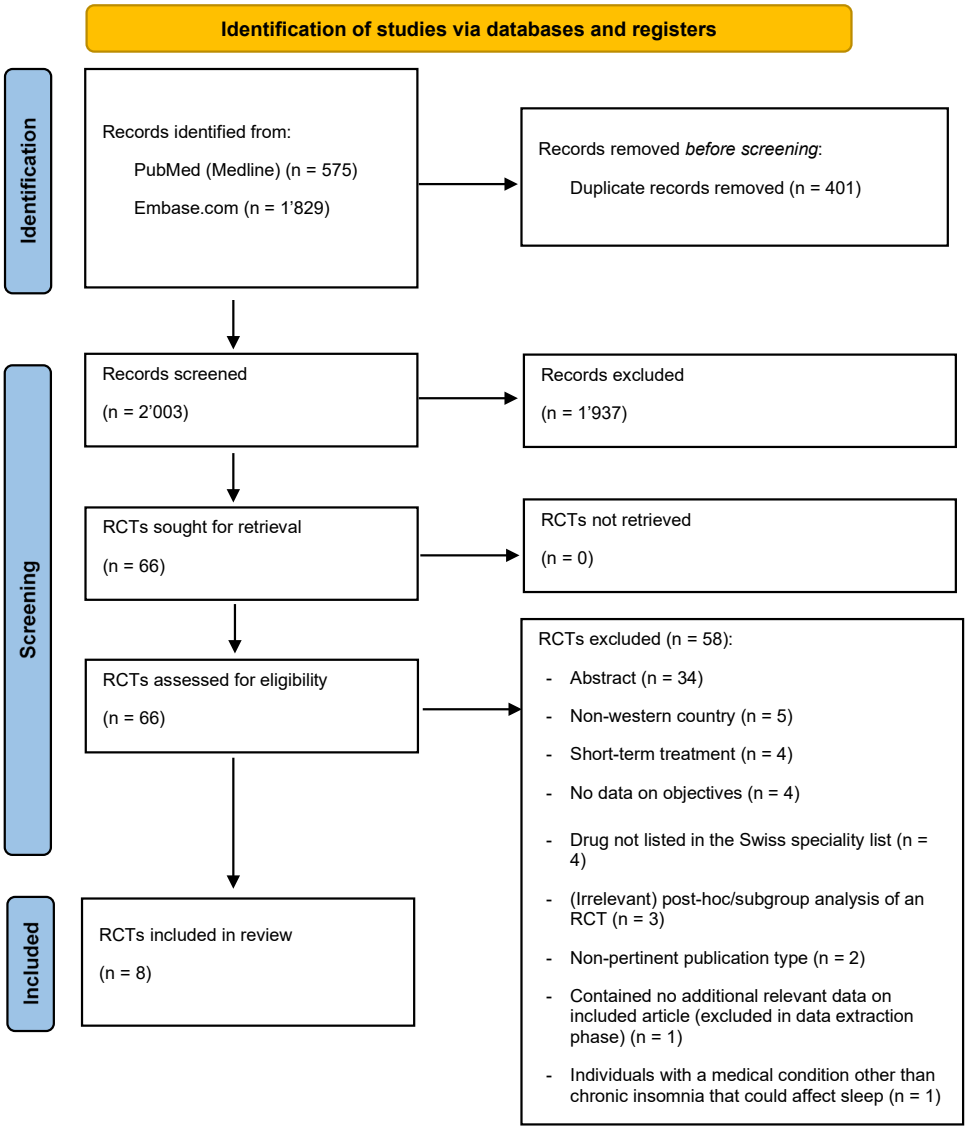
Keys: BZRA = benzodiazepine derivates and Z-drugs, SRs = systematic reviews

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, eight RCTs were included. Only studies on Z-drugs were found. None of the studies on benzodiazepines derivates fulfilled the inclusion/exclusion criteria and were therefore excluded.

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) and a complete overview of the reasons for exclusion by each excluded RCT is enclosed in Appendix 15.2.

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



Keys: RCT = randomised control trial

7.2.3 Study characteristics and quality assessment of included studies

The study characteristics and risk of bias is presented using two levels of stratification, since only RCTs on Z-drugs fulfilled our inclusion criteria and were included in the SR. Firstly, the data is stratified by comparator: Z-drugs compared with CBT-I/BT-I and Z-drugs compared with placebo. No RCTs were found with short-term use (≤1 month) of sedative-hypnotic as direct comparator. Secondly, the data is stratified for intermediate treatment duration (1-6 months) and long treatment duration (≥6 months).

7.2.3.1 RCTs on Z-drugs versus behaviour therapy

Three RCTs were included in this HTA report that compared Z-drugs versus behaviour therapy in adults with primary chronic insomnia disorder. The treatment duration of all three RCTs on Z-drugs versus behaviour therapy was 6 weeks (intermediate treatment duration), no studies were found that reported on long treatment duration.

Intermediate treatment duration (1-6 months)

Two RCTs were performed in Norway and included subjects aged ≥55 years meeting DSM-IV criteria for insomnia for 6 months[33] and 3 months (without comorbidities).[27] The other RCT was performed in the USA and Canada and included subjects aged ≥21 years meeting a combination of DSM-IV-TR criteria for 1 month, Insomnia Research Diagnostic Criteria, and ICSD for chronic insomnia disorder without comorbidities.[28] Zopiclone (7.5 milligram [mg], continuous use) was used in two RCTs[27,33] and Zolpidem (5 mg, continuous use) in one RCT.[28] The number of included cases ranged from 16[27] to 107[28] in the intervention group. Night-time sleep outcomes were reported in two RCTs,[27,28] daytime sleepiness outcomes and QoL were reported in one RCT[33], and safety data was reported in two RCTs.[27,33] A summary of the study characteristics is included in Table 5 and the risk of bias of the study designs of the individual RCTs in Table 6. The study design of two RCTs had a moderate/unclear risk of bias[28,33] and of one RCT the study design had a low risk of bias.

Long treatment duration (≥6 months)

No studies were identified that reported for primary chronic insomnia disorder patients using long-term use of Z-drugs for more than six months compared with behaviour therapy.

Table 5. Study characteristics of the RCTs included on Z-drugs versus behaviour therapy

First author, year	Country	Study population*	Sample size in baseline table RCT	Intervention - Dose - Frequency - Duration	Comparator Other instructions	Outcomes
Intermediate treatment duration (1-6 months)						
Morin, 2020[28]	USA and Canada	Subjects aged ≥21 y meeting criteria (combination of DSM-IV-TR[†] for 1 month, Insomnia Research Diagnostic Criteria, and ICSD) for chronic insomnia disorder without comorbidities *Age (mean ± SD in y)* 45.6 ± 14.9 *Sex (% male)* 37.4%	I: n = 107 C: n = 104	**Zolpidem** - 5 mg (10 mg possible in men) - Continuous use - 6 weeks	**BT-I** - Sleep restriction and stimulus control procedures Generic sleep hygiene education on impact of stimulants, alcohol, caffeine, and exercise on sleep	- Night-time sleep outcomes: TST[‡](S), WASO[‡](S), sleep latency[‡](S) - Daytime sleepiness outcome: NR Treatment response and insomnia remission - QoL: NR - Safety: NR
Omvik, 2008[33]	Norway	Subjects aged ≥55 y meeting DSM-IV[§] diagnosis of primary insomnia for 6 months with comorbidities *Age (mean ± SD in y)* 60.8 ± 5.5 *Sex (% male)* 52.2%	I: n = 22 C: n = 23	**Zopiclone** - 7.5 mg - Continuous use - 6 weeks	**CBT-I** - Sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, progressive relaxation technique Encouraging to adhere to program	- Night-time sleep outcomes: NR - Daytime sleepiness outcomes: sleepiness[#](O) - QoL: PCS, MCS, QoL - Safety[‖]: withdrawal due to adverse events
Sivertsen, 2006[27]	Norway	Subjects aged ≥55 y meeting DSM-IV[§] criteria for insomnia for 3 months without comorbidities *Age (mean ± SD in y)* 60.8 ± 5.4[¶] *Sex (% male)* 52.2%	I: n = 16 C: n = 18	**Zopiclone** - 7.5 mg - Continuous use - 6 weeks	**CBT-I** - Sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, progressive relaxation technique Encouraging to adhere to program	- Night-time sleep outcomes: TST[‡#](O;S), SE[‡#](O;S), total wake time[‡#](O;S) Daytime sleepiness outcomes: NR - QoL: NR - Safety[‖]: withdrawal due to adverse events
Long treatment duration (≥6 months)						
No studies identified						

Keys: BT-I = behaviour therapy – insomnia, C = comparator, CBT-I = cognitive behaviour therapy – insomnia, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders-fourth edition-Text Revision, I = intervention, ICSD = International Classification of Sleep Disorders, MCS = mental component summary, mg = milligram, n = number, NR = not reported, O = objective measured sleep outcome, PCS = physical component summary, QoL = quality of life, QoLI = Quality of life inventory, RCT = randomised controlled trial, S = subjective measured sleep outcome, SD = standard deviation, SE = sleep efficiency, TST = total sleep time, USA = United States of America, WASO = wake after sleep onset, y = years. * Without comorbidities implies the exclusion of subjects with (untreated) (neuro)psychiatric disorder or having other sleep disorders (e.g. periodic limb movement disorder, sleep apnoea), condition with a potential to affect sleep, or conditions which could interact with pharmacokinetics or pharmacodynamics of intervention treatment. [†] DSM-IV-TR primary insomnia criteria: The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month (the predominant complaint is difficulty initiating sleep, or the predominant complaint is difficulty maintaining sleep, or the predominant complaint is nonrestorative

sleep); The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or parasomnia; The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalised anxiety disorder, a delirium); The disturbance is not due to the direct physiological effects of a substance.[40] ‡ Subjective sleep measures are based one's perception on e.g. the ease falling asleep, how long they were asleep, and the period of wakefulness occurring after sleep onset. Instruments used for subjective sleep outcomes can be survey documents filled out at the clinic, daily diaries, or morning questionnaires filled out at home. § DSM-IV primary insomnia criteria: The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month; The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia; The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalised anxiety disorder, a delirium); The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.[41] ‖ Safety outcomes were reported to the investigator at the each clinic visit. ¶ The baseline age and sex in Sivertsen et al., 2006 applies to all three treatment groups zopiclone, baseline, and CBT-I. # Objective measured sleep outcome. Polysomnogram (PSG) is the standard test providing valid measures of ample sleep outcomes like sleep latency, TST, WASO, SE, and NAW.[42]

Table 6. Risk of bias of the RCTs included on Z-drugs versus behaviour therapy

First author, year	Allocation concealment	Blinding	Loss to follow-up - treatment duration - loss to FU per trial arm (%) - reasons for loss to FU reported per trial arm (y/n) - clinically relevant difference in loss to FU per trial arm (y/n/?)	Intention to treat	Selective outcome reporting	Other limitations	RISK OF BIAS
Intermediate treatment duration (1-6 months)							
Morin, 2020[28]	Yes (sealed envelopes)	Single blind (rater)	- 6 weeks - zolpidem 25.2%; BT-I 15.3% - no - unclear	Yes	Adverse events were monitored but NR; not all p-values reported	Funded by non-industry	Moderate/ unclear
Omvik. 2008[33]	NR	Single blind (not described)	- 6 weeks - zopiclone 9.1%; CBT-I 4.3% - yes - no	NR	Placebo group was left out of the statistical analyses	Funded by non-industry	Moderate/ unclear
Sivertsen, 2006[27]	Yes (sealed boxes)	Single blind/ double blind (participants/ researchers)	- 6 weeks - zopiclone 6.3%; placebo 0%; CBT-I 0% - yes - no	Yes	No	Funded by non-industry	Low
Long treatment duration (≥6 months)							
No studies identified							

Keys: BT-I = behaviour therapy – insomnia, CBT-I = cognitive behaviour therapy – insomnia, FU = follow-up, NR = not reported. Low risk of bias; Moderate or unclear risk of bias.

7.2.3.2 RCTs on Z-drugs versus placebo

Six RCTs were included in this HTA report that compared Z-drugs with placebo in adults with primary chronic insomnia disorder. In three RCTs, the treatment duration ranged between 6 weeks to three months (intermediate treatment duration), and in three RCTs the treatment duration ranged between 6 months and 12 months (long treatment duration). Zolpidem was the most commonly used intervention drugs (in five RCTs). A summary of the study characteristics is included in Table 7 and the risk of bias of the study designs of the individual RCTs in Table 8. The most common risk of bias arises for allocation concealment (not reported in three RCTs) and loss to follow-up (two RCTs).

Intermediate treatment duration (1-6 months)

Of the three RCTs with intermediate treatment duration, one study was conducted in Norway[27] and for two RCTs the country in which the study was conducted was not reported (authors based in the USA).[29,30] All three studies included subjects meeting DSM-IV criteria for (primary) insomnia without comorbidities but the applied age ranges and the duration for which people need to meet the DSM-IV criteria varied (see Table 7). Zopiclone (7.5 mg, continuous use) was the intervention drugs used in the study of Sivertsen et al., 2006[27] for 6 weeks in total. Zolpidem (10 mg, intermittent use) was used in Walsh et al., 2000[30] and Perlis et al,. 2004[43] for a duration of 8 weeks and 3 months, respectively. The number of cases in the intervention group ranged from 16 cases[27] to 98 cases.[29] Night-time sleep outcomes were reported in two RCTs,[27,30] QoL in one RCT[30], and safety data in all three RCTs. [27,29,30] None of the studies reported daytime sleepiness outcomes. The study design of two RCTs had a low risk of bias and of one RCT had a moderate/unclear risk of bias (see Table 8).

Long treatment duration (≥6 months)

Two out of the three RCTs with long treatment duration were performed in the USA.[32,34] In the third RCT, no country was reported but all authors were based in the USA.[31] All three studies applied different age ranges and DSM-IV(-TR) criteria the patients needed to fulfil to participate in the study (see Table 7). Zolpidem (10 mg, continuous use) was the intervention drugs in two RCTs, for respectively 8 months and 12 months.[31,34] Zolpidem extended release (12.5 mg, intermittent use) was the intervention drug in one RCT for 6 months.[32] The number of cases in the intervention group ranged from 44 cases[31]to 669 cases. [32] Night-time[31,32] and daytime[32,34] sleep outcomes were reported in two different RCTs and none of the RCTs with long treatment duration reported on QoL. Safety outcomes were reported in two RCTs.[31,34] The study design of two RCTs had a moderate/unclear risk of bias and of one RCT the study design had a high risk of bias (see Table 8).

Table 7. Study characteristics of the RCTs included on Z-drugs versus placebo

First author, year	Country	Study population*	Sample size in baseline table RCT	Intervention - Dose - Frequency - Duration	Comparator Other instructions	Outcomes
Intermediate treatment duration (1-6 months)						
Sivertsen, 2006[27]	Norway	Subjects aged ≥55 y meeting DSM-IV† criteria for insomnia for 3 months without comorbidities *Age (mean ± SD in y)* 60.8 ± 5.4‖ *Sex (% male)* 52.2%‡	I: n = 16 C: n = 12	**Zopiclone** - 7.5 mg - Continuous use - 6 weeks	**Placebo** Encouraging to adhere to program	- Night-time sleep outcomes: TST§‖(O;S),SE§‖(O;S), total wake time§‖(O;S) - Daytime sleepiness outcomes: NR - QoL: NR - Safety¶: withdrawal due to adverse events

First author, year	Country	Study population*	Sample size in baseline table RCT	Intervention - Dose - Frequency - Duration	Comparator Other instructions	Outcomes
Walsh, 2000[30]	NR (authors from USA)	Subjects aged 21-65 y meeting DSM-IV† diagnosis of primary insomnia for 1 month without comorbidities *Age (mean ± SD in y)* NR *Sex (% male)* NR	I: n = 82 C: n = 81	**Zolpidem** - 10 mg - Intermittent use; 3-5 tablets/ week - 8 weeks	**Placebo** Other instructions NR	- Night-time sleep outcomes: TST‖ #(S), sleep latency‖(S) - Daytime sleepiness outcomes: NR - Withdrawal due to lack of efficacy -QoL: SF-36 Safety¶: withdrawal due to adverse events, tolerance
Perlis, 2004[29]	NR (authors from USA)	Subjects aged 18-64 y meeting DSM-IV† criteria for primary insomnia for 1 month without comorbidities *Age (mean ± SD in y)* 41.0 ± 12.8 *Sex (% male)* 29.0%	I: n = 98 C: n = 101	**Zolpidem** - 10 mg - Intermittent use; 3-5 tablets/ week - 3 months	**Placebo** Abstain from psychotropic medications, medications with effects on sleep; not consume large meals <2 hours of bedtime, drink alcohol, use CNS-active medications within several hours of bedtime	- Night-time sleep outcomes: TST‖#(S), WASO‖#(S), sleep latency‖#(S), NAW‖#(S) - Daytime sleepiness outcomes: NR - QoL: NR Safety¶: withdrawal due to adverse events, serious adverse events, tolerance
Long treatment duration (≥6 months)						
Randall, 2012[31]	NR (authors from USA)	Subjects aged 23-70 y meeting DSM-IV-TR** criteria for primary insomnia for 1 month without comorbidities *Age (mean ± SD in y)* 50.4 ± NR *Sex (% male)* 40.7%	I: n = 44 C: n = 47	**Zolpidem** - 10 mg (5 mg if >60 y) - Continuous use - 8 months	**Placebo** Abstain from alcohol 3-4 hours prior bedtime	- Night-time sleep outcomes: TST§(O), SE§(O), WASO§(O), sleep latency§(O) - Daytime sleepiness outcomes: NR - QoL: NR - Safety¶: withdrawal due to adverse events, tolerance
Roehrs, 2011[34]	USA	Subjects aged 21-70 y meeting DSM-IV-TR† criteria for primary insomnia for 1 month, show sleep efficiencies ≤85% without comorbidities *Age (mean ± SD in y)* NR *Sex (% male)* NR	I: n = 50 C: n = 45	**Zolpidem** - 10 mg (5 mg if >60 y) - Continuous use - 12 months	**Placebo** Other instructions NR	- Night-time sleep outcomes: NR - Daytime sleepiness outcomes: Sleepiness§(O) - QoL: NR - Safety: NR
Krystal, 2008[32]	USA	Subjects aged 18-64 y	I: n = 669 C: n = 349	**Zolpidem extended release**	**Placebo**	- Night-time sleep outcomes: QoS‖(S), TST‖#(S),

First author, year	Country	Study population*	Sample size in baseline table RCT	Intervention - Dose - Frequency - Duration	Comparator Other instructions	Outcomes
		meeting DSM-IV† criteria for chronic primary insomnia for 3 months without comorbidities *Age (mean ± SD in y)* 45.7 ± 11.0 *Sex (% male)* 38.8%		- 12.5 mg - Intermittent use; 3-7 tablets/ week - 6 months	Sleep hygiene instructions, refrain from alcohol	WASO‖#(S), sleep latency‖#(S), NAW‖#(S) - Daytime sleepiness outcomes: sleepiness‖(S), sleepiness‖#(S), concentration‖#(S) - Withdrawal due to lack of efficacy - QoL: NR Safety¶: withdrawal due to adverse events, serious adverse events, tolerance

Keys: C = comparator, CNS = central nervous system, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision, I = intervention, mg = milligram, n = number, NAW = nocturnal awakenings, NR = not reported, O = objective measured sleep outcome, QoS = quality of sleep, S = subjective measured sleep outcome, SD = standard deviation, SE = sleep efficiency, TST = total sleep time, USA = United States of America, WASO = wake after sleep onset, y = year. * Without comorbidities implies the exclusion of subjects with (untreated) (neuro)psychiatric disorder or having other sleep disorders (e.g. periodic limb movement disorder, sleep apnoea), condition with a potential to affect sleep, or conditions which could interact with pharmacokinetics or pharmacodynamics of intervention treatment. † DSM-IV primary insomnia criteria: The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month; The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia; The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalised anxiety disorder, a delirium); The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.[44] ‡ The baseline age and sex in Sivertsen et al., 2006 applies to all three treatment groups zopiclone, baseline, and cognitive behaviour therapy. § Objective measured sleep outcome. Polysomnogram (PSG) is the standard test providing valid measures of ample sleep outcomes like sleep latency, TST, WASO, SE, and NAW.[42] ‖ Subjective measured sleep outcome are based one's perception on e.g. the ease falling asleep, how long they were asleep, and the period of wakefulness occurring after sleep onset. Instruments used for subjective sleep outcomes can be survey documents filled out at the clinic, daily diaries, or morning questionnaires filled out at home. ¶ Safety outcomes were reported to the investigator at the each clinic visit. # Figure only. **DSM-IV-TR primary insomnia criteria: The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month (the predominant complaint is difficulty initiating sleep, or the predominant complaint is difficulty maintaining sleep, or the predominant complaint is nonrestorative sleep); The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or parasomnia; The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalised anxiety disorder, a delirium); The disturbance is not due to the direct physiological effects of a substance.[40]

Table 8. Risk of bias of the RCTs included on Z-drugs versus placebo

First author, year	Allocation concealment	Blinding	Loss to follow-up - treatment duration - loss to FU per trial arm (%) - reasons for loss to FU reported per trial arm (y/n) - clinically relevant difference in loss to FU per trial arm (y/n/?)	Intention to treat	Selective outcome reporting	Other limitations	RISK OF BIAS
Intermediate treatment duration (1-6 months)							
Sivertsen, 2006[27]	Yes (sealed boxes)	Single blind/ double blind (participants/ researchers)	- 6 weeks - zopiclone 6.3%; placebo 0%; CBT-I 0% - yes - no	Yes	No	Funded by non-industry	Low
Walsh, 2000[30]	Yes (randomisation schedule supplied)	Double blind (not described)	- 8 weeks - zolpidem 22.0%; placebo 12.3% - yes - no	Yes	No	Funded by industry	Low
Perlis, 2004[29]	NR	Double blind (not described)	- 12 weeks - zolpidem 18.4%; placebo 20.8% - yes - no	Yes	No	Funded by industry	Moderate/ unclear
Long treatment duration (≥6 months)							
Randall, 2012[31]	NR	Double blind (participants/ researchers)	- 8 months - zolpidem 26.7%; placebo 27.7% - yes - no	Yes	No	Not funded by industry (other funding NR)	Moderate/ unclear
Roehrs, 2011[34]	NR	Double blind (not described)	- 8 months - zolpidem NR; placebo NR - NR - NR	NR	WASO, TST, and SL only reported for baseline	Not funded by industry (other funding NR)	High
Krystal, 2008[32]	Yes (randomisation schedule supplied)	Double blind (not described)	- 6 months - zolpidem-ER 34.8%; placebo 47.2% - yes - no	Yes	No	Funded by industry	Moderate/ unclear

Keys: FU = follow-up, NR = not reported, zolpidem-ER = zolpidem – extended release, SL = sleep latency, TST = total sleep time, WASO = wake after sleep onset. Low risk of bias; Moderate or unclear risk of bias; High risk of bias.

7.2.4 Findings efficacy

The efficacy results are grouped by outcome and presented using several levels of stratification. Firstly, the data is stratified by comparator: Z-drugs compared with CBT-I/BT-I and Z-drugs compared with placebo. Secondly, the data is stratified for intermediate treatment duration (1-6 months) and long treatment duration (≥6 months). And thirdly, night-time sleep outcomes and daytime sleepiness outcomes are separately presented for outcomes measured objectively and subjectively. An explanation on how to interpret the baseline values and the change from baseline of sleep outcomes is provided in footnotes below the tables.

7.2.4.1 Z-drugs versus behaviour therapy

7.2.4.1.1 Intermediate treatment duration (1-6 months)

Night-time sleep outcomes

One RCT reported on objective measured night-time sleep outcomes of Z-drugs (zopiclone) compared with CBT-I for intermediate-term treatment of primary chronic insomnia disorder.[27] The results of three different outcomes were given: total sleep time (TST), sleep efficiency, and total wake time (see Table 9). All three outcomes were in favour of CBT-I, but the adjusted change from baseline was only significant for the outcome total wake time (-4% in the zopiclone group, -52% in the CBT-I group; $p<0.001$).

Two RCTs reported on five subjective measured night-time sleep outcomes of Z-drugs (zolpidem, zopiclone) compared with CBT-I/BT-I for intermediate-term treatment of primary chronic insomnia disorder.[27,28] TST was reported in both studies, sleep efficiency, wake after sleep onset (WASO), sleep latency, and total wake time were reported in one study each (see Table 9). The improvement of TST was higher in the Z-drugs group compared with the BT-I/CBT-I in both studies, but in none of the studies this difference was significant. Contrary, for the remaining outcomes BT-I/CBT-I was in favour of Z-drugs, but only for sleep latency the change from baseline was significantly larger in the BT-I group (-21.1%) compared with the zolpidem group (-11.7%) with a p-value of 0.04.[28]

Table 9. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus behaviour therapy: night-time sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	TST* Mean (SD) baseline value, minutes Adjusted change from baseline, % or minutes (SD)	Treatment difference; p-value	Sleep efficiency† Mean (SD) baseline value, % Adjusted change from baseline, %	Treatment difference; p-value	WASO‡ Mean (SE) baseline value, minutes Adjusted change (SE) from baseline, minutes	Treatment difference; p-value	Sleep latency§ Mean (SE) baseline value, minutes Adjusted change (SE) from baseline, minutes	Treatment difference; p-value	Total wake time‖ Mean (SD) baseline value, minutes Adjusted change from baseline, %	Treatment difference; p-value
Objective outcomes												
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	388.3 (58.3) -17%	NR; p=0.5	82.3 (8.2) -1%	NR; p=0.09	- -	-	- -	-	102.8 (54.9) -4%	NR; p<0.001
	CBT-I (6 weeks)	18	370.0 (63.6) -7.1%		81.4 (7.4) 9%		- -		- -		107.8 (41.0) -52%	
Subjective outcomes												
Morin, 2020[28] Moderate/unclear risk of bias	Zolpidem (5 mg, 6 weeks, continuous use)	107	357.6 (SE 9.6) 33.1 (11.7)	NR; p=0.09	- -	-	59.4 (3.8) -16.6 (5.5)	NR; p=0.53	41.6 (4.1) -11.7 (3.5)	NR; p=0.04	- -	-
	BT-I (6 weeks)	104	360.4 (SE 8.6) 10.6 (5.9)		- -		60.6 (3.9) -33.0 (3.6)		42.2 (3.6) -21.1 (3.2)		- -	
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	304.9 (67.6) 11%	NR; p=0.82	63.2 (12.5) 13%	NR; p=0.17	- -	-	- -	-	157.9 (75.1) -16%	NR; p=0.45
	CBT-I (6 weeks)	18	319.1 (60.7) 5%		69.0 (12.4) 17%		- -		- -		143.2 (63.4) -34%	

Keys: BT-I = behavioural therapy – insomnia, CBT-I = cognitive behavioural therapy – insomnia, ITT = intention to treat, mg = milligram, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, SE = standard error, TST = total sleep time, WASO = wake after sleep onset. * Higher values indicate more actual sleep time. A larger positive change from baseline indicates more increase in actual sleep time. † Higher values indicate a high ratio sleep time / time in bed. A larger positive change from baseline indicates more increase in the ratio sleep time / time in bed. ‡ Lower values indicate less periods of wakefulness occurring after sleep onset. A larger negative change from baseline indicates more decrease in the periods of wakefulness occurring after sleep onset. § Lower values indicate less time between the lights are turned off until the person actually falls asleep. A larger negative change from baseline indicates more decrease in time between the lights are turned off until the person actually falls asleep. ‖ Lower values indicate less time awake (sum of sleep-onset latency, wake time after sleep onset, and early morning awakening). A larger negative change from baseline indicates more decrease in the time awake. Statistically significant results

Daytime sleepiness outcomes

One RCT compared zopiclone with CBT-I for intermediate-term treatment of primary chronic insomnia disorder and reported on the subjective measured daytime sleepiness outcome sleepiness (see Table 10).[33]The zopiclone group showed a significantly larger positive change from baseline compared with the CBT-I group, 0.51 and -0.10 respectively (p<0.05).

Table 10. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus behaviour therapy: daytime sleepiness outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Sleepiness* Mean (SD) baseline value, score 1-5 Effect size within groups from pre- to post-assessment	Treatment difference; p-value
Objective outcomes				
No studies identified				
Subjective outcomes				
Omvik, 2008[33] Moderate/unclear risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	22	2.81 (0.79) 0.51	NR; p<0.05
	CBT-I (6 weeks)	23	3.04 (0.66) -0.10	

Keys: CBT-I = cognitive behavioural therapy – insomnia, ITT = intention to treat, mg = milligram, NR = not reported, RCT = randomised controlled trial, SD = standard deviation. * Higher values indicate feeling alert (i.e. less sleepy) during the day. A positive change from baseline indicates feeling more alert during the day. Statistically significant results

Treatment response and insomnia remission

One RCT reported both treatment response rates and insomnia remission rates of patients on zolpidem and patients following BT-I for intermediate-term treatment of primary chronic insomnia disorder (see Table 11).[28] More people in the zolpidem group were considered to be treatment responders. The opposite was observed for the outcome insomnia remission where a higher percentage of remitters was observed in the BT-I group compared with zolpidem group. However, none of the outcomes were significantly different. Another RCT examined the clinical significance of the treatment effects by calculating the proportion of participants who reached polysomnography-recorded sleep efficiency level of at least 85%.[27] At baseline already 40% of the participants in the zopiclone group and 33% in the CBT-I group were above this threshold. After 6 weeks of treatment a statistically significant (p=0.01) higher percentage of clinical significant treatment effects was reported in the CBT-I group of 72% versus 47% for zopiclone.

Table 11. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus behaviour therapy: treatment response and insomnia remission

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Treatment response rate*		Insomnia remission rate†		Clinical significance of the treatment effects‡	
			Adjusted percentage of responders, %	OR (95% CI); p-value	Adjusted percentage of remitters, %	OR (95% CI); p-value	Percentage of participants with sufficient sleep efficiency at baseline, %	Group difference at 6 weeks; p-value
							Percentage of participants with sufficient sleep efficiency after 6 weeks, %	
Morin, 2020[28] Moderate/ unclear risk of bias	Zolpidem (5 mg, 6 weeks, continuous use)	107	49.7%	1.18 (0.60-2.33); NR	30.3%	0.71 (0.38-1.33); NR	-	-
							-	
	BT-I (6 weeks)	104	45.5%		38.0%		-	
							-	
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	-	-	-	-	40%	NR; p=0.01
							47%	
	CBT-I (6 weeks)	18	-		-		33%	
							72%	

Keys: BT-I = behaviour therapy – insomnia, CI = confidence interval, ITT = intention to treat, mg = milligram, NR = not reported, OR = odds ratio, RCT = randomised controlled trial. * Treatment response is a reduction of 8 points or more on the ISI (insomnia severity score) compared with baselines score. A higher percentage indicates more people have a reduction of 8 points or more on the ISI compared with baseline score and are considered treatment responders. † Insomnia remission is a ISI score less than 8. A higher percentage indicates more people have a ISI score less than 8 and are considered insomnia remitters. ‡ The clinical significance of the treatment effects was examined by calculating the proportion of participants who reached polysomnography-recorded sleep efficiency level of at least 85%.

Quality of life

One RCT compared zopiclone with CBT-I for intermediate-term treatment of primary chronic insomnia disorder and reported three different QoL outcomes: Physical Component Summary of the 36-Item short-form health survey (SF-36), Mental Component Summary of the SF-36, and the Quality of Live Inventory (see Table 12).[33] The change from baseline was higher in the zopiclone group compared with the CBT-I group for both the outcomes Physical Component Summary and the Mental Component Summary. Those on CBT-I showed more increase in the Quality of Live Inventory score compared with the zopiclone group. The difference between the zopiclone and CBT-I was not significant in any of the three QoL outcomes.

Table 12. Efficacy results on Z-drug intermediate treatment duration versus behaviour therapy: quality of life

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Physical Component Summary (SF-36)*		Mental Component Summary (SF-36)*		Quality of Live Inventory†	
			Mean (SD) baseline value, score Effect size within groups from pre- to post-assessment	Treatment difference; p-value	Mean (SD) baseline value, score Effect size within groups from pre- to post-assessment	Treatment difference; p-value	Mean (SD) baseline value, overall score –6 to 6 Effect size within groups from pre- to post-assessment	Treatment difference; p-value
Omvik, 2008[33] Moderate/ unclear risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	22	47.02 (10.25) 0.14	NR; p>0.05	45.27 (7.67) 0.20	NR; p>0.05	2.59 (1.28) -0.17	NR; p>0.05
	CBT-I (6 weeks)	23	49.22 (9.16) 0.09		45.69 (10.70) 0.15		2.43 (1.08) 0.08	

Keys: CBT-I = cognitive behavioural therapy – insomnia, ITT = intention to treat, mg = milligram, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, SF-36 = 36-Item short-form health survey. * A score of 50 (SD = 10) is the standardised population mean score. A score above 50 indicates a higher score on the physical/mental component summary than the standardised population score. A higher positive change from baseline indicates more increase in the physical/mental component summary score. † Higher scores indicate a higher product of satisfaction and importance of problems and strengths in 16 areas of life. A larger positive change from baseline indicates more increase in the Quality of Life inventory score.

7.2.4.1.2 Long treatment duration (≥6 months)

No studies were identified that reported on the efficacy for primary chronic insomnia disorder patients using long-term use of Z-drugs for more than six months compared with behaviour therapy.

7.2.4.2 Z-drugs versus placebo

7.2.4.2.1 Intermediate treatment duration (1-6 months)

Night-time sleep outcomes

One RCT reported on objective measured night-time sleep outcomes of Z-drugs (zopiclone) compared with placebo for intermediate-term treatment of primary chronic insomnia disorder. [27] The results of three different night-time sleep outcomes were given: TST, sleep efficiency, and total wake time (see Table 13). The outcomes TST and total wake time were in favour of the placebo group, and the opposite was observed for sleep efficiency. However, none of these results were significant.

Two RCTs reported on four subjective measured night-time sleep outcomes: TST, sleep efficiency, sleep latency, and total wake time (see Table 13).[27,30] The change from baseline was in favour of Z-drugs for the outcomes TST[27] , sleep efficiency[27] , and for sleep latency.[30] The total wake time decreased more in the placebo group than in the zopiclone group. [27] There was no significant difference between Z-drugs and placebo in any of these four outcomes.

Table 13. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus placebo: night-time sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	TST* Mean (SD) baseline value, minutes Adjusted change from baseline, %	TST* Treatment difference; p-value	Sleep efficiency† Mean (SD) baseline value, % Adjusted change from baseline, %	Sleep efficiency† Treatment difference; p-value	Sleep latency‡ Mean (SE) baseline value, minutes Adjusted change (SE) from baseline, minutes	Sleep latency‡ Treatment difference; p-value	Total wake time§ Mean (SD) baseline value, minutes Adjusted change from baseline, %	Total wake time§ Treatment difference; p-value
Objective outcomes										
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	388.3 (58.3) -17%	NR; p=0.5	82.3 (8.2) -1%	NR; p=0.62	- -	-	102.8 (54.9) -4%	NR; p=0.62
	Placebo (6 weeks)	12	346.0 (59.3) -7%		78.9 (16.2) -3%		- -		153.6 (145.5) -16%	
Subjective outcomes										
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	304.9 (67.6) 11%	NR; p=0.82	63.2 (12.5) 13%	NR; p=0.17	- -	-	157.9 (75.1) -16%	NR; p=0.45
	Placebo (6 weeks)	12	313.1 (54.1) 7%		65.8 (9.9) 9%		- -		159.9 (67.9) -21%	
Walsh, 2000[30] Low risk of bias	Zolpidem (10 mg, 8 weeks, intermittent use)	82	- -	-	- -	-	75.88 (6.89) -18.86 (5.20)	NR; p=0.61	- -	-
	Placebo (8 weeks)	81	- -		- -		67.29 (5.08) -14.67 (4.23)		- -	

Keys: ITT = intention to treat, mg = milligram, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, SE = standard error, TST = total sleep time. * Higher values indicate more actual sleep time. A larger positive change from baseline indicates more increase in actual sleep time. † Higher values indicate a high ratio sleep time / time in bed. A larger positive change from baseline indicates more increase in the ratio sleep time / time in bed. ‡ Lower values indicate less time between the lights are turned off until the person actually falls asleep. A larger negative change from baseline indicates more decrease in time between the lights are turned off until the person actually falls asleep.§ Lower values indicate less time awake (sum of sleep-onset latency, wake time after sleep onset, and early morning awakening). A larger negative change from baseline indicates more decrease in the time awake.

Figure only data

Two RCTs showed four different subjective measured night-time sleep outcomes in figures without reporting quantitative data. TST was reported in both studies[29,30], with only one study indicating a significant higher TST at the end of the study in the zolpidem group[29]. The mean number of awakenings (NAW) was significantly higher in the placebo group compared to zolpidem after 12 weeks of treatment,

while both sleep latency and WASO did not differ between the zolpidem and placebo group at the end of the study.[29]

Table 14. Figure only efficacy results on Z-drug intermediate treatment duration (1-6 months) versus placebo: night-time sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	TST*		Sleep latency†		WASO‡		NAW§	
			Value at end of study, minutes Value at end of study, minutes	p-value at end of the study for the between-group comparison	Value at end of study, minutes Value at end of study, minutes	p-value at end of the study for the between-group comparison	Value at end of study, minutes Value at end of study, minutes	p-value at end of the study for the between-group comparison	Value at end of study, number Value at end of study, number	p-value at end of the study for the between-group comparison
Objective outcomes										
No studies identified										
Subjective outcomes										
Walsh, 2000[30] Low risk of bias	Zolpidem (10 mg, 8 weeks, intermittent use)	82	Higher value	p>0.05	-	-	-	-	-	--
	Placebo (8 weeks)	81	Lower value		-		-		-	
Perlis, 2004[29] Moderate/unclear risk of bias	Zolpidem (10 mg, 12 weeks, intermittent use)	89	Higher value	p≤0.05	Lower value	p>0.05	Lower value	p>0.05	Lower value	p≤0.05
	Placebo (12 weeks)	101	Lower value		Higher value		Higher value		Higher value	

Keys: ITT = intention to treat, mg = milligram, NAW = nocturnal awakenings, RCT = randomised controlled trial, TST = total sleep time, WASO = wake after sleep onset. * Higher values indicate more actual sleep time. † Lower values indicate less time between the lights are turned off until the person actually falls asleep. ‡ Lower values indicate less periods of wakefulness occurring after sleep onset. § Lower value indicates less waking up in the middle of the night. Statistically significant results

Withdrawal due to lack of efficacy

One RCT reported the withdrawal due to lack of efficacy of patients with primary chronic insomnia disorder on intermediate-term treatment duration of zolpidem and placebo (see Table 15).[30] Only one patient in the zolpidem group withdrew due to lack of efficacy and no patient in the placebo group. No tests were performed to detect treatment differences.

Table 15. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus placebo: withdrawal due to lack of efficacy

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Withdrawal due to lack of efficacy	
			n of patients (%)	Treatment difference; p-value
Walsh, 2000[30]	Zolpidem (10 mg, 8 weeks, intermittent use)	82	1 (1.2%)	NR; NR
Low risk of bias	Placebo (8 weeks)	81	0 (0%)	

Keys: ITT = intention to treat, mg = milligram, n = number, NR = not reported, RCT = randomised controlled trial.

Quality of life

One RCT compared zolpidem with placebo for intermediate-term treatment of primary chronic insomnia disorder and reported ten different QoL domains of the SF-36 (see Table 16).[30] In seven QoL domains, the QoL score was more increased from baseline in the patients using zolpidem compared with placebo. In three QoL domains, the change in baseline was in favour of the placebo group. However, the differences between the zolpidem group and the placebo were not significant in any of the ten QoL domains.

Table 16. Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus placebo: quality of life

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Physical functioning (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Role limitation due to physical health (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Bodily pain (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	General health (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Vitality (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value
Walsh, 2000[30] Low risk of bias	Zolpidem (10 mg, 8 weeks, intermittent use)	82	90.29 (1.61)	NR; p≥0.05	69.93 (4.12)	NR; p≥0.05	79.78 (2.18)	NR; p≥0.05	80.23 (2.19)	NR; p≥0.05	47.03 (2.49)	NR; p≥0.05
			1.36 (1.45)		5.47 (3.67)		0.78 (2.14)		-0.34 (1.56)		12.06 (2.51)	
	Placebo (8 weeks)	81	87.24 (1.90)		70.00 (4.23)		75.07 (2.47)		79.25 (1.99)		45.00 (2.36)	
			1.16 (1.19)		0.47 (4.56)		3.72 (2.60)		0.04 (1.20)		7.32 (2.55)	

Table 16 (continued). Efficacy results on Z-drug intermediate treatment duration (1-6 months) versus placebo: quality of life

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Social functioning (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Role limitation due to emotional problems (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Mental health (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Physical component (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Emotional component (SF-36)* Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value
Walsh, 2000[30] (continued) Low risk of bias	Zolpidem (10 mg, 8 weeks, intermittent use)	82	86.05 (2.15)	NR; p≥0.05	81.16 (3.96)	NR; p≥0.05	78.26 (1.62)	NR; p≥0.05	50.85 (0.78)	NR; p≥0.05	49.21 (0.99)	NR; p≥0.05

Reference Risk of bias RCT	Intervention (dose, duration)	Sample size (ITT)	Social functioning (SF-36)*		Role limitation due to emotional problems (SF-36)*		Mental health (SF-36)*		Physical component (SF-36)*		Emotional component (SF-36)*	
	Comparator (duration)		Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value	Mean (SE) baseline value, score 0-100 Adjusted mean change (SE) from baseline, score	Treatment difference; p-value
			0.59 (2.09)		1.61 (5.28)		2.37 (1.49)		0.48 (0.83)		2.19 (1.19)	
	Placebo (8 weeks)	81	81.00 (2.37)		78.22 (3.98)		76.43 (1.47)		49.92 (1.02)		48.00 (0.97)	
			-0.35 (2.61)		-3.76 (4.80)		-2.14 (1.90)		1.32 (0.80)		-0.34 (1.16)	

Keys: ITT = intention to treat, mg = milligram, NR = not reported, RCT = randomised controlled trial, SE = standard error, SF-36 = 36-Item short-form health survey. * Higher values indicate a higher QoL score. A larger positive change from baseline indicates more increase in QoL score.

7.2.4.2.2 Long treatment duration (≥6 months)

Night-time sleep outcomes

One RCT reported on objective measured night-time sleep outcomes of zolpidem compared with placebo for long-term treatment of primary chronic insomnia disorder.[31] The results of four different outcomes were given: TST, sleep efficiency, WASO, and sleep latency (see Table 17). After eight months, the change from baseline was significantly different in three of these outcomes and all in favour of zolpidem: 51 minutes in zolpidem groups versus 17 minutes in placebo group for TST (p=0.007); 10.8% in zolpidem group versus 5.2% in placebo group for sleep efficiency (p=0.007); and -40 minutes in zolpidem group versus -15.4 minutes in placebo group for WASO (p=0.026). The change of baseline or treatment difference was not provided for the outcome sleep latency, but at eight months the difference between the zolpidem group and the placebo group was significant (p=0.001) in favour of zolpidem while no significant difference was observed at baseline (p=0.231).

One RCT reported on subjective measured night-time sleep outcomes of zolpidem extended release compared with placebo for long-term treatment of primary chronic insomnia disorder.[32] Patients in the zolpidem extended release group showed a significant higher increase in the quality of sleep score (-1.04) compared with the placebo group (-0.80; p<0.001), see Table 17.

Table 17. Efficacy results on Z-drug long treatment duration (≥6 months) versus placebo: night-time sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	TST*		Sleep efficiency†		WASO‡		Sleep latency§		QoS‖	
			Mean (SD) baseline value, minutes Adjusted change from baseline, minutes	Treatment difference (95% CI), minutes; p-value	Mean (SD) baseline value, % Adjusted change from baseline, %	Treatment difference (95% CI), %; p-value	Mean (SD) baseline value, minutes Adjusted change from baseline, minutes	Treatment difference (95% CI), minutes; p-value	Mean (SD) baseline value, minutes Adjusted change from baseline, minutes	Treatment difference (95% CI); p-value	Mean (SD) baseline value, score 1-4 Adjusted least squares mean change from baseline, score	Treatment difference (95% CI); p-value
Objective outcomes												
Randall, 2012[31] Moderate/unclear risk of bias	Zolpidem (10 mg, 8 months, continuous	44	354.6 (43.3) 51	40 (NR); p=0.007	73.7 (9.0) 10.8%	7 (NR); p=0.007	99.7 (39.9) -40	≤20 (NR); p=0.026	45.6 (37.3) NR¶	NR; p=0.001	- -	-
	Placebo (8 months)	47	359.9 (49.1) 17		74.9 (10.2) 5.2%		98.0 (42.6) -15.4		36.9 (30.6) NR¶		- -	
Subjective outcomes												
Krystal, 2008[32] Moderate/ unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	667	- -	-	- -	-	- -	-	- -	-	3.21 (0.43) -1.04	NR; p<0.001
	Placebo (6 months)	349	- -		- -		- -		- -		3.24 (0.43) -0.80	

Keys: CI = confidence interval, ITT = intention to treat, mg = milligram, NR = not reported, QoS = quality of sleep, RCT = randomised controlled trial, SD = standard deviation, TST = total sleep time, WASO = wake after sleep onset. * Higher values indicate more actual sleep time. A larger positive change from baseline indicates more increase in actual sleep time. † Higher values indicate a high ratio sleep time / time in bed. A larger positive change from baseline indicates more increase in the ratio sleep time / time in bed. ‡ Lower values indicate less periods of wakefulness occurring after sleep onset. A larger negative change from baseline indicates more decrease in the periods of wakefulness occurring after sleep onset. § Lower values indicate less time between the lights are turned off until the person actually falls asleep. A larger negative change from baseline indicates more decrease in time between the lights are turned off until the person actually falls asleep. ‖ Lower values indicate more quality of sleep. A larger negative change from baseline indicates more increase in quality of sleep. ¶ No change from baseline or treatment difference reported for sleep latency. However, it was decided to include this outcome in this HTA report as the baseline values of mean latency to persistent sleep were comparable (p=0.231) while it was significantly lower at month 1 and month 8 in the zolpidem group compared with placebo. Statistically significant results

Figure only data

One RCT showed four different subjective measured night-time sleep outcomes in figures without reporting quantitative data.[32] For all subjective measured night-time sleep outcome at month six, patients who received zolpidem extended release reported significantly greater improvement in TST (p<0.001), sleep latency (p=0.0014), WASO (p<0.0001), and NAW (p<0.001), see Table 18.

Table 18. Figure only efficacy results on Z-drug long treatment duration (≥6 months) versus placebo: night-time sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	TST*		Sleep latency†		WASO‡		NAW§	
			Increase at end of study, minutes Increase at end of study, minutes	p-value at end of the study for the between-group comparison	Decrease at end of study, minutes Decrease at end of study, minutes	p-value at end of the study for the between-group comparison	Decrease at end of study, minutes Decrease at end of study, minutes	p-value at end of the study for the between-group comparison	Decrease at end of study, number Decrease at end of study, number	p-value at end of the study for the between-group comparison
Objective outcomes										
No studies identified										
Subjective outcomes										
Krystal, 2008[32] Moderate/ unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	667	Larger increase	p<0.0001	Larger decrease	p=0.0014	Larger decrease	p<0.0001	Larger decrease	p<0.0001
	Placebo (6 months)	349	Smaller increase		Smaller decrease		Smaller decrease		Smaller decrease	

Keys: ITT = intention to treat, mg = milligram, NAW = nocturnal awakenings, RCT = randomised controlled trial, TST = total sleep time, WASO = wake after sleep onset. * A larger increase from baseline indicates more increase in actual sleep time. † A larger decrease from baseline indicates more decrease in time between the lights are turned off until the person actually falls asleep. ‡ A larger decrease from baseline indicates more decrease in the periods of wakefulness occurring after sleep onset. § A larger decrease from baseline indicates more decrease in the number of waking up in the middle of the night. Statistically significant results

Daytime sleepiness outcomes

Two RCTs compared zolpidem with placebo for long-term treatment of primary chronic insomnia disorder and reported on daytime sleepiness outcome (see Table 19). One RCT objectively measured daytime sleepiness by multiple sleep latency test (MSLT).[34] In this study, sleepiness did not significantly differ between zolpidem and placebo at baseline, after one month, nor after eight months. The other RCT subjectively measured sleepiness by using the Epworth Sleepiness Scale (ESS). After six months, the two study arms did not significantly differ in ESS score.

Table 19. Efficacy results on Z-drug long treatment duration (≥6 months) versus placebo: daytime sleep outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Sleepiness* (MSLT) Mean (SD) baseline value, minutes Adjusted change from baseline, minutes	Treatment difference; p-value	Sleepiness (ESS)† Mean (SD) baseline value, score Adjusted lease squares mean change from baseline, score	
Objective outcomes						
Roehrs, 2011[34] High risk of bias	Zolpidem (10 mg, 8 months, continuous use)	50	12.8 (4.91) NR‡	NR; NS	- -	-
	Placebo (8 months)	45	14.0 (4.37) NR‡		- -	
Subjective outcomes						
Krystal, 2008[32] Moderate/ unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	669	- -	-	7.5 -2.3	NR; p=0.3137
	Placebo (6 months)	349	- -		7.2 -2.0	

Keys: ITT = intention to treat, mg = milligram, NR = not reported, NS = not significant, RCT = randomised controlled trial, SD = standard deviation. * Lower values indicate shorter time before falling asleep in a quit environment during the day. A larger negative change from baseline indicates more decrease in time falling asleep in a quit environment during the day. † A lower score indicates more less daytime sleepiness. A larger negative lease square mean change from baseline indicates less daytime sleepiness. ‡ No change from baseline or treatment difference reported for sleepiness. There was no significant difference between the zolpidem and placebo group at any time points (i.e. not at baseline, month 1, nor after eight months). At eight months, the mean average over four test was exactly the same in both groups (i.e. 12.9 minutes). As the start value was higher in the placebo group, it was decided that for the outcome sleepiness the placebo group was in favour.

Figure only data

One RCT showed two different subjective measured daytime sleepiness outcomes in figures without quantitative data.[32] Patients who received zolpidem extended release reported significantly greater reduction in morning sleepiness (p=0.0014) and ability to concentrate (p<0.0001), see Table 20.

Table 20. Figure only efficacy results on Z-drug long treatment duration (≥6 months) versus placebo: daytime sleepiness outcomes

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Sleepiness*		Concentration†	
			Increase at end of study, score Increase at end of study, score	p-value at end of the study for the between-group comparison	Increase at end of study, score Increase at end of study, score	p-value at end of the study for the between-group comparison
Objective outcomes						
No studies identified						
Subjective outcomes						
Krystal, 2008[32] Moderate/ unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	667	Larger increase	p=0.0014	Larger increase	p<0.0001
	Placebo (6 months)	349	Smaller increase		Smaller increase	

Keys: ITT = intention to treat, mg = milligram, RCT = randomised controlled trial. * A larger increase from baseline indicates more reduction in the level of level of sleepiness in the morning † A larger increase from baseline indicates more improvement in the ability to concentrate in the morning. Statistically significant results

Withdrawal due to lack of efficacy

One RCT reported the withdrawal due to lack of efficacy of patients with primary chronic insomnia disorder on long-term treatment duration of zolpidem and placebo (see Table 21).[32] 4.8% in the zolpidem extended release group and 23.5% of the placebo withdrew due to lack of efficacy. No tests were performed to detect treatment difference.

Table 21. Efficacy results on Z-drug long treatment duration (≥6 months) versus placebo: withdrawal due to lack of efficacy

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (ITT)	Withdrawal due to lack of efficacy	
			n of patients (%)	Treatment difference; p-value
Krystal, 2008[32] Moderate/ unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	669	32 (4.8%)	NR; NR
	Placebo (6 months)	349	82 (23.5%)	

Keys: ITT = intention to treat, mg = milligram, n = number, NR = not reported, RCT = randomised controlled trial.

7.2.5 Findings effectiveness

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

7.2.6 Findings safety

Safety data was extracted from the RCTs that were included for the study results on efficacy. Six of the eight included RCTs reported safety data and three safety outcomes were reported: withdrawal due to

adverse events, serious adverse events, and tolerance to the drugs (i.e. reduced reaction to a drug following its repeated use with a need to increase the dose in order to get a therapeutic effect). None of the included RCTs reported data on the safety outcome development of addiction or physical dependence on Z-drugs. The data on withdrawal due to adverse events and serious adverse events is presented using two levels of stratification, the comparator and treatment duration. This stratification is not applied to tolerance. The safety data is summarised in a summary table without stratification. As two or more RCTs reported on the same outcome, the safety data was subsequently pooled and summarised in GRADE evidence profiles, see Table 25.

7.2.6.1 Z-drugs versus behaviour therapy

7.2.6.1.1 Intermediate treatment duration (1-6 months)

Two RCTs reported on safety of Z-drugs compared with CBT-I for intermediate-term treatment of primary chronic insomnia disorder.[27,33] In both articles, the percentage withdrawal due to adverse events was higher in the zopiclone group compared to the CBT-I group (see Table 22). No tests were performed to detect treatment differences. Omvik et al., 2008[33] did not report details on the type of adverse events. Also Sivertsen et al., 2006[27] did not specify the event which resulted in withdrawal, however the general reported adverse events by the participants where all mild.

Table 22. Safety results on Z-drug intermediate treatment duration versus behaviour therapy: withdrawal due to adverse events

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (safety)	Withdrawal due to adverse events n of patients (%)
Omvik, 2008[33] Moderate/unclear risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	22	2 (9.1%)
	CBT-I (6 weeks)	23	1 (4.3%)
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	1 (6.3%)
	CBT-I (6 weeks)	18	0 (0%)

Keys: CBT-I = cognitive behavioural therapy – insomnia, mg = milligram, n = number, RCT = randomised controlled trial.

7.2.6.1.2 Long treatment duration (≥6 months)

No studies were identified that reported on safety for primary chronic insomnia disorder patients using long-term use of Z-drugs for more than six months compared with behaviour therapy.

7.2.6.2 Z-drugs versus placebo

7.2.6.2.1 Intermediate treatment duration (1-6 months)

Three RCTs reported on safety of Z-drugs compared with placebo for intermediate-term treatment of primary chronic insomnia disorder. [27,29,30] One RCT used zopiclone[27] and two RCTs used zolpidem as intervention drugs.[29,30] In all three RCTs reporting on withdrawal due to adverse events, the percentage was higher in the intervention group compared to the placebo group. Only one RCT reported the percentage of serious advents, but no cases were reported in the zolpidem group nor in the placebo group.[29] No tests were performed to detect treatment differences. Sivertsen et al., 2006[27] did not specify

the event which resulted in withdrawal, however the authors stated that the general reported adverse events by the participants where all mild. Perlis et al, 2004[29] reported the non-severe adverse events which resulted in withdrawal from the study in the zolpidem group (i.e. excessive sleepiness, headache, drowsiness, dizziness, mood alteration and anxiousness, grogginess, hallucinations) and in the placebo group (i.e. cold symptoms, bad dreams, body rash). Walsh et al., 2000[30] did not report details on the type of adverse events.

Table 23. Safety results on Z-drug intermediate treatment duration (1-6 months) versus placebo: withdrawal due to adverse events and serious adverse events

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (safety)	Withdrawal due to adverse events n of patients (%)	Serious adverse events n of patients (%)
Sivertsen, 2006[27] Low risk of bias	Zopiclone (7.5 mg, 6 weeks, continuous use)	16	1 (6.3%)	-
	Placebo (6 weeks)	12	0 (0%)	-
Perlis, 2004[29] Moderate/unclear risk of bias	Zolpidem (10 mg, 12 weeks, intermittent use)	98	7 (7.1%)	0 (0%)
	Placebo (12 weeks)	101	3 (3.0%)	0 (0%)
Walsh, 2000[30] Low risk of bias	Zolpidem (10 mg, 8 weeks, intermittent use)	82	4 (4.9%)	-
	Placebo (8 weeks)	81	1 (1.2%)	-

Keys: mg = milligram, n = number, RCT = randomised controlled trial.

7.2.6.2.2 Long treatment duration (≥6 months)

Two RCTs reported on safety of Z-drugs compared with placebo for long-term treatment of primary chronic insomnia disorder.[31,32] Both studies reported a higher percentage of withdrawal due to adverse events in the zolpidem/zolpidem extended release group compared with the placebo group. In the one RCT that reported on serious adverse events, the percentage was higher in the zolpidem extended release group compared to placebo. No tests were performed to detect treatment differences. The two adverse events in the zolpidem group which resulted in study discontinuation in Randall et al., 2012[31] were mild (i.e. dizziness and heart sensations). The adverse events most commonly leading to discontinuation in the zolpidem and placebo groups in the RCT of Krystal et al., 2008[32] were psychiatric disorders, nervous system disorders, and general disorders. These adverse events were not unexpected and consistent with the pharmacologic effects and known safety profile of zolpidem. None of the reported serious adverse events was considered to be related to the study medication.

Table 24. Safety results on Z-drug long treatment duration (≥6 months) versus placebo: withdrawal due to adverse events and serious adverse events

Reference Risk of bias RCT	Intervention (dose, duration) Comparator (duration)	Sample size (safety)	Withdrawal due to adverse events n of patients (%)	Serious adverse events n of patients (%)
Randall, 2012[31] Moderate/unclear risk of bias	Zolpidem (10 mg, 8 months, continuous use)	60	2 (3.3%)	-
	Placebo (8 months)	65	0 (0%)	-
Krystal, 2008[32] Moderate/unclear risk of bias	Zolpidem Extended Release (12.5 mg, 6 months, intermittent use)	669	57 (8.5%)	19 (2.8%)
	Placebo (6 months)	349	16 (4.6%)	6 (1.7%)

Keys: mg = milligram, n = number, RCT = randomised controlled trial.

7.2.6.3 Tolerance

Four RCTs reported data on possible tolerance to Z-drugs.[29–32] The effect of Z-drugs over time is visualised in three studies[29,30,32] and these figures are enclosed in Appendix. All four RCTs used zolpidem as intervention drugs with a treatment duration range from eight weeks to eight months and reported a stable effect of Z-drugs over time, i.e. the treatment remained efficacious across the duration of the study without evidence for tolerance.

7.2.7 GRADE table

Table 25. GRADE evidence profile: withdrawal from treatment due to adverse events

Keys: CBT-I = cognitive behavioural therapy – insomnia.

[a] Downgraded for serious risk of bias due to bias associated with allocation concealment (not reported), the analysis was not performed according to intention to treat-principal, and the placebo group was left out of the statistical analysis in Omvik et al., 2008.

[b] Downgraded for serious imprecision due to low total number of patients and events.

[c] It was decided not to downgrade the risk of bias for the one study (out of three) that did not report the allocation concealment.

[d] Downgraded for serious imprecision due to low total number of patients and events.

[e] Downgraded for serious risk of bias due to bias associated with allocation concealment (not reported) in Randall et al., 2012 and bias associated with high loss to follow-up in Krystal et al., 2008.

Certainty assessment							**№ of patients**		**Effect**		
№ of studies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indi-rectness**	**Impreci-sion**	**Other considera-tions**	**Z-drug**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Withdrawal from treatment due to adverse events; Z-drug intermediate treatment duration (1-6 months) versus behaviour therapy											
2[27,33]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	**Zopiclone** 3/38 (7.9%)	**CBT-I** 1/41 (2.4%)	RR 2.47 (0.38 to 16.03)	52 more per 1,000 (from 15 more to 99 more)	⨁⨁◯◯ LOW
Withdrawal from treatment due to adverse events; Z-drug intermediate treatment duration (1-6 months) versus placebo											
3[27,29,30]	randomised trials	not serious[c]	not serious	not serious	serious[d]	none	**Zopiclone or zolpidem** 12/196 (6.1%)	**Placebo** 4/194 (2.1%)	RR 2.69 (0.93 to 7.79)	41 more per 1,000 (from 28 more to 54 more)	⨁⨁⨁◯ MODERATE
Withdrawal from treatment due to adverse events; Z-drug long treatment duration (≥6 months) versus placebo											
2[31,32]	randomised trials	serious[e]	not serious	not serious	not serious	None	**Zolpidem or Zolpidem-ER** 59/729 (8.1%)	**Placebo** 16/414 (3.9%)	RR 1.92 (1.13 to 3.27)	46 more per 1,000 (from 31 more to 38 more)	⨁⨁⨁◯ MODERATE

Figure 3. Z-drug intermediate treatment duration (1-6 months) versus behaviour therapy. Withdrawal from treatment due to adverse events. [d]

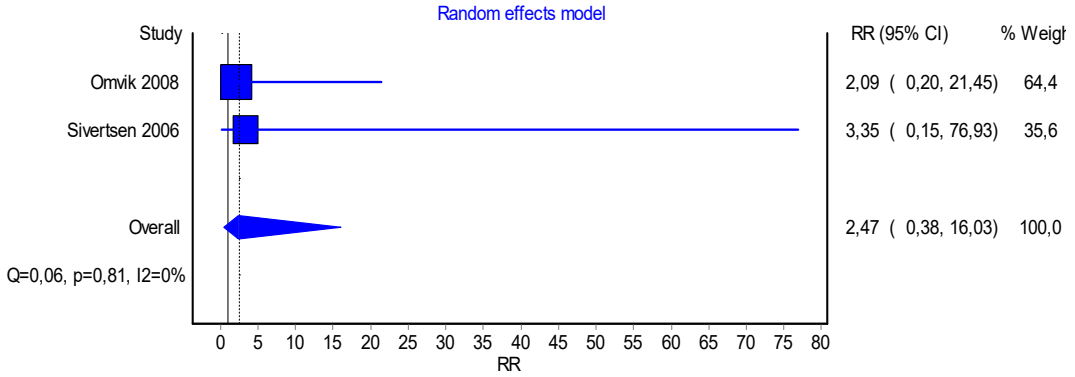


Figure 4. Z-drug intermediate treatment duration (1-6 months) versus placebo. Withdrawal from treatment due to adverse events. [d]

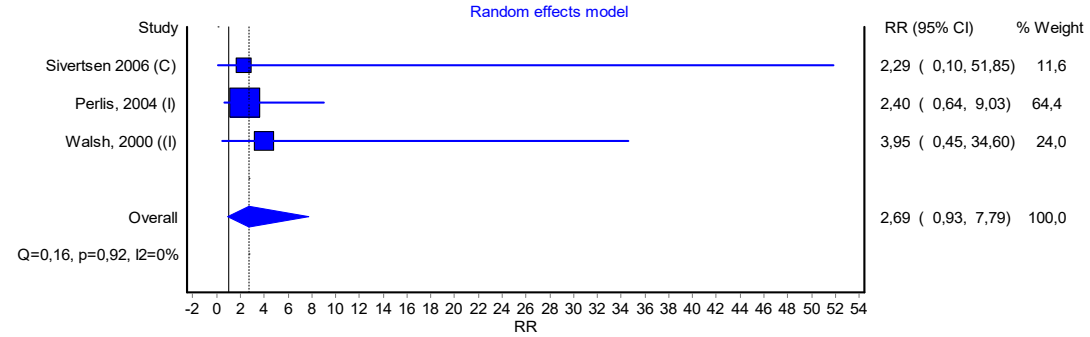
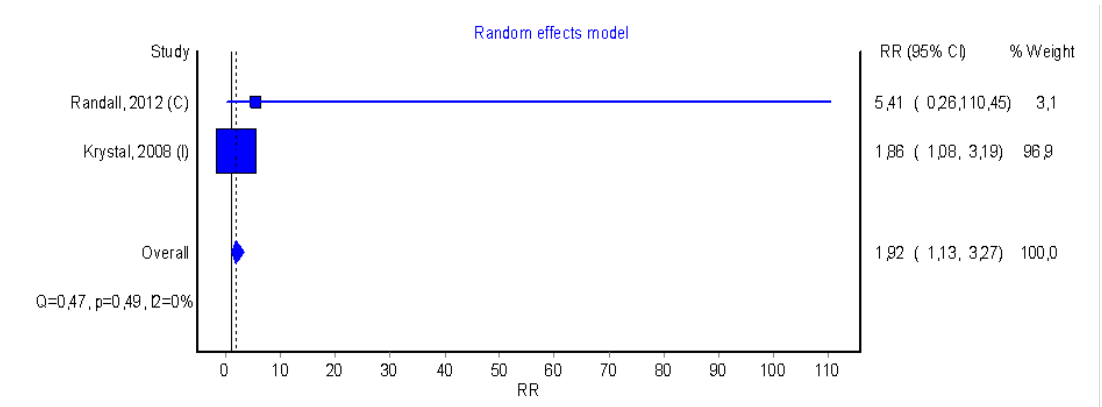


Figure 5. Z-drug long treatment duration (≥6 months) versus placebo. Withdrawal from treatment due to adverse events. [d]



[d](Cochran's) Q is a measure of heterogeneity in study outcomes between studies.

8 Cost-effectiveness and budget impact

Summary statement cost-effectiveness and budget impact

A cost-effectiveness model was built using a microsimulation approach. Costs, utilities, and probabilities were collected from literature. Results show that the long-term Z-drug use is more costly than the comparators (i.e. no treatment, CBT-I, short-term Z-drug, short-term Z-drug followed by CBT-I) in the model, except in the one-year time horizon scenario, where it resulted to be less expensive than CBT-I and short-term Z-drug use followed by CBT-I. At the same time, the effectiveness of the comparators exceeded the effectiveness of the long-term Z-drug treatment for all analyses in the model. Therefore, most of the analyses resulted in long-term Z-drug treatment being dominated by the other treatments, meaning the other treatments results in better health outcomes while being cost saving. This is further reflected in the budget impact analyses, with potential savings from adopting any of the other treatments.

8.1 Methodology cost-effectiveness and budget impact

8.1.1 Databases and search strategy

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 (Appendix 15.4). The search terms for economic evaluations were developed together with an information specialist of the Erasmus University Medical Centre and validated extensively with other search terms for economic evaluations. The search terms for the CRD databases are a combination of search terms related to sleep or insomnia and benzodiazepines. The database output, including all indexed fields per hit (e.g. title, authors, abstract), was exported to Endnote version X9.2. 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 Table 26. 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 Endnote library by one of the reviewers. This method provides transparency regarding all selection steps and assures reproducibility. A PRISMA flowchart is presented in Figure 8, 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 26. An overview of search terms applied for the cost-effectiveness systematic literature search are listed in Appendix 15.4.

Table 26. 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-minimisation • Cost-benefit • Costing studies (including budget impact analyses) • Resource use measurement	
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 <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 primary chronic insomnia disorder as primary reason	• Patients who use benzodiazepine derivatives/Z-drugs for treatment of drug addiction • Palliative care
Study intervention	• Benzodiazepine derivatives/Z-drugs listed in the Swiss speciality list† • Treatment duration >1 month	• Benzodiazepine derivatives /Z-drugs with treatment duration ≤1 month • 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) 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.

8.1.2 Other sources

Not applicable.

8.1.3 Assessment of quality of evidence

The identified studies were 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.[45,46]

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

Relevant data from the included articles found in the peer-reviewed literature were summarised using a data-extraction spreadsheet in Excel. This spreadsheet included:

- First author, year
- Country
- Type of study
- Study population
    - Sample size (n)
    - Mean age and age range
    - Proportion male/female

- Intervention
- Comparator
- Time Horizon
- Discounting
- Price year
- Perspective of cost assessment
- Outcome measures
- Cost categories
- Total/Incremental costs and QALYs
- Model used (Yes/No)
    - Type of model
    - Health states

No statistical analyses or synthesis were applied to the identified studies on cost-effectiveness. The extracted information can be reviewed in the following Table 27.

8.1.5 De novo-health economic model

The identified studies did 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-pharmacological treatment, nor short-term use of sedative-hypnotic drugs treatment in the Swiss context. The lack of cost-effectiveness studies in the Swiss context as well as the lack of cost-effectiveness 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 (Switzerland-specific) evidence is appropriate.

8.1.5.1 Target population and perspective

The target population of the de novo-health economic model were adult patients with primary chronic insomnia disorder. The analysis was performed for the Swiss healthcare setting. This means that, where possible, relevant input parameters were based on data from Switzerland, e.g. Swiss lifetables for background mortality and Swiss sources for healthcare costs. The analysis was performed from a health insurance payer perspective. This means that only direct healthcare costs were included. While mandatory health insurance payer is the prominent perspective, as direct health care costs of accidents are included, part of the payments can stem from accidents insurance payers. Societal costs, such as informal care and productivity costs, were not included.

8.1.5.2 Intervention and comparator(s)

The intervention was the long-term use (> one month) of sedative-hypnotic drugs. In the PICO (Population, Intervention, Comparator and Outcomes), the sedative-hypnotic drugs of ATC categories benzodiazepine derivatives (N05BA, N05CD), or benzodiazepine related drugs/Z-drugs (N05CF) listed in

the Swiss speciality list were included. The systematic review of efficacy and safety, however, did not yield any outcome on benzodiazepine derivatives. Therefore, the economic analysis focused on benzodiazepine related drugs/Z-drugs (from now on called Z-drugs) only. Furthermore, while clinical effectiveness was able to stratify duration of use of Z-drugs into intermediate and long-term, in the cost-effectiveness model the duration was kept to short-term (≤ one month) and long-term (> one month) as further stratification would require assumptions on transition rates based on already scarce data.

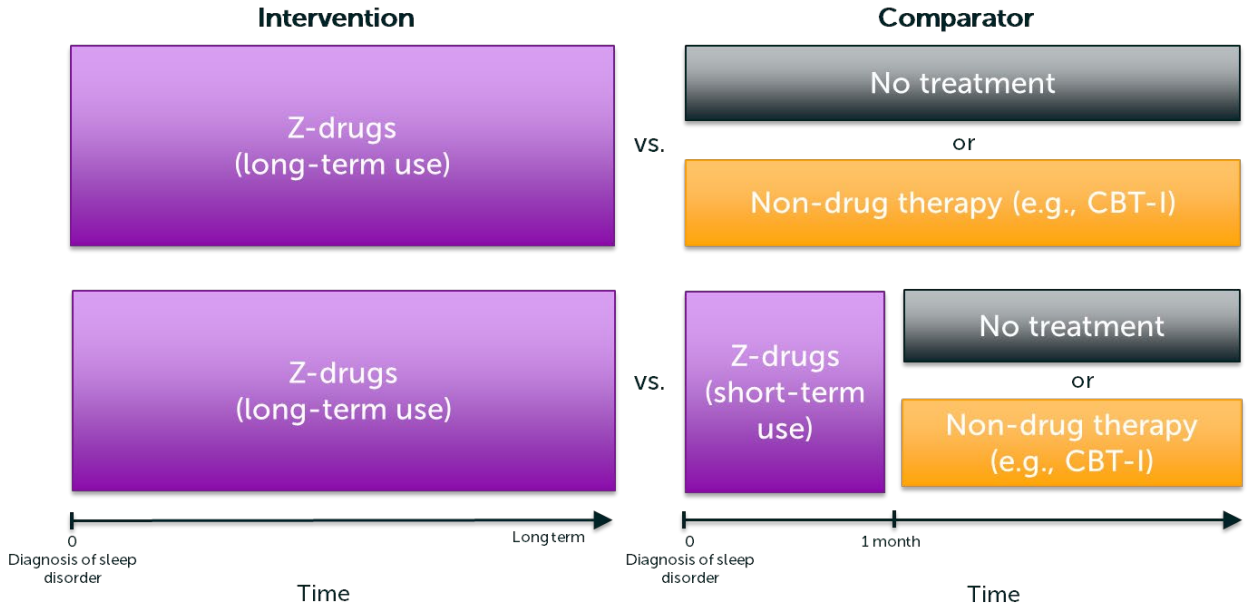
Two comparators were analysed:

1. No treatment with sedative-hypnotic drugs:
    a. No treatment
    b. Other non-pharmacological treatment (i.e. behavioural therapy and/or cognitive therapy for insomnia (CBT-I)) with a duration of 6 weeks based expert opinion and the RCT that will be used for the utility of CBT-I.[33]
2. Short-term use (≤ one month) of Z-drugs.

The intervention and comparators resulted in four comparisons (see Figure 6):

- PICO 1a: long-term use of Z-drugs versus no treatment.
- PICO 1b: long-term use of Z-drugs versus CBT-I.
- PICO 2a: long-term versus short-term use of Z-drugs followed by no treatment.
- PICO 2b: long-term versus short-term use of Z-drugs followed by CBT-I.

Figure 6. Visualisation of interventions and comparators in the PICOs.



8.1.5.3 Model structure

The model structure and included events were informed by discussions with clinical experts and the available scientific literature. The model is an individual-based state-transition model. This means that patients transition through the model individually through a set of health states during which they could experience specific events. The model was programmed in statistical programming language R based on the microsimulation framework developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup.[47–50] The conceptual model is illustrated in Figure 7, and described below.

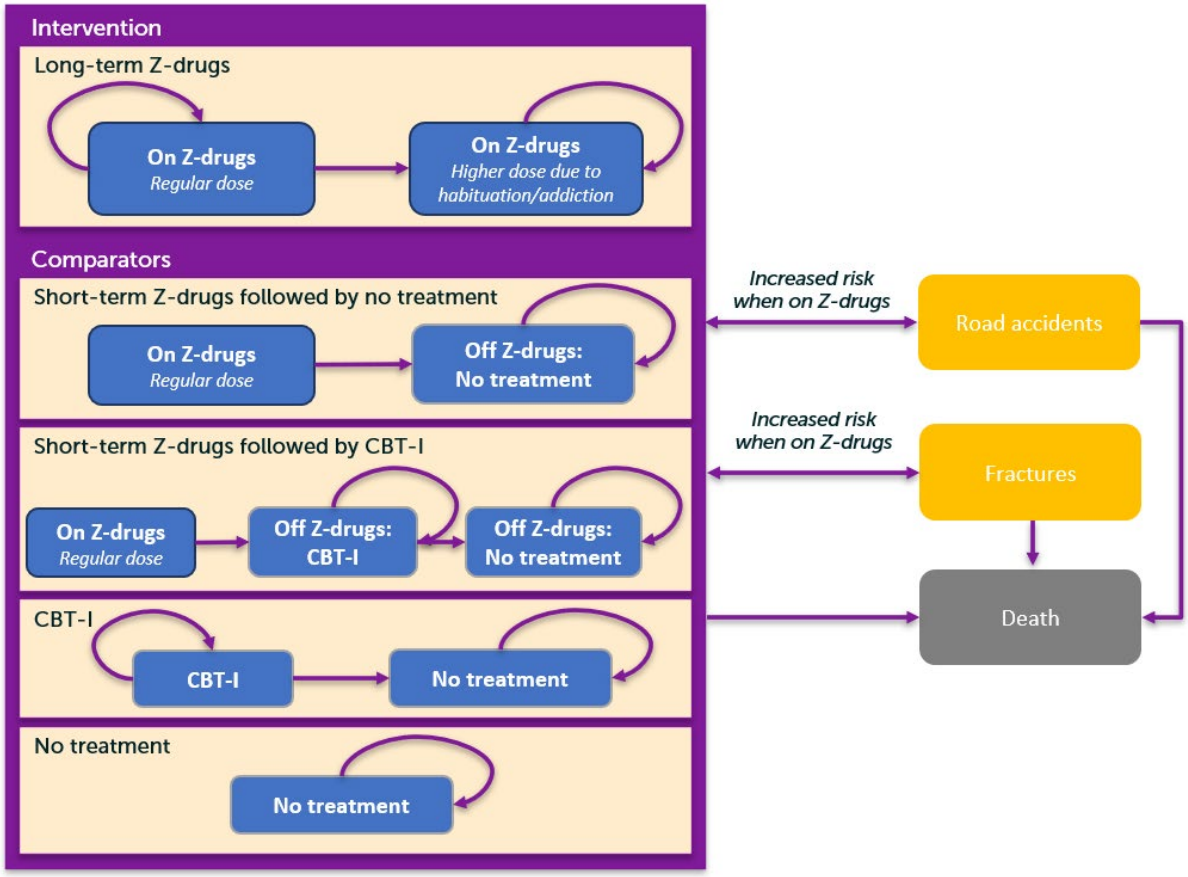
On Z-drugs (short- or long-term)

In both short- and long-term Z-drug treatment arms of the model, patients start on a regular dose of Z-drugs. In the following cycles, patients could discontinue using Z-drugs (short-term use) or continue using them (long-term use). In long-term use of Z-drug, a proportion of patients transition to the 'On Z-drugs, higher dose' health state directly after the first cycle of Z-drug treatment on regular dose. This represents the proportion of patients who exceed the maximal recommended daily dose of Z-drugs because of habituation or addiction. In the subsequent cycles, we assumed that patients on long-term Z-drug treatment (either regular or higher dose) stay in this health state until the end of the time horizon of the model. In every health state, patients could experience road accidents, fractures (due to, for example, falls), or death. These adverse events were found prominent in sleep disorder guidelines and drug warning label, and where further substantiated by the expert opinions of multiple clinical experts.[12,51] Risk of these events is elevated due to Z-drug use, as described in later sections of this document. In PICO2b, patients in the comparator arm (short-term use of Z-drugs followed by CBT-I) transition to 'off Z-drugs' after their short-term Z-drug use and receive CBT-I, with a limited duration.

Off Z-drugs (CBT-I or no treatment)

In the comparator arm without Z-drug treatment, patients start in the 'Off Z-drugs' health state and they remain there until they die. In the meantime, they could experience road accidents or fractures, but not at elevated risk. The 'off Z-drugs' health state could either reflect receiving CBT-I for a limited period of time, or no treatment.

Figure 7. Conceptual model



The time horizon of the base-case analysis was 10 years, because data on longer than 10 years use of Z-drugs is not available. This means that the surviving long-term users of Z-drugs are assumed to consume until the end of the time horizon. While real world data on the Swiss population would be preferable, the base-case horizon was based on the reported mean duration of 9.9 years of long-term use of zolpidem, zopiclone, and temazepam in an observational study among long-term users of Z-drug for primary insomnia treatment by Puustinen et al (2018).[52] Time horizons of different length (i.e. 1 year, 5 years, and lifetime) were applied in scenario analyses. The cycle lengths were one month. In the base-case analysis, costs and effects were discounted at 3.0%. In scenario analyses, the impact of not discounting or using a discount rate of 5.0% were explored.

Health outcomes were reported in life years (LYs) and quality-adjusted life years (QALYs). Costs were reported in Swiss Franc (CHF) adjusted for inflation to current price levels using healthcare sector-specific inflation rates ('Gesundheitspflege') from the Swiss Federal Statistical Office.

8.1.5.4 Input parameters

The model input parameters on clinical outcomes and utilities were informed from the results of the data extraction of the systematic literature search of efficacy, and safety and pragmatic literature searches. While the clinical effectiveness search yielded outcomes, few were quality of life estimates, and none

covered utilities which are needed for the cost-effectiveness model. Therefore, mapping transformation was applied to one of the clinical effectiveness outcomes. The pragmatic literature search was conducted to populate the model with effectiveness components not covered by the clinical effectiveness outcomes. Costs were based on databases available at the FOPH or pragmatic literature searches. Details on the effectiveness and cost inputs are specified in the following sections. Clinical expert opinion was used when data was unavailable from the literature. In absence of a long-term dataset on Z-drug users in Switzerland, this modelling approach, which combines different data sources, is the best estimate of cost and benefits related to Z-drugs. An overview of the input parameters is provided in Table 30.

8.1.5.4.1 Baseline characteristics

The baseline age and male/female distribution was based on the population-based, cross-sectional study that used a large health insurance database in Switzerland performed by Landolt *et al*. 2021[53] Based on this study, the baseline age in the model was 66 years and the proportion of females was 66.7%.

Details on baseline utilities of treatments and events, as well as costs can be reviewed in the following sections and in Table 30.

8.1.5.4.2 Events

As road traffic accidents and fractures were not as an outcome reported in the RCTs included with our systematic review of efficacy, effectiveness, and safety, we performed a pragmatic search to find the relevant data for the model. The results of the pragmatic search were used to populate our model with inputs for adverse events. An overview of the values and sources for each input can be viewed in Table 31. Swiss specific general population estimates of road traffic accidents and fractures were used as background risk to which risk ratios were applied to account for the additional risk in Z-drug users.

Background mortality

The background mortality was based on Swiss lifetables from 2018 derived from the Human Mortality Database.[54]

Road traffic accidents

The risk of a road traffic accident (RTA) in Switzerland in the general population was based on data on transport accidents from the Swiss Federal Statistical Office.[55] There were 16,897 RTAs with casualties of which 3,793 people (22.4%) were seriously injured after the RTA and 227 people (0.1%) were killed by the RTA in Switzerland in 2020. The total adult population in Switzerland in 2020 was 6,884,800 translating to an annual rate of an RTA of 0.245%.

The increased risk of a RTA when on Z-drugs was based on the study from Orriols et al. 2011 who matched data from three French national databases (the health care insurance database, police reports, and the police database of injury-related traffic accidents) to investigate the association between the

use of Z-drugs and the risk of RTA.[56] Their results showed that the odds ratio (OR) for being 'responsible' for a RTA in users of zolpidem was 1.29 (95% confidence interval [CI] 1.09–1.52) while there was no association with the use of zopiclone (OR: 0.94; 95% CI 0.77–1.14). Since Orriols et al. 2011 do not report the crude data to correctly calculate the OR for both Z-drugs (i.e. zopiclone and zolpidem) and given that zolpidem represents 88% of the Z-drugs used in Switzerland (based on COGE©, Tarifpool ©SASIS AG data 2019-2021), we used the OR from zolpidem only (see Orriols et al. 2011, Table 30). Separate ORs were applied to patients on normal (OR 1.08, 95% CI 0.90-1.30) and high dose of zolpidem (OR 2.46, 95% CI 1.70-3.56).[56] In a scenario analysis, the risk of a RTA was set equal for patients on normal and higher dose of Z-drugs (i.e. OR = 1). These ORs were converted to a risk ratio (RR) using the formula of Gidwani and Russell for inclusion in the model.[57]

Fractures

The risk of a fracture in the general population was based on age-dependent data on hospitalisations for fractures from the Swiss Federal Statistical Office.[58] The annual rate of a hospitalisation for a fracture of people between 60 and 64 years old is 1.22%. This rate increases by age until 7.42%/year for people above 95 years. Data on fractures that did not result in hospitalisation were not available and therefore were not included in the model.

The increased risk of a fracture when on Z-drugs was based on the meta-analysis by Treves et al. 2018 who found an OR for fractures of 1.63 (95% CI: 1.42-1.87).[59] We assumed that the underlying mechanism of Z-drugs causing a road traffic accident, such as drowsiness and reduced reaction, may be similar for the underlying mechanism causing fractures. There was no data on the increased risk of fractures when on a higher dose of Z-drugs. Therefore, we applied the same proportional increase in risk of RTAs when on higher Z-drugs to the OR of Treves et al. 2018 to estimate the impact of higher dose of Z-drugs on the risk of fractures, resulting in an OR of 1.36 for patients on a normal dose and 3.11 for patients on a higher dose. In a scenario analysis, the risk of a fracture was set equal for patients on normal and higher dose of Z-drugs (i.e. OR 1.63). These ORs were converted to a risk ratio (RR) using the formula of Gidwani & Russell for inclusion in the model.[57]

The probability to die from a fracture was based on an Austrian cohort study of surgeries for hip fractures from Nia et al. 2021 where 6.1% of patients died within 30 days and 15.2% within 180 days.[60] However, besides mortality that is directly attributed to the hip fracture, this probability also includes increased all-cause excess mortality which has been suggested to be partly attributable to existing comorbidities. According to Kanis et al. 2003 25% of the all-cause mortality can be attributed to the hip fracture. [61] Therefore we corrected the probabilities reported in Nia et al. 2021 to only reflect the mortality directly attribute to a hip fracture: probability of mortality within 30 days of 1.5% and within 180 days of 3.8%. We used data on hip fractures, because this is the most often occurring fracture that results into hospitalisations, accounting for almost half of all hospitalisations for fractures (46% in 2007) in Switzerland.[62] We assumed that this mortality was also applicable to other fractures for which patients are admitted to the hospital and we assumed the same mortality rates for patients of all ages.

To avoid double counting of fractures as a result of RTAs, we assumed every RTA is associated with one fracture and we subtracted the number of RTAs from the number of fractures.

8.1.5.4.3 Regular and increased dosage use of Z-drugs

The definition of regular and increased dosage of Z-drugs was derived from an observational study in the Swiss adult population of Petitjean *et al*. 2007.[63] This study included only data on zolpidem. However, as zolpidem represents 88% of the Z-drugs used in Switzerland (based on COGE©, Tarifpool ©SASIS AG data 2019-2021), this data is the most relevant. The defined daily dose (DDD) of zolpidem is 10 mg or 6.25 and 12.5 mg in controlled release forms of zolpidem, which is equal to 1 pill per day.[63] However, in practice there are patients who use less than the regular dosage and patients who use increased dosages due to habituation or addiction. In Petitjean et al. 2007, 71% of long-term users of zolpidem used a regular dose or less (with an average of 0.61 pills per day) and 29% exceeded the maximal recommended dose (with an average use of 3 pills per day). Therefore, we assumed patients on a regular Z-drug dosage in the model would use 0.61 pills per day and 29% of patients transitioned to a higher dosage of Z-drugs of 3 pills per day after the first cycle. To estimate the impact of these input parameter, the proportion of patients on a higher dose and the DDD for regular and higher dosages were varied in sensitivity analyses.

For patients on an increased dosage of Z-drugs, we applied increased drug use costs due to the higher DDD and increased risk of RTAs and fractures compared to patients on a regular dosage of Z-drugs, as described in section 8.1.5.4.2. Input values are reported in Table 31.

8.1.5.4.4 Utilities

There were two studies that reported outcomes on quality of life in the systematic review of efficacy, effectiveness, and safety.[32,64] However, none of these studies reported utilities, which are required for the calculation of quality adjusted life years. Therefore, we transformed the Epworth Sleepiness Scale (ESS) outcomes reported by Krystal et al. 2008 for treatment with zolpidem versus placebo to utilities using the mapping algorithm of Sharples et al. 2014[32,65] Assuming the same utility for users of zopiclone, it resulted in a utility of 0.873 when on Z-drugs and 0.870 when not on Z-drugs. The study of Omvik et al. 2008 showed that there was no statistically significant difference between the quality of life (measured with the SF-36) of people on zopiclone or on behaviour therapy.[64] Therefore, we assumed that individuals on CBT-I had the same utility as individuals on Z-drugs (i.e. 0.873). In contrast to Z-drugs, the treatment effect of CBT-I continues after treatment. Castronovo et al. 2018 demonstrated that the effect of CBT-I on insomnia is maintained up to 10 years after the end of the treatment.[66] Therefore, we assumed in the model that the effect of CBT-I persisted up to 10 years, but this assumption was varied in sensitivity analysis.

When patients had an RTA or fracture, a disutility was applied. The disutility of a slight RTA was assumed to be minimal (disutility of 0.05). The disutility of a RTA resulting in serious injury was based on the estimate by Bell et al. 2001, that is 0.33, under the assumption of Maximum Abbreviated Injury Score (MAIS) of 4, which is the equivalent to a serious injury.[67] These disutilities were for six cycles, assuming RTAs have an impact on health-related quality of life for six months. This assumption was varied in sensitivity analyses.

The disutility of a fracture was based on the average quality of life of patients after a hip fracture of 0.60 derived from a systematic review of Peeters et al. 206[68] This utility was subtracted from the utility of

individuals on Z-drugs to calculate the disutility of a fracture resulting in a disutility of 0.28. This disutility was applied for six cycles, assuming hospitalisations for fractures had an impact on health-related quality of life for six months. This assumption was varied in sensitivity analyses.

8.1.5.4.5 Resource use and costs

Acquisition costs of Z-drugs

The monthly costs of Z-drugs acquisition were calculated by multiplying the per pill drug acquisition costs with 30.4 days.

Per pill drug acquisition costs were calculated from the annual receipts submitted for reimbursement by the Swiss statutory health insurance for all types of Z-drugs available in Switzerland (i.e. zolpidem and zopiclone) in 2019-2021, obtained from COGE©, Tarifpool ©SASIS AG.[69,70] For each formulation (i.e. in terms of the active substance and dosage) and for each brand, the package size (in terms of number of pills), number of packages sold, and annual turnover in terms of CHF were available from Tarifpool: © SASIS AG. The total number of pills sold was calculated by multiplying the number of packages sold with the package size. The total number of pills sold was divided by the annual turnover to calculate the per pill price of Z-drugs. This calculation resulted in a per pill price of 0.402 CHF for Z-drugs.

As described previously, we assumed that patients on regular Z-drug use will use on average 0.61 pill per day resulting in monthly costs of 7.47 CHF, and patients on higher Z-drug use used on average 3 pills per day resulting in monthly costs of 36.75 CHF.

GP costs when on Z-drugs

All patients, regardless of which treatment strategy, had one visit at the GP in the first cycle. This first visit was similar to follow-up visits (Table 28) with an additional 15 minutes to fill in the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), and differential diagnosis of sleep apnoea or restless legs, resulting in a total cost of CHF 188.77.

The frequency of follow-up visits for the different treatment strategies were based on expert opinion (Table 27). Unit costs of one GP visit (with a duration of 40 minutes) were 138.52 CHF based on TARMED (Table 28).

Table 27. Number of follow-up visits in every treatment strategy

	Expert opinion	Frequency included in the model
Short-term Z-drug treatment	Weekly follow-up visits for 1 month	4/month
Long-term Z-drug treatment	2-4 follow-up visits per year	3/year
CBT-I	2-3 additional follow-up visit before starting CBT-I 1 follow-up visit after CBT-I	2.5/year
No treatment	No follow-up visits	0

Table 28. Estimation of costs of a follow-up visit at the GP when on Z-drugs

TARMED Position	Task	Duration	Costs
00.0010	Consultation first 5 min	5 min	CHF 16.75
00.0015	+ Surcharge for general practitioner services in the physician's office		CHF 9.79
00.0020	+ Consultation for people over 6 years of age and under 75 years of age every additional 5 minutes (consultation surcharge)	15 min	CHF 50.25
00.0415	Preliminary discussion of diagnostic / therapeutic interventions with patients / relatives by the specialist for people over 6 years of age and under 75 years of age every 5 min.	15 min	CHF 53.35
00.0030	+ Consultation last 5 minutes	5 min	CHF 8.38
	Total	**40 min**	**CHF 138.52**

CBT-I costs

Table 29 provides the average costs of one session of CBT-I with a psychiatrist (CHF 239.94) or psychologist (CHF 179.39). The frequencies of patients receiving CBT-I from a psychiatrist or psychologist are unknown, therefore we assumed 50% would receive CBT-I from a psychiatrist and 50% from a psychologist, resulting in a cost of CHF 209.66 per session. According to clinical expert opinion, patients have 12-16 sessions per treatment. Therefore, we assumed 14 sessions on average over 3 months. The costs were derived from TARMED version 1.09, resulting in a total cost of CBT-I of CHF 2'935. Alternatively, patients can have internet-based CBT-I with a maximum cost of CHF 2'570 for 16 sessions. These costs were not included in the base-case analysis, but the value is included in the range of the costs of CBTI-I in the OWSA, so the impact of a change in these costs can be derived from the OWSA results.

Table 29 Estimation of costs of first and follow-up visits at psychiatrist and psychologist for CBT-I

	Psychiatrist		
TARMED position	**Task**	**Duration**	**Costs**
02.0010	Psychiatric diagnosis and therapy, individual therapy	60 min	CHF 186.30
02.0071	+ Study of files in the absence of the patient by the specialist in psychiatry, per 1 min.	10 min	CHF 31.05
02.0166	+ Drafting of detailed reports, unless otherwise compensated, in the absence of the patient by the treating psychologist / psychotherapist	10 min	CHF 22.50
	Total	**80 min**	**CHF 239.85**
	Psychologist		
	Task	**Duration**	**Costs**
02.0210	Delegated psychotherapeutic treatment in the doctor's office, individual setting	60 min	CHF 134.57
02.0266	+ Study of files in the absence of the patient by delegated psychologists / psychotherapists	10 min	CHF 22.41
2.0261	+ Drafting of detailed reports, unless otherwise compensated, in the absence of the patient by the treating psychologist / psychotherapist	10 min	CHF 22.41
	Total	**80 min**	**CHF 179.39**

Healthcare costs of road accidents

The healthcare costs (including public subsidies) of road accidents were based on estimates from Wieser et al. 2009. In Wieser et al. 2009 the road accidents are classified by severity. We assumed that 'slightly injured' road accidents would fall into our category of non-serious road accidents and 'moderate injury', 'severely injury' and 'disability pension' in our category of serious road accidents. The cost estimates of Wieser et al. 2009 originated from 2007 and were therefore corrected for inflation in the model, resulting in costs of a non-serious road accident of 1'740 CHF and costs of a serious road accident of 38'300 CHF. The costs of a fatal road accident were 18'038 CHF. [71]

Healthcare costs of fractures

The healthcare costs of fractures with hospitalisations are based on the statistics of diagnosis-related case costs from 2014.[72] We selected fractures of the pelvis and the femur with one or more days of hospitalisation and including those that required surgery, using the Swiss Diagnosis Related Groups (SwissDRG) I66B, I68C, I08B, I08C and I08D . The total costs of these DRGs were divided by the total number of cases and the resulting weighted average of the costs (adjusted for inflation to current price levels using inflation rates website specific to Switzerland from the Organisation for Economic Co-operation and Development (OECD) [73]) was 12'110 CHF. The costs of the selected SwissDRG cases are reported in the Appendix.

Table 30. Input parameters

Input parameter	Value	Distribution in PSA	Source
Baseline characteristics			
Baseline age, in years	66	Truncated normal (range 18-100 years, SD: 17.23 years)	Landolt et al. (2021)[53]
Proportion of females, in %	66.7%	Not varied in PSA	Landolt et al. (2021)[53]
Road traffic accidents			
Annual rate of RTA in general population	0245%	Not varied in PSA	Swiss Federal Statistical Office [55]
OR of RTA when on Z-drugs (normal and high doses)	1.29	Not varied in PSA, only used in scenario analysis	Orriols et al. (2011)[56]
OR of RTA when on Z-drugs (normal dose)	1.08	Lognormal (mean, CI 0.90-1.30)	Orriols et al. (2011)[56]
OR Of RTA when on Z-drugs (high dose)	2.46	Lognormal (mean, CI 1.70-3.56)	Orriols et al. (2011)[56]
Fractures			
Annual rate of fractures with hospitalisations in the general population:		Not varied in PSA	Swiss Federal Statistical Office[74]
55-59 years	1.07%		
60-64 years	1.18%		
65-69 years	1.36%		
70-74 years	1.77%		
75-79 years	2.53%		
80-84 years	4.16%		
85-89 years	6.19%		
90-94 years	7.54%		
95+ years	6.60%		
OR of fractures when on Z-drugs (normal and high doses)	1.63	Not varied in PSA, only used in scenario analysis	Treves et al. (2018)[59]
OR of fractures when on Z-drugs (normal dose)	1.36	Lognormal (mean, SD assumption 10% of mean)	Assumed equal relative decrease in OR as with RTAs
OR of fractures when on Z-drugs (high dose)	3.11	Lognormal (mean, SD assumption 10% of mean)	Assumed equal relative increase in OR as with RTAs
Probability to die within 30 days after fracture	1.5%	Beta (alpha 76, beta 1037)	Nia et al.(2021)[60] Kanis et al.(2003)[61]
Probability to die within 180 days after fracture	3.8%	Beta (alpha 100, 934)	Nia et al. (2021)[60] Kanis et al. (2003)[61]
Z-drugs dosages			
Proportion with increased dosage of long-term users	29.28%	Beta (alpha 3.08, beta 7.44)	Petitjean et al. (2007)[63]

Regular dose (in DDD)	0.61	Normal (assumption SD 10% of the mean)	Petitjean et al. (2007)[63]
Higher dose (in DDD)	3.00	Normal (assumption SD 10% of the mean)	Petitjean et al. (2007)[63]
Utilities			
On Z-drugs	0.873	Beta (assumption SD 10% of the mean)	Krystal et al. (2008) and Sharples et al.(2014)[32,65]
Off Z-drugs	0.870	Beta (assumption SD 10% of the mean)	Krystal et al. (2008) and Sharples et al. (2014)[32,65]
CBT-I	0.873	Beta (assumption SD 10% of the mean)	Assumption same as 'On Z-drugs' based on findings of Omvik et al. (2008)[64]
Disutilities events *(expressed as annual disutilities but in the model applied as monthly by dividing by 12)*			
Disutility RTA (not seriously injured)	0.05	Beta (assumption SD 10% of the mean)	Assumption
Disutility seriously injured by an RTA (under the assumption of MAIS 3)	0.33	Beta (assumption SD 10% of the mean)	Bell et al. (2001)[67]
Disutility fracture with hospitalisation	0.27	Beta (assumption SD 10% of the mean)	Peeters et al. (2016)[68]
Costs			
Monthly costs of Z-drugs on regular dose	42.09 CHF	Monthly costs regular dose; 3 follow-up visits per year = 1 every four months. Z-drug costs vary in the PSA due to variation in DDD. Follow-up costs are not varied in PSA.	COGE©, Tarifpool ©SASIS AG 2019-2021[69,70], Petitjean et al. (2007)[63], expert opinion and TARMED
Monthly costs of Z-drugs on higher dose	71.34 CHF	Monthly costs higher dose; 3 follow-up visits per year = 1 every four months. Z-drug costs vary in the PSA due to variation in DDD. Follow-up costs are not varied in PSA.	COGE©, Tarifpool ©SASIS AG 2019-2021[69,70], Petitjean et al. (2007)[63], expert opinion and TARMED
Monthly costs of follow-up when off Z-drugs	0 CHF	Not varied in PSA	Assumption
Monthly costs of CBT-I	1'025 CHF	Not varied in PSA	Omvik et al.(2008)[64], expert opinion, and TARMED Costs for one month of CBT-I, applied for four cycles in the model when patients are on CBT-I.
Healthcare costs of non-serious RTA per case	1'740 CHF	Not varied in PSA	Wieser et al. (2009)[71] 1'842 CHF (2007)
Healthcare costs of serious RTA per case	38'300 CHF	Not varied in PSA	Wieser et al. (2009)[71] 40'555 CHF (2007)
Healthcare costs of fracture with hospital admission per case	12'110CHF	Not varied in PSA	BFS - Statistik diagnosebezogener Fallkosten (2014) adjusted for inflation to current price levels using healthcare sector-specific inflation rates from the Swiss Federal Statistical Office.

Abbreviations: BFS: Bundesamt für Statistik; CBT-I: cognitive behaviour therapy for insomnia; DDD: defined daily dose; MAIS: Maximum Abbreviated Injury Score; OR: odds ratio; RTA: road traffic accident; PSA: probabilistic sensitivity analysis; SD: standard deviation.

8.1.5.4.6 Analytical methods

Base-case analysis

The base-case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. The number of patients per simulation that was required for stable outcomes was determined by calculating the cost-effectiveness outcomes for the long-term use of Z-drugs for 20 different seeds for random draws with varying sizes of the simulated patient population. The model was internally validated by multiple clinical experts, however external validation using real world data was not feasible due to data scarcity.

Scenario analyses

Structural uncertainty was explored in several scenario analyses.

- No discounting
- Discount rate of 5%
- Different time horizon than 10 years (i.e. 1, 5 years, and lifetime)
- Risk of fractures and RTAs not dependent on use of regular or higher dosage of Z-drugs

One-way sensitivity analyses (OWSA)

Parameter uncertainty was first tested using one-way sensitivity analyses (OWSA) where model parameters were systematically and independently varied over a range of 20% increase/decrease or between lower and upper bound of the confidence interval when available of the parameter value used in the base-case. The incremental cost-effectiveness ratio (ICER) was recorded at the upper and lower limits to produce tornado diagrams.

The monthly probability of a road accident in the general population was very small (0.304%, i.e. 3 road accidents in 10’000 people) and hence varying this probability in the OWSA would have no impact on the cost-effectiveness results and therefore this parameter was excluded from the OWSA.

Probabilistic sensitivity analyses (PSA)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) where all parameters to which probability distributions are assigned were varied jointly. The distributions that were applied in the PSA are provided in Table 30. Monte Carlo simulations were performed with 1000 runs, and the results were recorded. Results were plotted on the cost-effectiveness plane (CE plane). From these results, a cost-effectiveness acceptability curve (CEAC) was estimated.

Budget impact analysis

The time horizon of the budget impact (BI) model was restricted to 5 years. The undiscounted individual five-year costs of every treatment strategy (i.e. long-term use of Z-drugs, short-term use of Z-drugs followed by no treatment, short-term use of Z-drugs followed by CBT-I, CBT-I, and no treatment) was calculated using the cost-effectiveness model. As we did not have access to data on chronic insomnia cases consuming Z-drugs, we multiplies these individual five-year costs by the number of people using

Z-drugs in Switzerland (i.e. 31'652 people in 2018) derived from Landolt et al. 2021 to calculate the population-level costs of every treatment strategy.[53] The BI was calculated as the difference between the costs of long-term use of Z-drugs and any of the four comparators (i.e. short-term use of Z-drugs followed by no treatment, short-term use of Z-drugs followed by CBT-I, CBT-I, and no treatment).

8.2 Results cost-effectiveness and budget impact

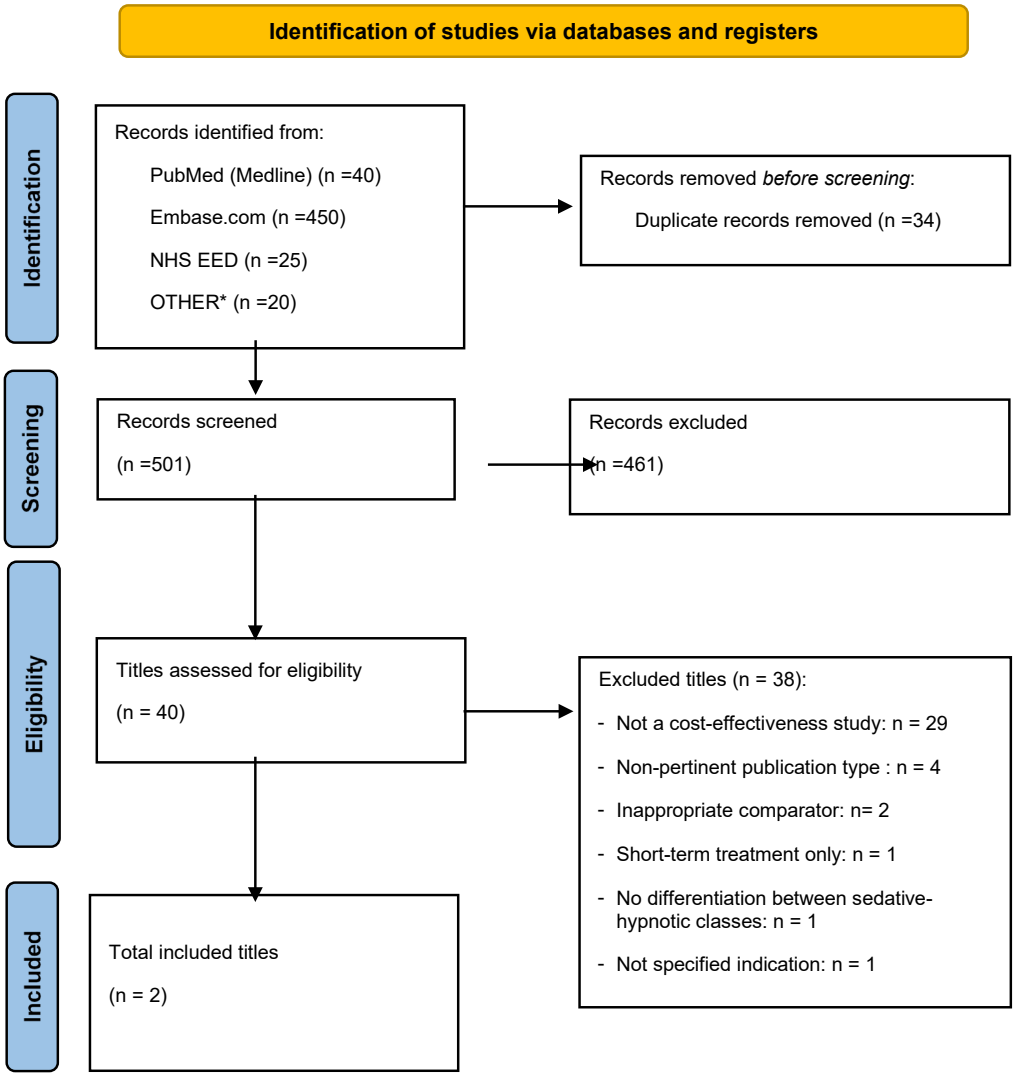
8.2.1 PRISMA flow diagram

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. (2004). 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 8).

Figure 8. 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
*Efficacy, effectiveness, and safety screening, references in articles, identified from pre-scoping report.

8.2.2 Study characteristics and quality assessment of included studies

Table 31 presents the study characteristics of the two included cost-effectiveness studies. The study of Morgan *et al*. 2004 was a cost-effectiveness analysis alongside a RCT of CBT compared to no treatment with or without continuation of hypnotic drugs in the United Kingdom.[75] The study of Moriarty et al. 2019 was a model-based study using a Markov model to estimate the cost-effectiveness of several drugs, including benzodiazepines, in community-dwelling elderly in Ireland. [76]

The completed CHEC checklist for these two studies is presented in Table 31. The study of Morgan et al. 2004 did not fulfil all the items of the CHEC because it was an economic evaluation besides an RCT, it did not extrapolate results to a time horizon longer than 6 months, and they did not include adverse events of hypnotic drugs.[75] The study of Moriarty et al. 2019 fulfilled all items of the CHEC, except that they did not include utilities as quality of life inputs but used EQ-5D VAS estimates instead. [76]

Table 31 Overview study characteristics of cost-effectiveness studies

Parameter	Morgan et al. 2004[75]	Moriarty et al. 2019[76]
Year	2003	2019
Country	United Kingdom	Ireland
Type of study	Pragmatic RCT	Cost-utility analysis
Study population	Long-term users (>1 month) of hypnotic drugs	Hypothetical community-dwelling
Mean age or age groups (in years)	Clinic group: 63.3 Control group: 67.7	65
Intervention	CBT in primary care (with/without continuation of hypnotic drugs)	Benzodiazepine ≥4 weeks
Comparator	No treatment (with/without continuation of hypnotic drugs)	No sedative medication
Type of model	CEA of RCT	Modelling study (Markov model)
Perspective	Healthcare (NHS)	Healthcare
Time horizon	6 months follow-up	35 years (= lifetime)
Price year	1999-2000	2014
Currency	Pound	Euro
Cost categories considered	Counsellor sessions, hypnotic drug use, all GP and other primary care contacts. Counsellor sessions included salary, on-cost, training, supervision, travel, clerical support, equipment, and capital costs.	Direct costs to health system (including residential care related costs): hospital inpatient care, general practitioner, outpatient department and emergency department visits, medicines and long-term (residential) care.
Discount rates (costs/ effects)	NA	5% per year (range: 0% to 6%)
Outcome measures	Pittsburgh global and component scores; TST; SE; SL; SF-36; frequency of hypnotic drug use; healthcare costs and cost utility.	Costs, QALYs. LYs and number/rate of adverse events (i.e. hip fracture and other fall injuries)
Health states used in model	N.A.	1.No fall injury; 2. Other fall injury; 3. Hip fracture; 4.Death

Abbreviations: CBT = cognitive behaviour therapy, CEA = Cost-effectiveness analysis, LY = life year, NA = not applicable, NHS = National Health Service, QALY = quality adjusted life year, RCT= randomised controlled trial, SE = sleep efficiency, SF-36 = short form health survey-36 items, SL = sleep latency, TST = total sleep time.

Table 32. Critical appraisal of cost-effectiveness studies using the CHEC checklist[77]

			Morgan, 2004	Moriarty, 2019
Study design	**1**	Is the study population clearly described?	✓	✓
	2	Are competing alternatives clearly described?	✓	✓
	3	Is a well-defined research question posed in answerable form?	✓	✓
	4	Is the economic study design appropriate to the stated objective?	✓	✓
	5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	X, 6 months	✓
	6	Is the actual perspective chosen appropriate?	✓	✓
Costs	**7**	Are all important and relevant costs for each alternative identified?	✓	✓
	8	Are all costs measured appropriately in physical units?	✓	✓
	9	Are costs valued appropriately?	✓	✓
Outcomes	**10**	Are all important and relevant outcomes for each alternative identified?	X, no adverse events	✓
	11	Are all outcomes measured appropriately?	-	X, EQ-5D VAS instead of utilities
	12	Are outcomes valued appropriately?	-	✓
Interpretation and results	**13**	Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓
	14	Are all future costs and outcomes discounted appropriately?	NA, because did not use a model	✓
	15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	NA, because did not use a model	✓
	16	Do the conclusions follow from the data reported?	✓	✓
	17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	✓	✓
	18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	✓
	19	Are ethical and distributional issues discussed appropriately?	✓	✓

Abbreviations: EQ-5D = EuroQol -5 dimensions, NA=not applicable, VAS = Visual Analog Scale

8.2.3 Evidence table

Table 33 presents the cost-effectiveness outcomes of the two included studies. Morgan et al. (2004) found that CBT was associated with additional costs and QALYs compared to no treatment (with or without withdrawal from hypnotic drugs). [75] Moriarty et al. (2019) found that long-term use of benzodiazepines in community-dwelling elderly in Ireland was associated with increased costs and less QALYs than not using benzodiazepines, thus the intervention treatment is dominated by the comparison treatment. [76]

Table 33. Overview of outcomes of cost-effectiveness studies

Reference		**Sample size**		**Costs**			**QALY**			**ICER (cost/QALY)**
		CBT	**No CBT**	**CBT**	**No CBT**	**Incremental**	**CBT**	**No CBT**	**Incremental**	
Morgan, 2004[75]	With hypnotic drug withdrawals	108	101	£263.6	£162.4	£101.2	0.007	-0.014	0.021	£4’819
	Without hypnotic drug withdrawals	64	59	£272.4	£142.6	£129.8	0.024	-0.014	0.038	£3’416
		Long-term drug use	**No drug use**	**Long-term drug use**	**No drug use**	**Incremental**	**Long-term drug use**	**No drug use**	**Incremental**	
Moriarty, 2019[76]		NA	NA	€28’628	€25’158	€3’470	8.72	8.78	-0.07	Dominated

Abbreviations: CBT = cognitive behaviour therapy, ICER = incremental cost-effectiveness ratio, NA = not applicable, QALY = quality adjusted life year.

8.2.4 Findings cost-effectiveness

8.2.4.1 Base-case analysis

The base-case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. The model produced stable results (i.e. similar results regardless of the seed that was used) when sampling >1'000 patients. Therefore, deterministic analyses were performed with 5'000 patients.

Table 34 shows the costs, QALYs and incremental costs and QALYs of long-term use of Z-drug versus the comparator defined in the four PICOs. The results were higher costs while having less QALYs compared to the comparators. Therefore, all the comparators dominate the long-term use of Z-drugs.

Table 34. Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Costs (CHF, discounted)	QALYs (discounted)	Incremental costs (CHF)	Incremental QALYs
1a	**No treatment**	2'019	7.169		
	Long-term Z-drug	8'983	7.138	6'965	-0.031
1b	**CBT-I**	5'240	7.189		
	Long-term Z-drug	8'983	7.138	3'743	-0.051
2a	**Short-term Z-drug**	2'061	7.169		
	Long-term Z-drug	8'983	7.138	6'922	-0.031
2b	**Short-term Z-drug + CBT-I**	5'282	7.189		
	Long-term Z-drug	8'983	7.138	3'701	-0.051

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

8.2.4.2 Scenario analyses

8.2.4.2.1 Discounting scenarios

Two scenario analyses were run adjusting for discounting. The results in Table 35 assume no discount rates, while results in Table 36 assume 5 % discount rate for both effects and costs. Regardless of the discount applied, the long-term Z-drug treatment remains dominated by the other treatments.

Table 35 No discount - Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	2'330	8.252			
	Long-term Z-drug	10'316	8.216	7'986	-0.036	Dominated
1b	**CBT-I**	5'563	8.276			
	Long-term Z-drug	10'316	8.216	4'753	-0.06	Dominated
2a	**Short-term Z-drug**	2'372	8.253			
	Long-term Z-drug	10'316	8.216	7'944	-0.037	Dominated
2b	**Short-term Z-drug + CBT-I**	5'605	8.276			
	Long-term Z-drug	10'316	8.216	4'711	-0.06	Dominated

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

Table 36 Discounting rate at 5% - Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	1'848	6.567			
	Long-term Z-drug	8'246	6.540	6'398	-0.027	Dominated
1b	**CBT-I**	5'063	6.585			
	Long-term Z-drug	8'246	6.540	3'183	-0.045	Dominated
2a	**Short-term Z-drug**	1'890	6.567			
	Long-term Z-drug	8'246	6.540	6'356	-0.027	Dominated
2b	**Short-term Z-drug + CBT-I**	5'105	6.585			
	Long-term Z-drug	8'246	6.540	3'141	-0.045	Dominated

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

8.2.4.2.2 Time horizon scenarios

Additional time horizon scenarios were analysed, assuming a time horizon of 1 year, 5 years, and life-time, results of these scenarios are in Table 37, Table 38, and Table 39 respectively. In the short time horizon of 1 year, the costs of CBT-I, and short-term Z-drug use + CBT-I exceed the costs of long-term Z-drug use, rendering the long-term use of Z-drug treatment not to be dominated by these treatments.

Table 37 Time horizon of 1 year - Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	375	0.922			
	Long-term Z-drug	1'565	0.921	1'190	-0.001	Dominated
1b	**CBT-I**	3'597	0.924			
	Long-term Z-drug	1'565	0.921	-2'032	-0.003	677'333
2a	**Short-term Z-drug**	417	0.922			
	Long-term Z-drug	1'565	0.921	1'148	-0.001	Dominated
2b	**Short-term Z-drug + CBT-I**	3'639	0.924			
	Long-term Z-drug	1'565	0.921	-2'074	-0.003	691'333

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

Table 38 Time horizon of 5 years- Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	1'065	3.997			
	Long-term Z-drug	5'004	3.987	3'939	-0.01	Dominated
1b	**CBT-I**	4'288	4.008			
	Long-term Z-drug	5'004	3.987	716	-0.021	Dominated
2a	**Short-term Z-drug**	1'108	3.997			
	Long-term Z-drug	5'004	3.987	3'896	-0.01	Dominated
2b	**Short-term Z-drug + CBT-I**	4'330	4.008			
	Long-term Z-drug	5'004	3.987	674	-0.021	Dominated

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

Table 39 Time horizon of lifetime - Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	5'645	12.928			
	Long-term Z-drug	19'600	12.779	13'955	-0.149	Dominated
1b	**CBT-I**	8'867	12.948			
	Long-term Z-drug	19'600	12.779	10'733	-0.169	Dominated
2a	**Short-term Z-drug**	5'687	12.938			
	Long-term Z-drug	19'600	12.779	13'913	-0.159	Dominated
2b	**Short-term Z-drug + CBT-I**	8'910	12.948			
	Long-term Z-drug	19'600	12.779	10'690	-0.169	Dominated

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

8.2.4.2.3 No increased risk of fractures and road traffic accidents in higher dose

A scenario with no increased risk of fractures and road traffic accidents due to a higher dose of Z-drugs was analysed. In PICO 1a and 2a, in which no treatment and short-term use of Z-drugs are compared to long-term Z-drug use, the effectiveness associated with long-term use of Z-drug is larger than the comparators. In these two cases, long-term use of Z-drugs is not dominated by the comparator treatments.

Table 40 No increased risk of fractures and road traffic accidents at higher dose of Z-drugs - Costs, QALYs, and corresponding incremental costs and QALYs by PICO

PICO	Treatment	Cost (CHF)	QA-LYs	Incremental costs (in CHF)	Incremental QA-LYs	ICER
1a	**No treatment**	2'019	7.169			
	Long-term Z-drug	7'936	7.172	5'917	0.003	Dominated
1b	**CBT-I**	5'241	7.189			
	Long-term Z-drug	7'936	7.172	2'695	-0.017	Dominated
2a	**Short-term Z-drug**	2'061	7.169			
	Long-term Z-drug	7'936	7.172	5'875	0.003	Dominated
2b	**Short-term Z-drug + CBT-I**	5'283	7.189			
	Long-term Z-drug	7'936	7.172	2'653	-0.017	Dominated

Abbreviations: CBT-I = cognitive behavioural therapy for insomnia

8.2.4.3 One-way sensitivity analyses

Figure 9 and Figure 10 show the tornado diagrams of incremental costs and incremental effects results of the one-way sensitivity analysis (OWSA) of PICO 1a. The width of the bars represents the potential range of the estimate given the potential variation in each variable with the other variables held constant. In the case of incremental costs, as indicated by their order (highest impact on top), the parameters with the largest impact on costs are age at baseline, followed by ORs of fractures and road accidents, and cost of Z-drug. For incremental effects, varying the utility of not being on Z-drugs, being on regular Z-drug dose, and being on high Z-drug dose has the largest impact. Tornado diagrams of incremental costs and effects for the other PICOs are reported in appendix 15.5.

Figure 9 Tornado diagram of One-Way Sensitivity Analysis for PICO 1a – incremental costs

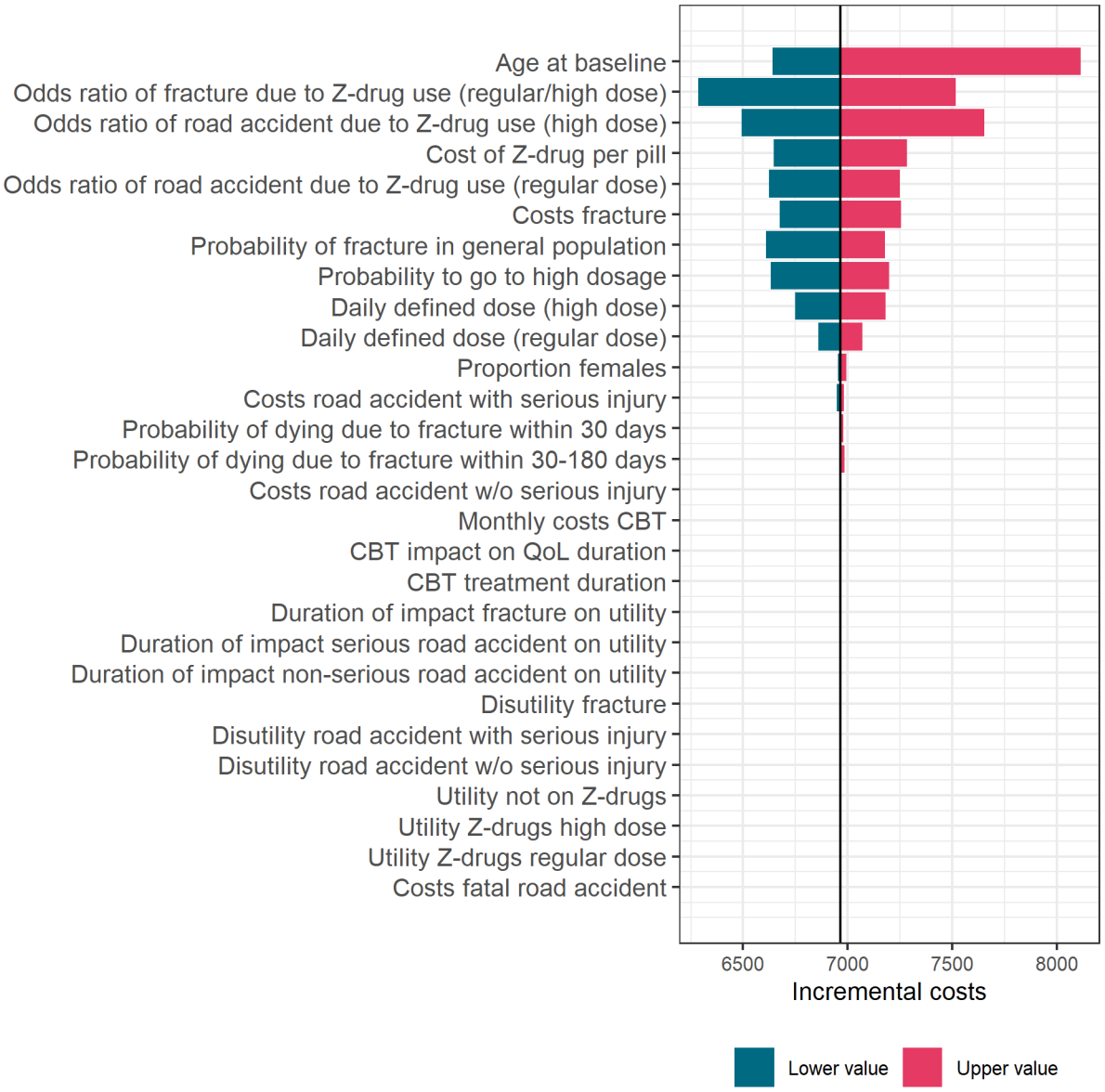
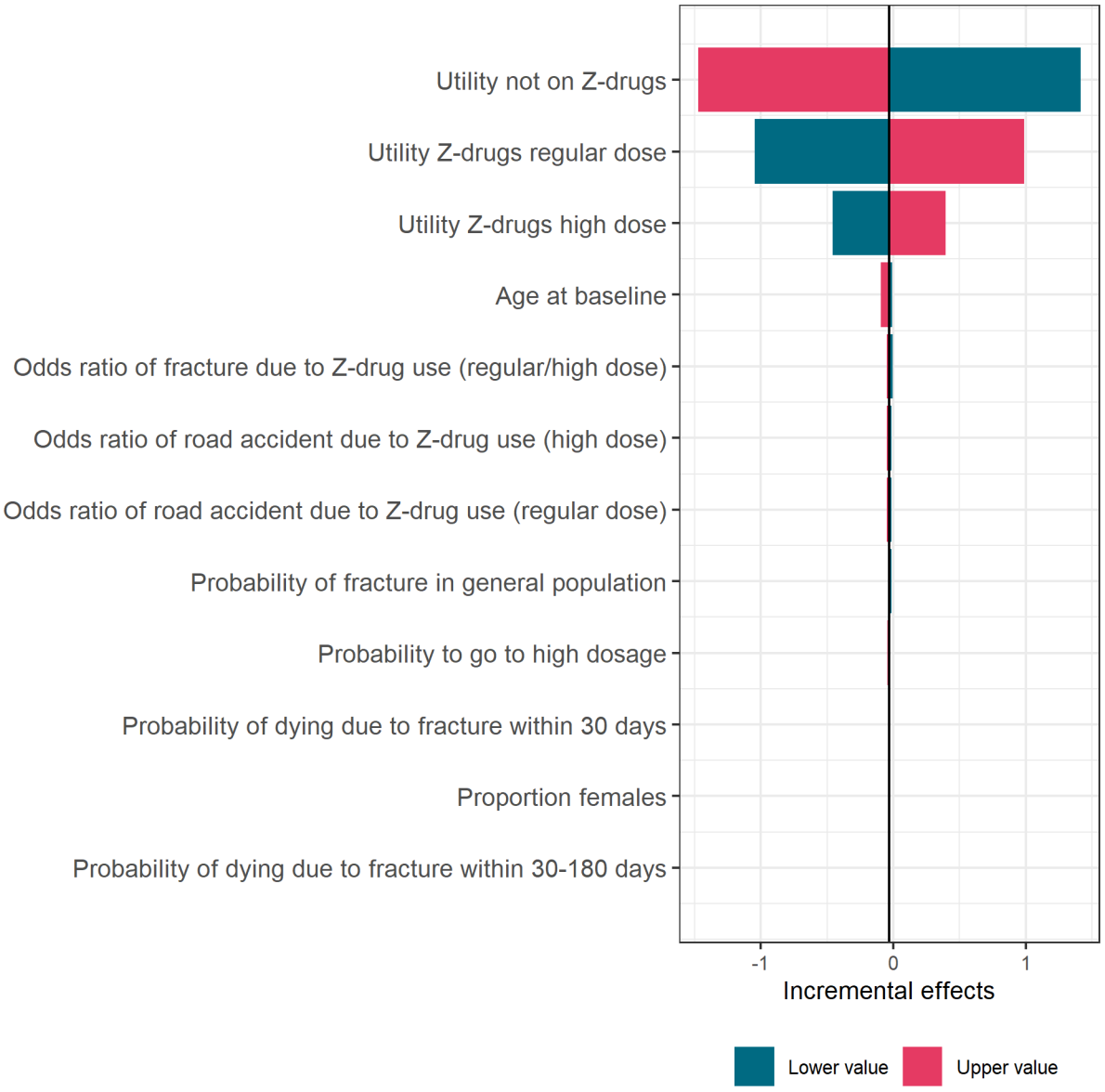


Figure 10 Tornado diagram of One-Way Sensitivity Analysis for PICO 1a – incremental effects



The OWSA showed that a univariate change of the input parameters (+/- 20% or confidence intervals for the OR of RTA) does not alter the incremental costs of long-term Z-drugs use to such an extent that it becomes cost saving: it is always a more costly option than the alternatives. The extent to which it is more costly depends most strongly on parameters such as the starting age of the model, the probability of adverse events such as road accidents and fractures, as well as the acquisition costs of the drugs. With regards to the effects, however, the OWSA shows that the model results are sensitive to the benefit (utility) derived from Z-drugs as well as the baseline quality of life. When benefit of Z-drugs is 20% higher than assumed in the base case setting of this model, there is a positive rather than a negative effect of

long-term Z-drugs use. It is worth noting, however, that studies that looked into quality of life benefits of Z-drugs with questionnaires such as the SF-36 did not find significant improvements, suggesting that the base-case setting has some validity. [30,33] Compared to utilities, the odds ratios from road traffic accidents and fractures have a relatively small impact on effects.

8.2.4.4 Probabilistic sensitivity analysis

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) of each individual PICO are presented in Figure 11 to Figure 18. The cost-effectiveness plane iterations for all the PICOs are located in the top section of the plane, meaning the costs are always higher for long-term use of Z-drug treatment. The iterations are scattered relatively evenly horizontally across both left and right section of the incremental QALYs, suggesting a larger impact of the variation in effectiveness in the model than seen in the cost. Reviewing the CEACs, the probability of long-term use of Z-drugs being optimal only approaches 50% even at a willingness to pay threshold of CHF 200'000.

Figure 11 Cost-effectiveness plane – PICO 1a

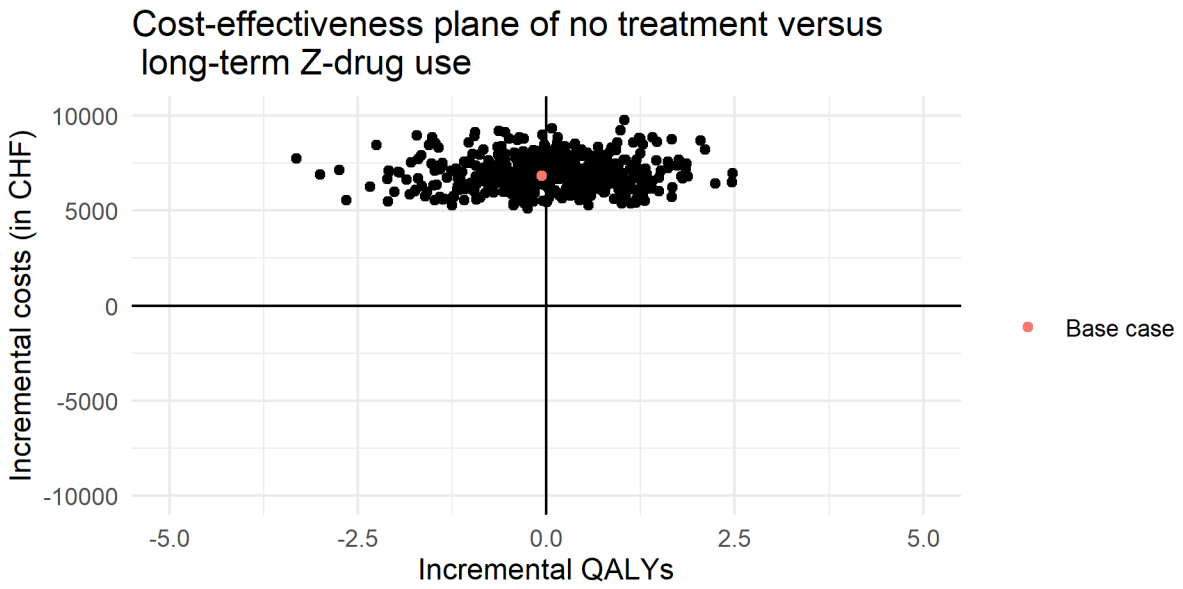


Figure 12 Cost-effectiveness acceptability curve – PICO 1a

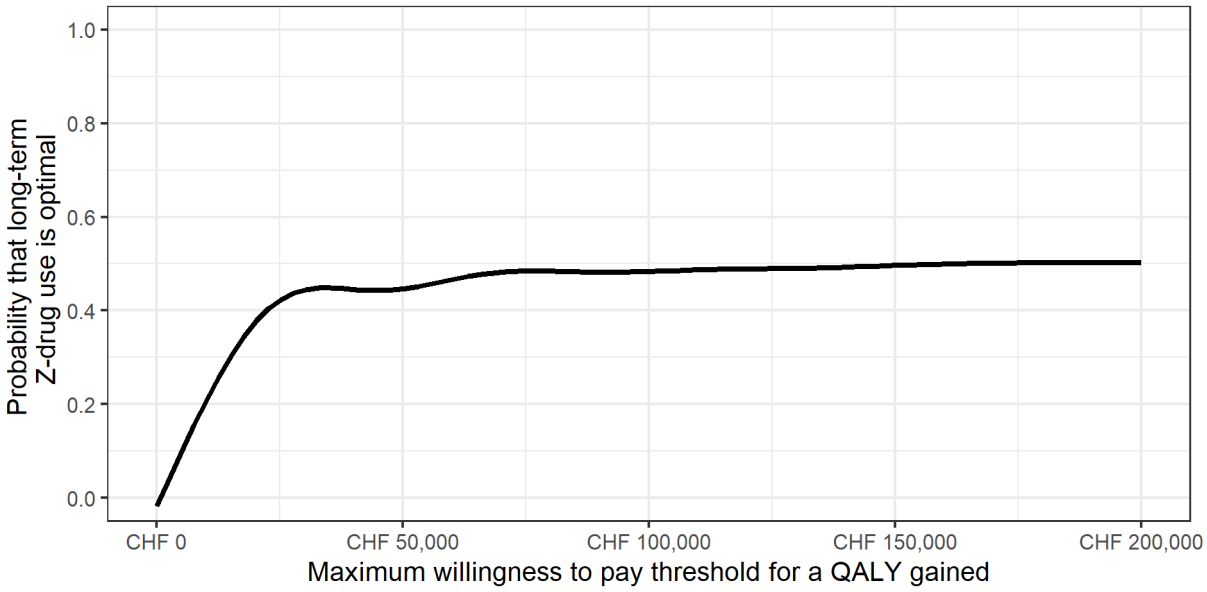


Figure 13 Cost-effectiveness plane – PICO 1b

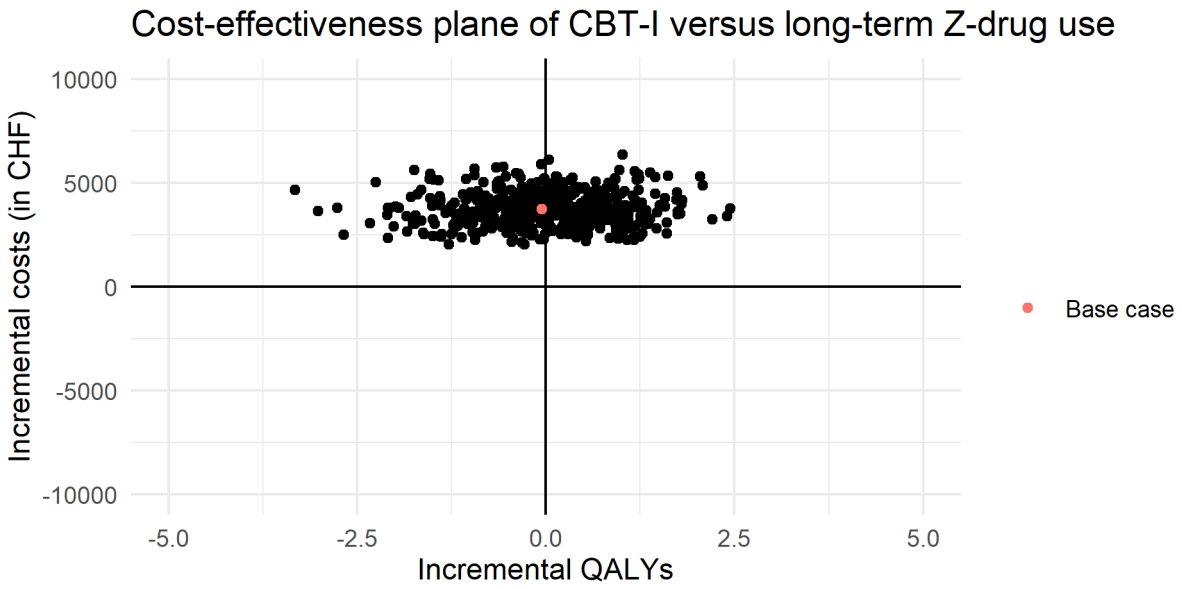


Figure 14 Cost-effectiveness acceptability curve – PICO 1b

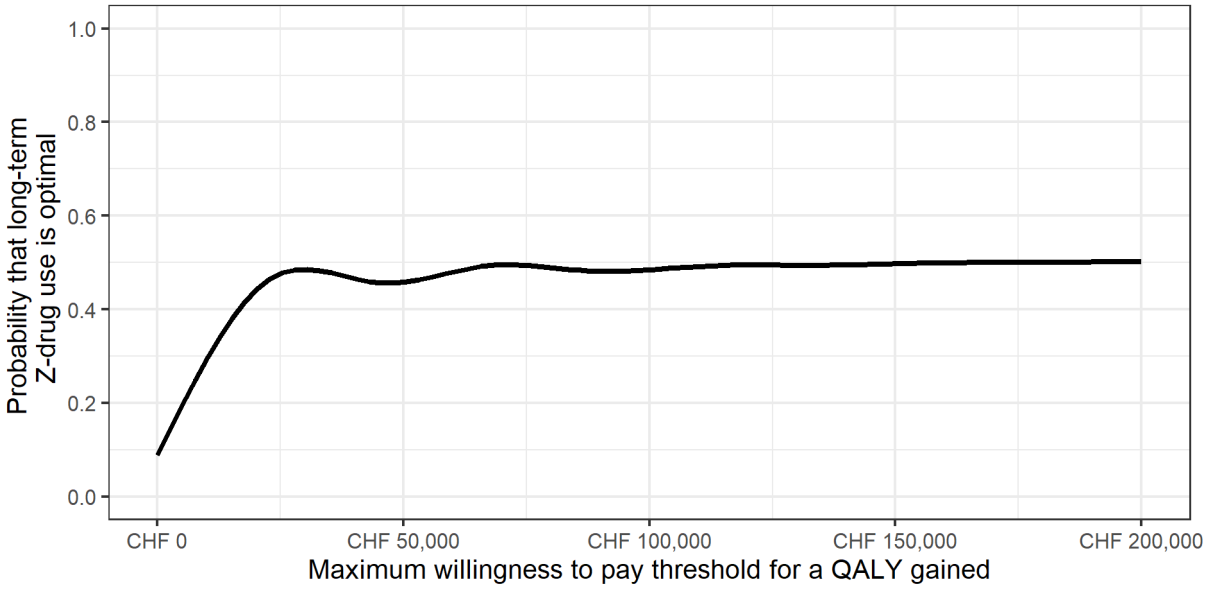


Figure 15 Cost-effectiveness plane – PICO 2a

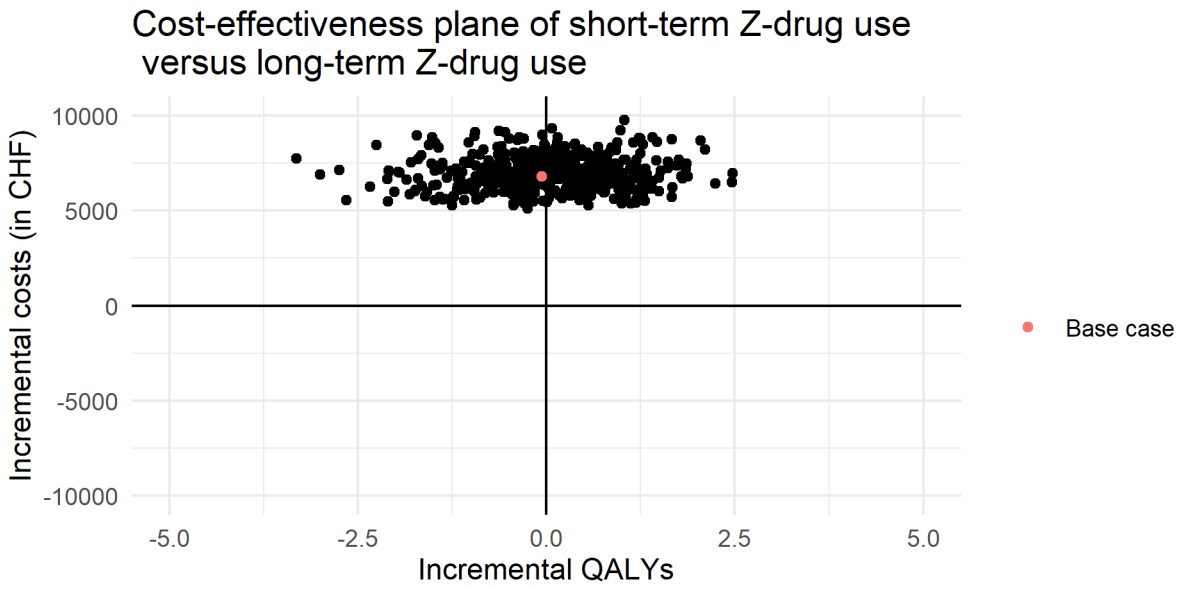


Figure 16 Cost-effectiveness acceptability curve – PICO 2a

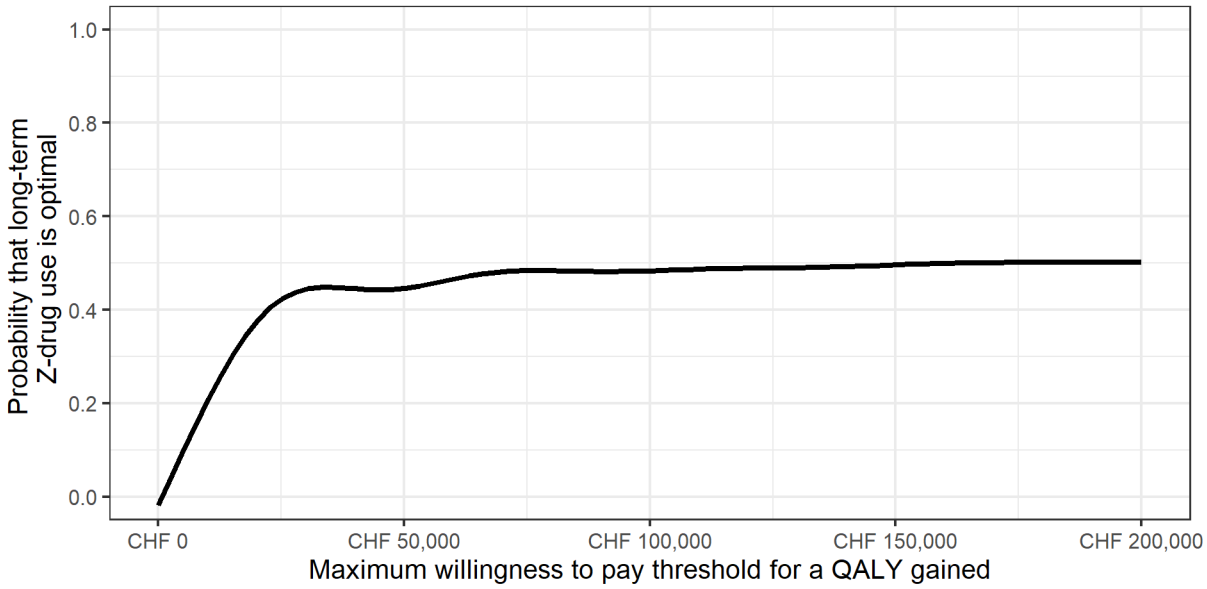


Figure 17 Cost-effectiveness plane – PICO 2b

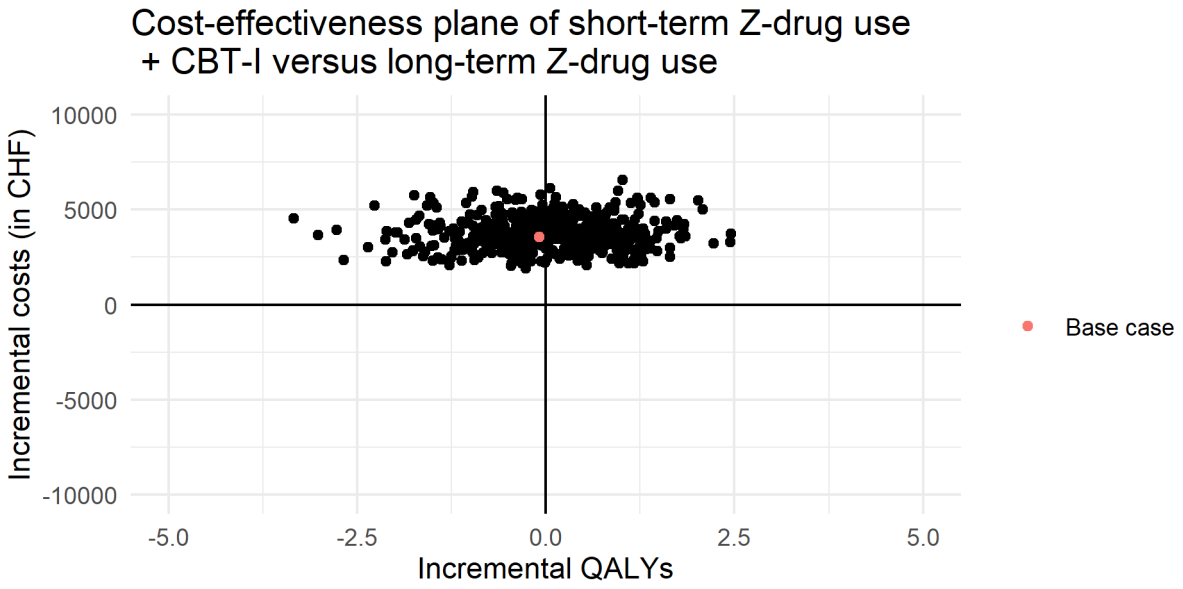
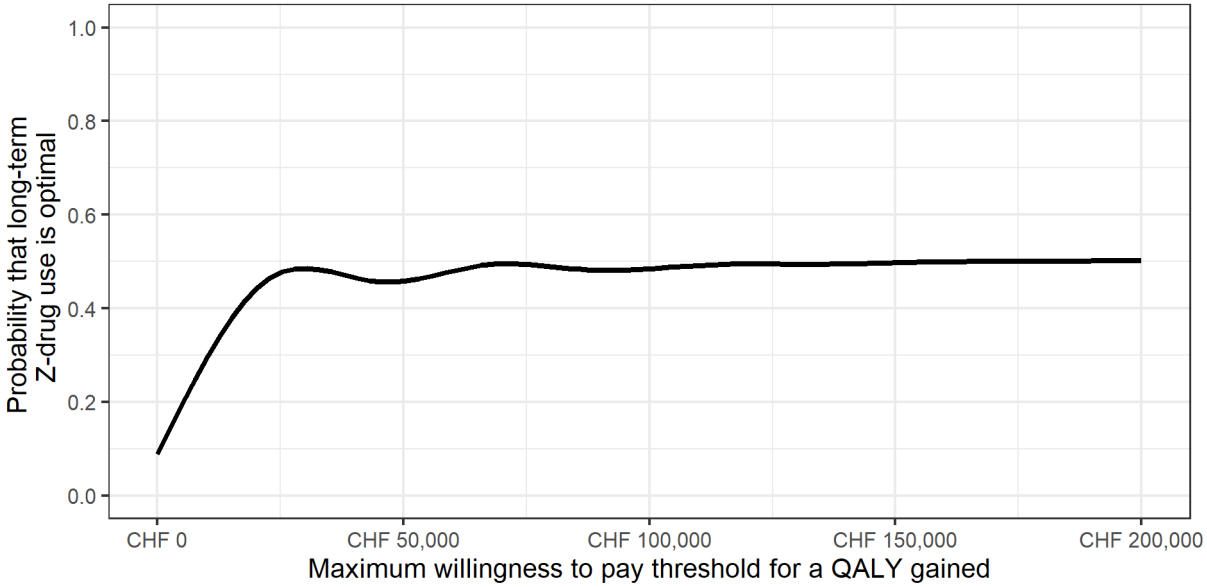


Figure 18 Cost-effectiveness acceptability curve – PICO 2b



The PSA presents findings similar to those of the OWSA. While the results on incremental costs are relatively certain, demonstrated by little variation on the y-axis of the PSA plots for all PICOs, the variation on the x-axis (i.e. incremental QALYs) is larger, ranging from negative to positive. The parameter uncertainty of utilities, however, has been taken by sampling from a beta-distribution round the mean utility value, which itself was derived indirectly from a mapping study. This has two consequences: first, the uncertainty around utility values does not really reflect parameter uncertainty but an assumed uncertainty; second, the statistical uncertainty of the regression equation of the mapping function itself is not represented. To summarize, the evidence of quality of life improvements due to Z-drugs are scarce and uncertain and the model results reflect this limitation. This uncertainty of long-term Z-drug use on effects is hence accompanied by certainty that long-term Z-drugs use increases costs.

8.2.5 Findings budget impact

The financial consequences for the pharmacy/hospital budget of long-term use of Z-drugs based on the number of potential patients and the average costs per patient per year were calculated and are presented in Table 41. Number of potential patients is based on the prevalence of Z-drug users of Landolt et al. (2021). [53] The analysis was performed for 5 years. The final column shows the potential savings per treatment when compared to the long-term use of Z-drug treatment. According to the results of the budget impact analysis, no treatment or short-term use of Z-drug could save in excess of CHF 130 million, while CBT-I or short-term use of Z-drug in combination with CBT-I could save around CHF 30 million.

Table 41 Budget impact analysis results

Treatment	Costs at 5 year at individual level [CHF]	Costs at 5 year at population level [CHF]	Potential savings by treatment [CHF]
Long-term Z-drug	5'342	169'080'974	0
Short-term Z-drug	1'176	37'208'730	131'872'244
Short-term Z-drug + CBT-I	4'408	139'527'168	29'553'806
No treatment	1'133	35'876'375	133'204'599
CBT-I	4'366	138'194'813	30'886'161

9 Ethical, legal, and social issues

Summary statement ethical, legal, and social issues

While generally considered to have a better safety profile than benzodiazepines, dependency and dosage increase is a risk that is also associated with Z-drug use. Long-term use of Z-drugs in the elderly may be accompanied with polypharmacy related side effects. The Swiss product information on Zopiclone and Zolpidem warns of increased risk of accidents and caution driving and operating machinery 12 hours post consumption of drug.Nonetheless, Z-drug use is associated with an increased risk of road traffic accidents and fractures. Educational campaigns as well as driver licence restrictions may reduce Z-drug use and/or accidents.

9.1 Methodology ethical, legal, and social issues

9.1.1 Databases and search strategy

Titles of interest for the ethical, legal, and social issues were gathered during the systematic literature searches for efficacy, effectiveness, and safety and for cost-effectiveness. Additionally, a pragmatic literature search was performed on relevant websites for grey literature. Key websites of interest were identified and accessed in April-May 2021 from an overview of national websites on the website for *Swiss Society for Sleep Research, Sleep Medicine and Chronobiology*, including:

- Institute of Pharmacology Zurich, Section of Psychopharmacology and Sleep Research (https://www.pharma.uzh.ch/en/research/chronobiology.html)
- Lungenliga Schweiz, Schweiz. Gesellschaft für Pneumologie (https://www.lungenliga.ch/de/startseite.html)
- Schweizerische Gesellschaft für Pneumologie (https://www.pneumo.ch/de/)
- Swiss Center for Chronobiology Basel (http://www.chronobiology.ch/)
- Swiss Neurological Society (https://www.swiss-neuro.ch/Home)
- Swiss Society for Neuroscience (https://www.swissneuroscience.ch/)
- Swiss Society for Psychiatry and Psychotherapy (https://www.psychiatrie.ch/sgpp/)

In addition to these websites, the publication database on the website of the *European monitoring centre for drugs and drug addiction(https://www.emcdda.europa.eu/),* was also searched. No restrictions were applied to time period of publication nor to language. Upon review, two more studies were included to cover the ethical issue of discontinuation of sedative-hypnotic drugs in elderly, based on the recommendation of expert reviewers.

Each included report was screened for information on ethical, legal, and social issues or consequences regarding the prescription and reimbursement of sedative-hypnotic drugs. The EUnetHTA Core Model was used to conceptualise the four HTA domains, i.e. the description and questions provided in the

EUnetHTA Core Model were used as framework for the screening of documents. The selection process was presented in a PRISMA flowchart.

9.1.2 Other sources

Not applicable.

9.1.3 Assessment of quality of evidence

Not applicable.

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

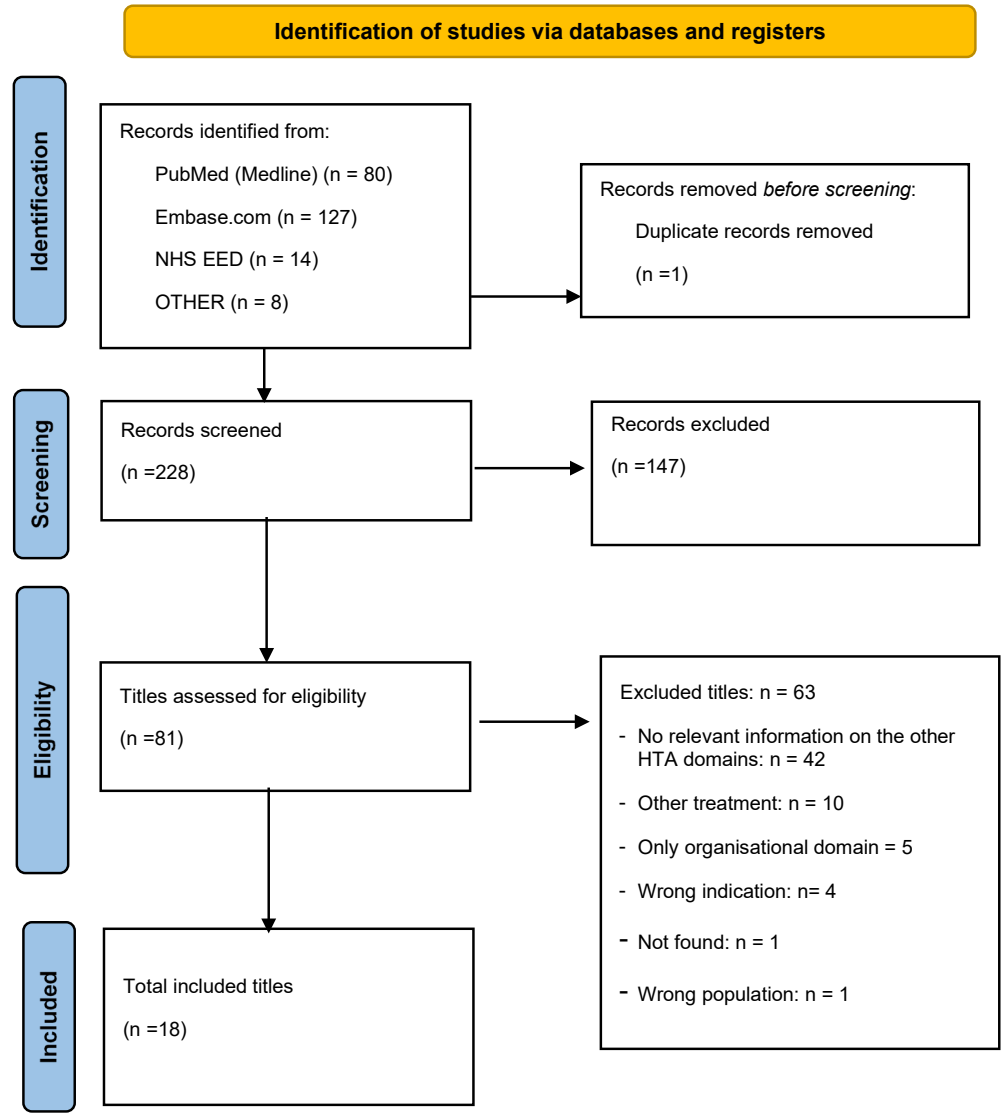
The summary of the findings related to the ethical, legal, and social domains was provided narratively. No statistical tests were applied to the literature search output of the above-mentioned domains.

9.2 Results ethical, legal, and social issues

9.2.1 PRISMA flow diagram

Figure 19 shows the PRISMA flowchart of the selection process which resulted in the inclusion of 14 documents on ethical, legal, and social issues. All the included documents were published between 1997 and 2020. Most documents discussed general sleep issues and insomnia, but the identified ethical, legal, and social aspects identified in the documents may also be applicable to our specific subgroup of long-term users of sedative-hypnotic drugs for chronic primary insomnia disorder.

Figure 19. PRISMA flowchart of the systematic literature search on ethical, legal, and social issues related to long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder



Abbreviations: HTA – Health Technology Assessment, *Other= websites and reviewer feedback

9.2.2 Study characteristics of included studies

The studies included in the ethical, legal, and social domains were predominantly observational on topics regarding benzodiazepine and Z-drug concerns, like limitations to discontinuation of drugs and complexities regarding inappropriate drug use among elderly. A few publications were guidelines or recommendation documents. The publications are mainly published in western European countries and USA. The included studies cover topics mostly in ethical and social domains. (see Table 42). Meanwhile, apart from drug warning labels and guidelines sources, only one case study was sourced for the legal domain, Paulke et al. 2015[78].

Table 42. Study characteristics of the 18 articles included in the Ethical, Legal, and Social domains.

First author, year	Title	Country	Study design	Aim	Outcomes/findings
Agravat et al. 2018[79]	'Z'-hypnotics versus benzodiazepines for the treatment of insomnia	UK	Review	To compare Z-drugs and benzodiazepines as hypnotic agents in terms of their efficacy, safety, tolerability and abuse potential.	All hypnotics should be used short-term or intermittently and be reviewed regularly. This caution should be explained to patients along with information about the hypnotic prescribed to limit abuse potential.
Airagnes et al. 2016[80]	Benzodiazepine Misuse in the Elderly: Risk Factors, Consequences, and Management	Various	Review	To describe the context of inappropriate BZD and BZD-related hypnotic use in the elderly, their medical consequences, and currently available management strategies.	BZD consumption becomes more prevalent as age increases. BZD prescriptions are inappropriate in two thirds of cases. The most frequent inadequate situations are excessive duration and/or dosage of a medical prescription. Female gender, polypharmacy, and the number of comorbidities is major risk factors. Inappropriate BZD prescriptions lead to severe complications, such as respiratory distress, falls, and accidents. Authors claim discontinuation of chronic benzodiazepines feasible despite many clinician's disbelief, when applying adequate psychotherapeutic or pharmacological strategies, and can lead to long-term abstinence.
Avorn and Gurwitz 1995[81]	Drug Use in the Nursing Home	USA	Review	To summarize pharmacotherapy in the nursing home and provide recommendations.	Nursing home patients are of particular risk of polypharmacy and adverse events. Additionally, the authors raise the issue of potential overuse of sedation of residents with dementia for non-clinical reasons, such as in cases of insufficient staffing.
Bain et al. 2008[82]	Discontinuing Medications: A Novel Approach for Revising the Prescribing Stage of the Medication-Use Process	USA	Guideline	To provide information to guide clinicians about the steps and challenges associated with discontinuing medications in geriatric population.	Article proposes a conceptual framework for revising the prescribing stage of the medication use process to include the challenges related to discontinuation. In particular, aimed at clinical care of older persons susceptible to adverse effects of medications.
Bramness et al. 2002[83]	Clinical impairment of benzodiazepines - relation between benzodiazepine concentrations and impairment in apprehended drivers	Norway	Observational	To estimate the relationship between benzodiazepine concentrations in the blood and impairment in apprehended drivers.	Clear concentration-effect relationship as measured by benzodiazepine drug concentrations and clinically assessed impairment, suggesting a discussion on legal limits for benzodiazepines in relation to driving.

Cateau et al. 2021[84]	Deprescribing in nursing homes: Protocol for nested, randomised controlled hybrid trials of deprescribing interventions	Switzerland	Observational	To understand the implementation of deprescribing plan in nursing homes.	The article presents a pragmatic, nested study of two consecutive deprescribing interventions, describing existing interprofessional quality circles in nursing homes, and the implementation of deprescribing plan for residents.
Gunja et al. 2013[85]	In the Zzz Zone: The Effects of Z-Drugs on Human Performance and Driving	USA	Review	To review the adverse effect profile of Z-drugs.	Zopiclone in particular have similar adverse effects to benzodiazepines, especially with regards to human performance and driving impairments. Zolpidem especially is associated with complex behaviours, hallucinations, and memory impairment. The increased risk of falls and motor vehicle collisions is notably significant for elderly insomniacs on Z-drugs. The risk–benefit analysis of Z-drugs for the management of insomnia in the elderly may not favour treatment. Prescribers should warn patients taking Z-drugs of minimum time thresholds before they operate machinery or drive motor vehicles.
Gurwitz et al. 2000[86]	Incidence and Preventability of Adverse Drug Events in Nursing Homes	USA	Observational	To study the incidence and prevalence of adverse drug events and potential adverse drug events in nursing homes.	About 350,000 adverse drug events—more than half of which are preventable— occur each year in the 1.55 million residents of US nursing homes. There are almost 20,000 fatal or life-threatening adverse drug events per year, of which 80% are preventable. Sedative/hypnotic drugs were among the most common drugs associated with adverse events.
Hajak et al. 2003	Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data	UK	Review	To review the potential abuse and dependence of zolpidem and zopiclone.	Zolpidem and zopiclone are relatively safe drugs. However, patients with a history of abuse or dependence, as well as those with psychiatric disease, seem to be at increased risk from abuse of these agents.
Jaffe et al. 2004	A post marketing study of relative abuse liability of hypnotic sedative drugs	USA	Review	To demonstrate the utility of post marketing studies using in-treatment drug and alcohol abusers as informants for assessing the relative abuse liability of sedative-hypnotic drugs.	This pilot study suggests that post marketing information on hypnotic drug use obtained from drug addicts entering treatment produces data consistent with other measures of abuse liability. The data suggest that the risk of misuse of newer non-benzodiazepine hypnotics may be less than that of benzodiazepine drugs, and similar to that of sedating antidepressants. The new methodology may serve to clarify or validate premarketing abuse liability data and may help to inform the regulatory process and physician practice.
Jenkins et al. 2012[87]	Development and evaluation of a	Wales	Survey	To identify the usefulness of a pack of resources	The resource pack was well received by the responders of the survey. How-

	national educational pack to support the appropriate prescribing of anxiolytics and hypnotics in Wales			in order to support deprescribing of benzodiazepines and Z-drugs in Wales.	ever, respondents identified limitations to progress and suggested further support.
Lader et al. 2009[88]	Withdrawing Benzodiazepines in Primary Care	UK	Review	To outline assessment of both effectiveness and feasibility of withdrawing benzodiazepines in primary care.	The method of discontinuation should always include tapering. However, the rate of tapering remains controversial, and it is advised to remain flexible. Adjunctive medication is not established, except for depressed individuals. Non-drug strategies range from advice to tapering off to CBT.
Luta et al. 2019[89]	Patterns of benzodiazepine prescription among older adults in Switzerland: a cross-sectional analysis of claims data	Switzerland	Observational	To examine the prevalence and determinants of benzodiazepine prescription, and the association with hospitalisation and costs among older adults.	The prescription of at least one benzodiazepine is high and increasing with age. The prescription trend varies across gender, cantons, and deductible level.
Paulke et al. 2015[78]	Sleep self-intoxication and sleep driving as rare zolpidem-induced complex behaviour	Germany	Case report	To investigate the so-called zolpidem-induced sleep-related complex behaviour as somnambulism and consequent sleep intoxication.	Amnesia and incoherence of speech, disorganization of behaviour, inability to realize the situation and mood changes may indicate a zolpidem-induced somnambulism-like state with sleep-related complex behaviour.
Schmalstieg-Bahr et al. 2019[90]	General practitioners' concepts on issuing out-of-pocket prescriptions for hypnotics and sedatives in Germany.	Germany	Observational	To understand the phenomenon of out-of-pocket (OOP) prescriptions for benzodiazepines and Z-drugs from general practitioners (GPs) in Germany.	Current regulations do not provide guidance to GPs regarding hypnotics and sedatives. A clear regulatory framework and guidelines could possibly reduce physicians' defensive attitudes about these drugs and their use of OOP prescriptions. The approach to use OOP prescriptions as a barrier to reduce patients' medication use lacks evidence regarding effectiveness.
Shaw et al. 2019[91]	Policies for Deprescribing: An International Scan of Intended and Unintended Outcomes of Limiting Sedative-Hypnotic Use in Community-Dwelling Older Adults	Canada	Review	To explore and compare outcomes of different policies aimed at deprescribing sedative-hypnotic medication in community-dwelling older adults.	Prescription monitoring have the highest rate of discontinuation, triggering inappropriate substitutions. Other financial deterrents and pay-for-performance incentives are inefficient. Driving safety policies and jurisdiction-wide educational campaigns promoting non-drug alternatives appear most promising for achieving intended outcomes and avoiding unintended harms. Sustainable change should be supported with direct-to-patient education and improved access to non-drug therapy.
Mathis et al. 2017[92]	Fahreignung bei Tagesschläfrigkeit "Fitness to drive in the event of daytime sleepiness"	Switzerland	Guideline	To give recommendations to doctors and accredited centres for sleep medicine on assessing fitness to drive in subjects with daytime sleepiness.	The legal situation in Switzerland is summarised by the authors and checklists provided for assessing fitness to drive from doctors and centres for sleep medicine.

Tinguely et al. 2014[93]	Schlafgewohnheiten, Schlafqualität und Schlafmittelkonsum der Schweizer Bevölkerung - Ergebnisse aus einer neuen Umfrage bei einer repräsentativen Stichprobe “	Switzerland	Survey	To provide an up-to-date data on the sleep habits in a representative sample of the Swiss population.	The use of medication to improve sleep was reported by 2.8% of the participants. Among the drugs, benzodiazepines made up 32.1% and Z-drugs 10.7%,

9.2.3 Evidence table

Not applicable.

9.2.4 Findings ethical issues

In this section, the ethical issues concerning the risk of abuse of sedative-hypnotic drugs, the high use of sedative-hypnotic drugs among elderly, and unknown consequences of discontinuation of sedative-hypnotic drugs will be discussed.

Abuse of sedative-hypnotic drugs

The summary of product characteristics for sedative-hypnotic drugs states that the hypnotic effect may diminish with prolonged use and induce dependency with the risk of increasing dosage and duration of drug intake. Hence, the treatment duration of sedative-hypnotic drugs is restricted to four weeks in clinical guidelines. [12,51]

When Z-drugs became available as an alternative to benzodiazepines, there was a perception of these new drugs being safer. However, according to Agravat et al. 2018 all sedative-hypnotic drugs have the potential for abuse. [79] On the other hand, other authors indicate the risk of abuse may be lower for Z-drugs compared to benzodiazepines. [94,95]

High use and increased risks of sedative-hypnotic drugs among elderly

While chronic insomnia disorders affect people of all ages, the large number of prescriptions of sedative-hypnotic drugs in elderly (often nursing home residents) is presented as an important social issue in terms of adverse effects and polypharmacy in several of the identified articles. [79,81,82,91] In addition, elderly may face issues adhering to a non-drug treatment such as CBT-I.

In a study based on prescription size (DDD) and duration of prescription among patients across nine Swiss cantons, Luta *et al*. 2020 estimated the prevalence of benzodiazepine drug overuse among elderly to likely be as high as 16%. They found that the proportion may be double in non-German-speaking cantons, in women of high age, and in multimorbid patients. In addition to over-prescription, elderly may be at a higher risk of the adverse drug events caused by consumption of sedative-hypnotic drugs, due to reduced physical ability to withstand the drug, or potential overuse of sedatives of due to non-clinical rationales such as understaffing.[79,81,84,86,89,91] According to findings from Gurwitz et al. 2000, 51% of adverse drug events in a nursing home setting could have been prevented. The observational study identified sedative-hypnotic drugs as one of the main drugs associated with adverse drug events, antipsychotics being the most associated drug. However, the underlying mechanism or reason for adverse drug events were not identified. [86]

Unknown consequences of discontinuation

Bain et al. 2008 comment that there is limited data on the consequences of discontinuing drugs, as clinical trials are not designed to rigorously demonstrate the effect of discontinuing a medication once a predetermined outcome has been achieved.[82] The paper points out that data on discontinuation collected in RCTs are generally related to the patients experiencing adverse effects or non-adherent, thus

not representative of discontinuation on a larger scale. Therefore, data on consequences of discontinuation for a larger population is typically based on observational or retrospective studies, which produce less robust findings. This issue is relevant when it comes to bridging the perceived gap between physicians and regulatory system, as policies based on less robust data may be scrutinised severely by physicians reluctant to deprescribe their patients off sedative-hypnotic drugs without knowing the consequences for the patients. Moreover, discontinuation of drugs in elderly can be additionally challenging, such as the length of tapering appropriate and coordination with other comorbidities. [88] Yet, Airagnes et al. 2016 maintain that, despite some clinicians disbelief, discontinuation of chronic benzodiazepine use in elderly is feasible and can lead to long-term abstinence (provided appropriate psychotherapeutic or pharmacological strategies). [80]

9.2.5 Findings legal issues

The identified legal issue related to chronic primary insomnia disorder and the use of sedative-hypnotic drugs was the impact of the drugs on driving performance.

Due to the risk of sedative-hypnotic drugs causing impaired driving performance, regulatory and advisory bodies can advise against driving post-consumption of sedative-hypnotic drugs.[12,83] Product information on Zopiclone and Zolpidem authorised by Swissmedic warns of increased risk of accidents due to drowsiness and reduced ability to react from Z-drugs, and for patients to be cautions of driving and operating machinery for the first 12 hours after consuming drug.[51] In 2014, The European Medicine Agency advised that after one single dose of zolpidem individuals should not drive for at least 8 hours.[79] In Switzerland, the Road Traffic Act SVG and the VZV Traffic Licensing Ordinance form the legal basis for fitness to drive regulations. According to this Act, physicians are entitled to assess a patient's fitness to drive and report to the road traffic authorities.[92]

If despite these regulations, people decide to drive while on sedative-hypnotic drugs, there is a higher risk of road accidents. If there is suspicion of driving under influence of drugs, this might lead to a court case. Yet, the legalities regarding responsibility of accidents while under influence of the sedative-hypnotic drugs appear complex. Gunja et al. 2013 discuss the legal requirements for establishing guilt in the context of criminal acts during somnambulism (sleepwalking) and parasomnia (other acts while asleep), and that American, UK, and Australian courts having a history of showing leniency in such cases.[85] Paulke et al. 2015 studied two court cases on involuntary self-intoxication and sleep-driving, i.e. individuals claiming continued unconscious consumption of a sedative-hypnotic drug while they were under the influence of the medically advised dose and subsequent actions were caused by this involuntary continued consumption. While the incidence of this involuntary self-intoxication and sleep-driving is rare, the consequences can be serious, including property damage and motor vehicle accidents. In both court cases presented by Paulke et al. 2015, the testimonies of involuntary drug intoxication were believed, and the accused were not held responsible for their actions while intoxicated.[78]

9.2.6 Findings social issues

In this paragraph, the social consequences of discontinuing sedative-hypnotic drugs for the patient and the physician-patient relationship will be discussed.

Patients may be reluctant to discontinue a drug that they have used for a long period of time. Agravat et al. 2018 state that patients and their families can experience discontinuation of a drug used for a chronic condition as substandard care and as if they are abandoned by physician and medical services with their condition left untreated. In addition, physical dependency may cause distress when patients are pushed to discontinue the drug.[79] For this reason, Bain et al. 2008 suggest that physicians may be reluctant to propose discontinuation of a drug, as they do not want to damage the patient-physician relationship.[82] This may explain why Luta et al. 2021 finds long-term prescription still occurs in a large proportion of sedative-hypnotic drug users, as80% of elderly have an estimated treatment duration of more than 15 days (defined as long-term in the study), although guidelines on sedative-hypnotic drugs in Switzerland do not recommend long-term use for chronic insomnia disorders. [51,89]

10 Organisational issues

Summary statement organisational issues

Reimbursement restrictions as well as discontinuing and delisting policies of sedative-hypnotic drugs may have an influence on use reduction but could potentially shift the burden of cost to patients seeking for substitutions. The literature on organisational issues suggests that educational programs targeting physicians and patients hold most promise.

10.1 Methodology organisational issues

10.1.1 Databases and search strategy

Titles of interest for the organisational issues were gathered alongside ethical, legal, and social domains using the same methodology and the same databases and websites, which were specified in section 9.1.

10.1.2 Other sources

Not applicable.

10.1.3 Assessment of quality of evidence

Not applicable.

10.1.4 Methodology data analysis organisational issues

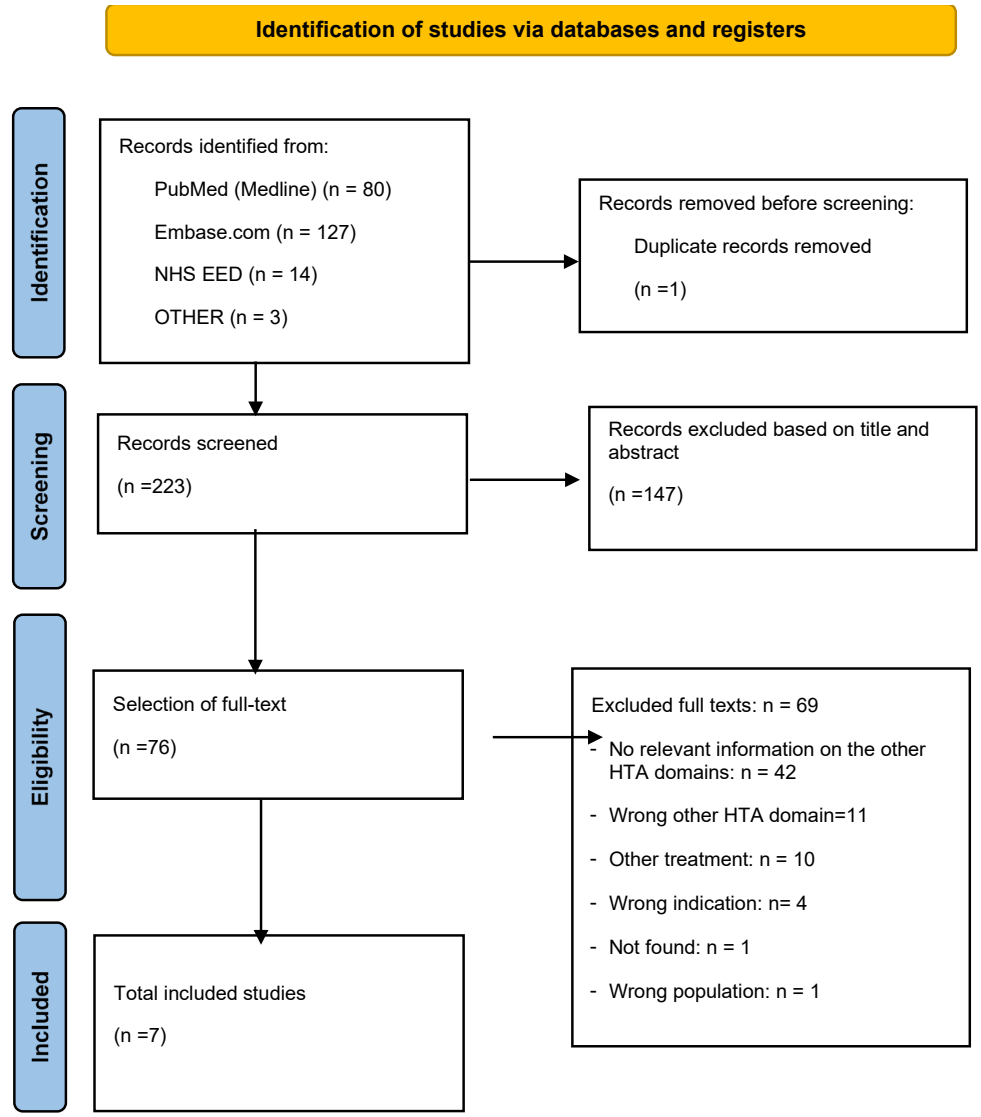
The summary of the findings related to the organisational domains was provided narratively. No statistical tests were applied to the literature search output of the organisational domain.

10.2 Results organisational issues

10.2.1 PRISMA flow diagram

Figure 20 shows the PRISMA flowchart of the selection process which resulted in the inclusion of 6 documents on organisational issues. All the included documents were published between 1997 and 2020. Most documents discussed either drugs discontinuation in general, or general sleep issues and insomnia, but the identified organisational aspects identified in the documents may also be applicable to our specific subgroup of long-term users of sedative-hypnotic drugs for chronic primary insomnia disorder.

Figure 20 PRISMA flowchart of the systematic literature search on organisational issues related to long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder



Abbreviations: HTA – Health Technology Assessment, Other= websites and reviewer feedback

10.2.2 Study characteristics of included studies

The included studies covering the organisational domain are presented in Table 42, namely Bain et al. 2008 [82], Cateau et al. 2021[84], Jenkins et al. 2012[87], Schmalstieg-Bahr et al. 2019[90], Shaw et al. 2019[91]. Hoebert et al. 2012[25] and Rat et al. 2014[96] covered the organisational domain only and the study's characteristics are presented in Table 43. The studies containing topic within the organisational domain were, like the other domain publications, mostly observational and review studies. The general topics concerned discontinuation or reimbursement restriction policies performance and limitations of implementations.

Table 43. Study characteristics of the 6* articles included in the organisational domains.

Author, year	Title	Country	Study design	Aim	Outcomes/findings
Hoebert et al. 2012[25]	Reimbursement Restriction and Moderate Decrease in Benzodiazepine Use in General Practice	The Netherlands	Observational	To assess the impact of a Dutch reimbursement restriction on the number of diagnosis of sleeping disorder or anxiety and subsequent prescription of benzodiazepines, the unintended consequences as for example change in prescription, and early discontinuation in general practice.	The reimbursement restriction was associated with a moderate decrease in the number of incident diagnoses and initiation of benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder. Suggesting reimbursement restriction allowed physicians to reduce benzodiazepine prescribing.
Rat et al. 2014	Did the new French pay-for-performance system modify benzodiazepine prescribing practices?	France	Observational	To report on the evolution of the prescribing practices of benzodiazepines of French GPs.	Despite the pay-for-performance strategy, the number of short half-life benzodiazepine prescriptions increased between 2011 and 2012, and the number of long half-life benzodiazepine initiations remained unchanged.
*Additionally, see **Table 42** for study characteristics of the articles by Bain et al. 2008 [82], Cateau et al. 2021[84], Jenkins et al. 2012[87], Schmalstieg-Bahr et al. 2019[90], Shaw et al. 2019[91]					

10.2.3 Evidence table

Not applicable.

10.2.4 Findings organisational issues

Organisational issues related to primary chronic insomnia disorder and sedative-hypnotic drugs include discontinuing policies.

Policies of discontinuing, delisting, or restricting sedative-hypnotic drugs from public health schemes or insurance programs have had varied effect by country and by specific policy implemented. The reimbursement restriction of benzodiazepines in the Netherlands in 2009 caused an 11%-14% reduction over a 2-year period, while the delisting of benzodiazepines in the US caused a 5% reduction over the course of one year. In France, a financial incentive program aimed at physicians had an unintended effect, as France experienced a 1.4% increase in patients initiating benzodiazepines over a one-year period (likely due to drug substitution from long to short half-life benzodiazepines). This program resulted to counterproductive as the short half-life benzodiazepines were significantly associated with treatment continuation beyond recommended duration.[25,91,96]

The most appropriate discontinuation policies according to Shaw et al. 2019 were educational campaigns. For example, an Australian regional awareness campaign that was aimed at healthcare provider engagement and education, public education, and the development of and distribution of patient education materials. This campaign resulted in a 19% reduction of benzodiazepine use which was sustained over a two-year period. In addition, Denmark produced several public awareness polices in 2003 and initiated a safe driving policy of driving license restrictions targeting seniors consuming sedative-hypnotic drugs in 2008. The driving license policy is associated with a 54% and a 35% decrease in sedative-hypnotic drugs, respectively, over a 5-year period. Shaw et al. 2019 did not find any unintended negative consequences associated with these educational campaigns. [91] Likewise, Jenkins et al. 2012 found that a national educational pack supporting appropriate prescription of (among others) sedative-hypnotic drugs produced in Wales in 2008 was useful. Sample letters, sleep and relaxation guides, and reduction schedules were found to be the most useful elements of the resource package.[87]

However, besides the effect on prescription and use of drugs, these policies may carry the risk of unintended consequences. They may for example lead to unintended substitution from prescribed to out-of-pocket (OOP) use of sedative-hypnotic drugs, meaning that the cost is transferred to the patients, without any actual reduction in prescription and use.[90,91]

11 Additional issues

Not applicable.

12 Discussion

The present HTA evaluated the efficacy, safety, cost-effectiveness, and budget impact of long-term drug use of treatment with sedative-hypnotic drugs in adult patients with primary chronic insomnia disorder compared to no treatment, or CBT-I, or compared to short-term use of these sedative-hypnotic drugs. In this section, the main findings, strengths, and limitations of this HTA are discussed.

In this HTA, a systematic literature search for studies on the efficacy, safety, and cost-effectiveness of the long-term use of sedative-hypnotic drugs for the treatment of primary chronic insomnia disorder in multiple peer-reviewed scientific literature databases was conducted. A rigorous methodology, adhering to international methodological standards such as Cochrane and PRISMA, was applied to identify, critically appraise, analyse, and summarise pertinent evidence on predefined outcomes of interest in order to minimise bias. The choices made for stratification of the clinical data extracted from the RCTs (i.e. comparator behaviour therapy or placebo, treatment duration, and subjective or objective measured sleep outcomes) were substantiated by the differences in results reported for these groups in the included RCTs.

Our analysis show that long-term use of Z-drugs was associated with more costs and less QALYs than short-term use of Z-drugs, CBT-I, or no treatment. Hence, long-term Z-drug use is inferior in terms of effectiveness as forecasted by the model applied in the HTA report, which means that the benefits of using Z-drugs is offset by the loss in QALYs due to the increased risk of road traffic accidents and fractures when using these drugs, although the analyses show large uncertainty around these findings. Long-term Z-drug use increases costs relative to its comparators. This is due to the acquisition costs of the drug and additional costs associated with increased road traffic accidents and fractures, although the latter two are, in absolute numbers, only a modest contributor.

Our findings are in line with the findings from Moriarty et al. 2019 that long-term use of benzodiazepines in community-dwelling elderly in Ireland was associated with increased costs and less QALYs than not using benzodiazepines. To note that our study focused on Z-drugs while Moriarty et al. 2019 looked at benzodiazepines in general [76]

The cost-effectiveness model that was developed in this HTA is the first model that compares long-term use of sedative-hypnotic drugs with short-term use of drugs. In addition, it is the first model that not only takes into account the adverse effect of having increased risk of fractures but also considers the increased risk of road traffic accidents. The cost-effectiveness model was specifically for the Swiss context developed, i.e. including Swiss-specific clinical and economic input parameters, whenever relevant and possible.

The HTA provided a comprehensive overview of the scientific literature on relevant ethical, legal, social, and organisational issues regarding (long-term) use of sedative-hypnotic drugs.

One challenge of the HTA report was the wide variety of outcomes to assess the efficacy of sedative-hypnotic drugs. The included RCTs within the systematic literature search did not use a standard set of sleep outcomes and results might show deviations depending on which outcomes are used. For example, patients' self-reported sleep outcomes have been shown to deviate from findings based on PSG,

ranging from underestimations to overestimations.[38] Discrepancy between objective and subjective sleep efficacy outcomes may be explained by sleep state misperception.[31]

The RCT findings showed that both intervention group receiving Z-drugs and the placebo groups experienced some improvements in sleep. This may be attributed to adherence to the study protocol procedures and/or nonspecific improvements associated with participating in an RCT.[31]

Limited data base providing efficacy and safety data on long-term use of Z-drugs relative to the selected comparators was considered a limitation to the report. Data on the clinical relevance in addition to the statistical difference was also lacking, for example the minimal clinically important difference (MCID) which defines the smallest amount an outcome must change to be meaningful to patients [97]. Only two of the eight included RCTs reported outcomes related to clinical relevance, one RCT [28]provided results on the treatment response and another RCT [27]] on the clinical significance of the treatment effects.
The effectiveness and safety outcomes reported in Chapter 7 originate from RCT evidence (high quality evidence). In these studies, no data on traffic accidents were reported. There was no need to search for lower quality data as the available body of evidence was sufficiently robust. To inform the cost-effectiveness model and ELSO domains, the search for evidence was broadened. Secondary and tertiary literature sources were consulted. The findings on traffic accidents originates from these literature sources and can be considered of lower quality as compared with those in Chapter 7.

The cost-effectiveness analysis was only performed for Z-drugs because the systematic review of efficacy and safety did not yield any outcome on benzodiazepine derivatives. In addition, there was often only data available for one of the Z-drugs (zopiclone or zolpidem). Therefore, the interpretation of the results is limited to answering the research questions regarding Z-drugs, not benzodiazepines nor benzodiazepine derivatives.
In the absence of RCT reporting outcomes required for the cost-effectiveness model in this HTA report, we applied data that are well documented in observational studies and confirmed by clinical experts. The modelling study gives the opportunity to combine different data sources for the input parameters and the opportunity to estimate the full impact of these parameters in absence of a RCT. Therefore, the model predicted an efficacy outcome that is different from the RCT reported outcomes in chapter 7.

The data on the number of pills used in patients on long-term use of Z-drugs was limited, therefore we had to rely on a relatively old study from 2007 which may not reflect the current use of Z-drugs. [63]

Due to limited data available on Swiss costs of healthcare used by patients with primary insomnia disorder and events, we had to rely on input from Swiss experts. This input data was subjected to sensitivity analyses to provide insight in the impact of the uncertainty around the estimates on the cost-effectiveness results.
Several assumptions were made due to the limited available data on road traffic accidents and fractures in patients using Z-drugs. We corrected the number of fractures for the fractures occurring during road accidents by assuming that every serious road accident was associated with a fracture. This assumption may be an under- or overestimation of the number of fractures during road accidents. The mortality rate

of hip fractures was also applied to other fractures which may result in an overestimation of the mortality after fractures. Likewise, we applied the disutility after a hip fracture to all other fractures. However, hip fractures accounted for almost half of all fractures and the OWSA showed that these parameters only had a limited impact on the incremental costs and effects. The OR for fractures did not distinguish between regular and higher dosages, therefore we assumed the same relative proportion between the OR of road traffic accidents for regular and higher dosages for fractures.

As data available on utilities in patients with primary chronic insomnia disorder were scarce, the utility of a U.S. study was used. The study patient population was younger than our target population (46 years instead of 66 years). The utilities were transformed using a mapping function (based on data with patients aged 50). These utilities may not be representative for the utilities in an older Swiss patient population, but there is no evidence base to adjust them. In addition, there was only one study on the utility of patients who received CBT-I for primary insomnia disorder.

With no data on chronic insomnia cases taking Z-drugs, the budget impact analysis relied on number of people using Z-drugs in Switzerland derived from Landolt et al. 2021 to calculate the population-level costs of every treatment strategy[53]. These numbers include individuals consuming Z-drugs for other indications than primary chronic insomnia, likely overestimating the budget savings estimated in our budget impact analysis.

Finally, we included the most severe adverse events of long-term use of Z-drugs, but there may be mild side effects, such as cognitive impairment, that were not taken into account in our cost-effectiveness analysis. Overall, the limitations of this study are mostly related to limited available data. Analyses on effectiveness of restrictions for example would have been interesting, but not feasible given lack of appropriate data to perform a restriction scenario setting. More research on the effect of long-term use of Z-drugs on adverse events, health-related quality of life and utilities, and (Swiss-specific) costs is necessary to fill these evidence gaps.

13 Conclusions

Clinical evidence showed that compared to placebo, long-term (≥6 months) use of Z-drugs seemed to be efficacious for the treatment of primary chronic insomnia disorders, although the evidence base was sparce. No tolerance to Z-drugs was observed. No RCTs on long-term use of benzodiazepine derivatives were found.

From a health economic perspective, long-term use of Z-drugs is likely to increase costs and reduce effects in terms of QALYs relative to short-term use of Z-drugs alone, short-term use of Z-drugs followed by cognitive behavioural therapy for insomnia (CBT-I), CBT-I alone or no treatment. Further, some evidence suggested that Z-drug use was associated with increased risk of road traffic accidents and fractures.

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94 Hajak G. New paradigms in the pharmacological treatment of insomnia. *Sleep Med* 2006;**7**:20–6. doi:10.1016/j.sleep.2006.03.003

95 Jaffe JH, Bloor R, Crome I, *et al.* A postmarketing study of relative abuse liability of hypnotic sedative drugs. *Addiction* 2004;**99**:165–73. doi:10.1111/j.1360-0443.2003.00631.x

15 Appendices

15.1 Search strategy for the efficacy, effectiveness, and safety systematic literature search for systematic reviews and RCTs

Table 44. 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 sleepwake 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 bromazepam[tiab] OR clobazam[tiab] OR ketazolam[tiab] OR alprazolam[tiab] OR 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 45. 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 bromazepam[tiab] OR clobazam[tiab] OR ketazolam[tiab] OR alprazolam[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 review*: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 metaa-nalys*: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 doubleblind*: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

15.2 Excluded studies effectiveness, efficacy and safety

Table 46. 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 zolpidem use by older adults. Exp Gerontol 2020;136:110962. doi: 10.1016/j.exger.2020.110962 [published Online First: 2020/05/04]	Short-term treatment

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 derivates 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 47. 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 speciality 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-	Abstract

67. doi: 10.1111/jsr.12751	
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 2019;42:A153-A54. doi: 10.1093/sleep/zsz067.377	Abstract
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 treat-	Abstract

ment of chronic insomnia: A randomized, double-blind, double-dummy, placebo-controlled, 3-ARM, parallel-group study. Sleep 2009;32:A273.	
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	Abstract

2018;27:165. doi: 10.1111/jsr.12751	
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 speciality 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 speciality list (Zaleplon)
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.	Contained no additional relevant data on included article (i.e. Walsh, 2000); excluded in data extraction phase)
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	Abstract

extended release on morning postural stability in older adults. Journal of Managed Care and Specialty Pharmacy 2019;25:S67.	
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 speciality 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)

15.3 Figures on tolerance to Z-drugs

Figure 21. Walsh, 2000[30] Mean subjective measured TST in the zolpidem group (solid line) for several time points during the study (intermediate treatment duration 1-6 months).

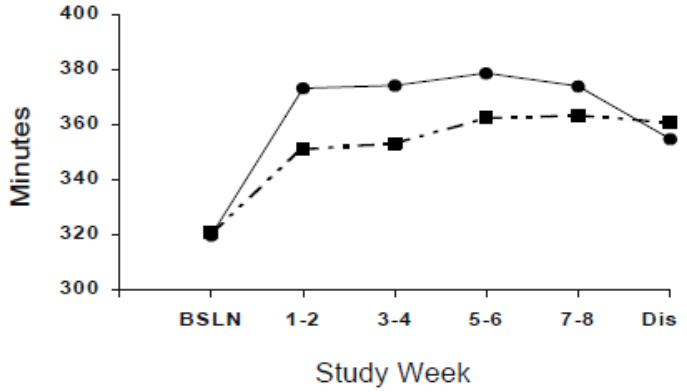


Figure 22. Perlis, 2004[29] Subjective measured TST in the zolpidem group (circle) for several time points during the study (intermediate treatment duration 1-6 months).

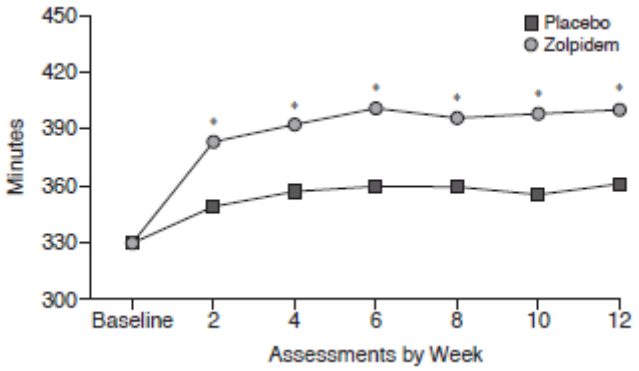


Figure 23. Perlis, 2004[29] Subjective measured sleep latency in the zolpidem group (circle) for several time points during the study (intermediate treatment duration 1-6 months).

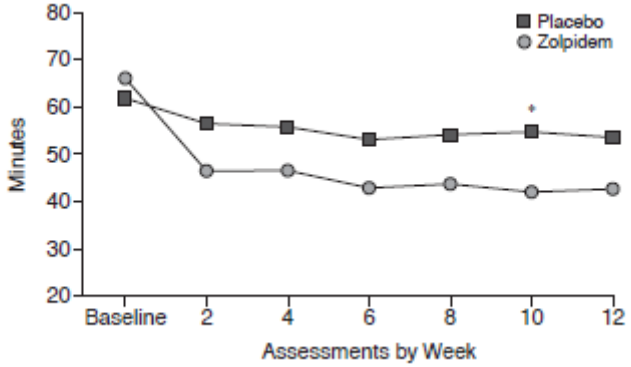


Figure 24. Perlis, 2004[29] Subjective measured WASO in the zolpidem group (circle) for several time points during the study (intermediate treatment duration 1-6 months).

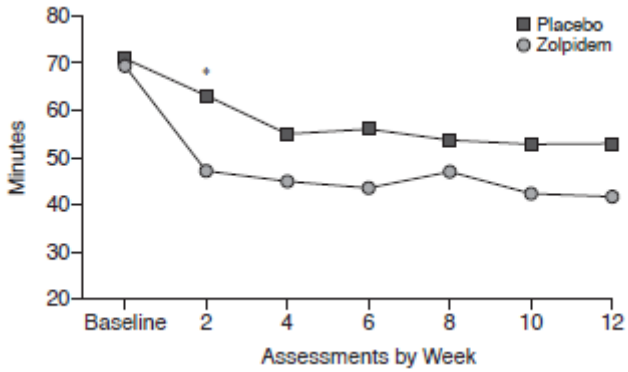


Figure 25. Perlis, 2004[29] Subjective measured NAW in the zolpidem group (circle) for several time points during the study (intermediate treatment duration 1-6 months).

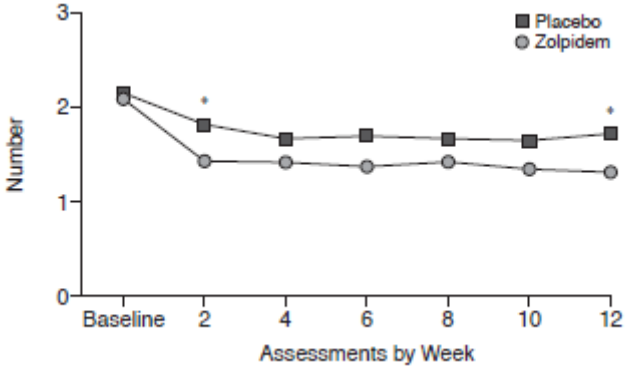


Figure 26. Krystal, 2008[32] Change from baseline in subjective measured TST in zolpidem extended-release group (solid square) for several timepoints during the study (long treatment duration ≥6 months).

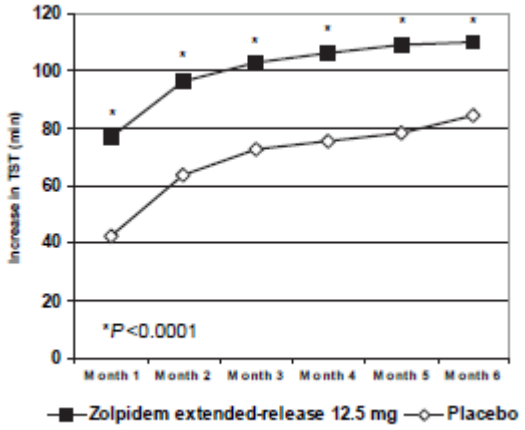


Figure 27. Krystal, 2008[32] Change from baseline in subjective measured sleep latency in the zolpidem extended-release group (solid square) for several timepoints during the study (long treatment duration ≥6 months).

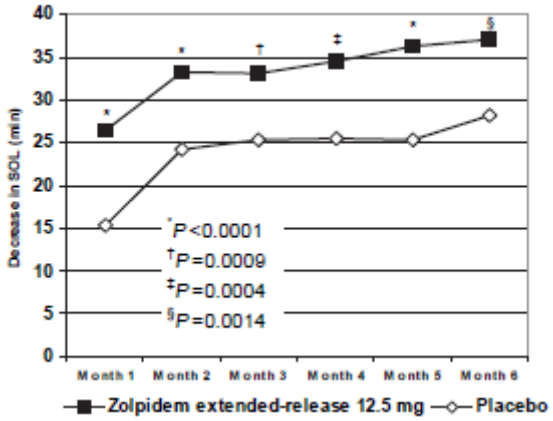


Figure 28. Krystal, 2008[32] Change from baseline in subjective measured WASO in the zolpidem extended-release group (solid square) for several timepoints during the study (long treatment duration ≥6 months).

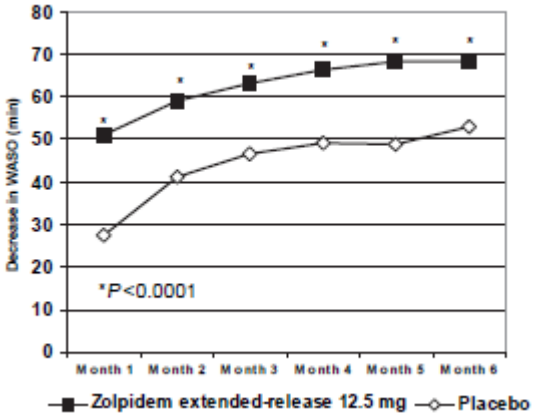
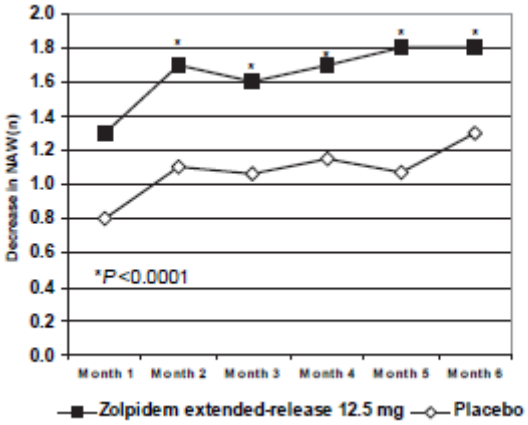


Figure 29. Krystal, 2008[32] Change from baseline in subjective measured NAW in the zolpidem extended-release group (solid square) for several timepoints during the study (long treatment duration ≥6 months).



15.4 Search strategy for cost-effectiveness systematic literature search

Table 48. 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 49. 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 assessment*) 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

15.5 Healthcare costs of fractures

Table 50 Costs of selected cases by Swiss Diagnosis Related Groups (SwissDRG)

Swiss DRG	Cases	Average cost (CHF)	Total costs (CHF)
I08B - Andere Eingriffe an Hüftgelenk und Femur mit Mehrfacheingriff, komplexer Prozedur od. komplexer Diagnose oder mit äuss. schw. CC oder Ersatz des Hüftgel. mit Eingr. an oberer Extrem. oder Wirbels. oder best. Eingriff, Alter > 11 J.	338	37’149	12’556’362
I08C - Andere Eingriffe an Hüftgelenk und Femur mit Mehrfacheingriff, komplexer Prozedur, komplexer Diagnose oder bestimmter Eingriff oder äusserst schwere CC	1’674	20’777	34’780’698
I08D - Andere Eingriffe an Hüftgelenk und Femur	4’415	14’615	64’525’225
I66B - Andere Erkrankungen des Bindegewebes, mehr als ein Belegungstag oder Frakturen an Becken und Schenkelhals ab einem Belegungstag	2’755	8’480	23’362’400
I68C - Nicht operativ behandelte Erkrankungen und Verletzungen im Wirbelsäulenbereich, mehr als ein Belegungstag, Alter > 55 Jahre oder mit schweren CC oder andere Frakturen am Femur	4’141	7’621	31’558’561
Total	13’323		166’783’246

15.6 OWSA tornado diagrams

Figure 30 Tornado diagram of one-way sensitivity analysis for PICO 1b – incremental costs

Figure 31 Tornado diagram of one-way sensitivity analysis for PICO 1b – incremental effects

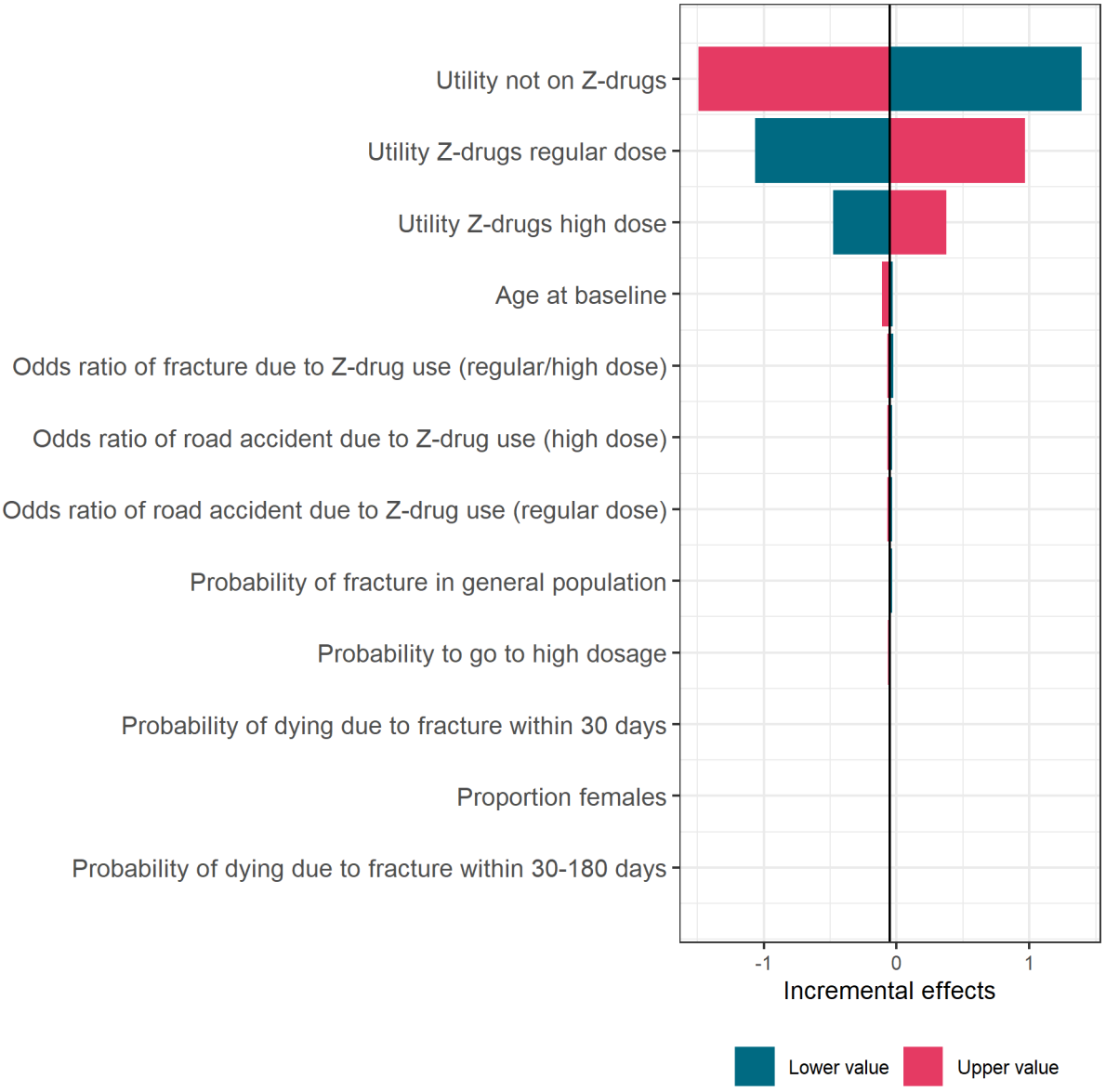


Figure 32 Tornado diagram of one-way sensitivity analysis for PICO 2a – incremental costs

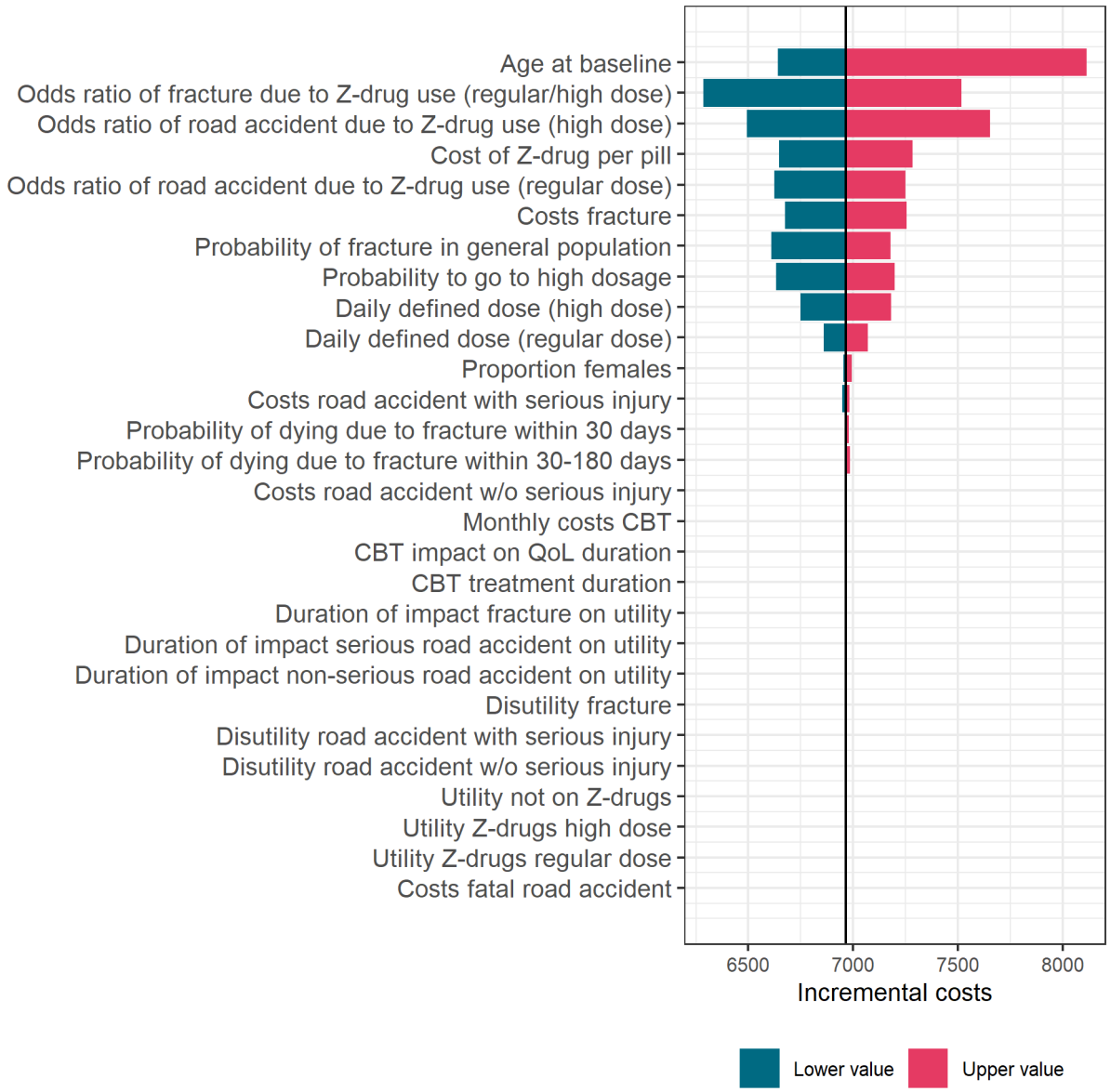


Figure 33 Tornado diagram of one-way sensitivity analysis for PICO 2a – incremental effects

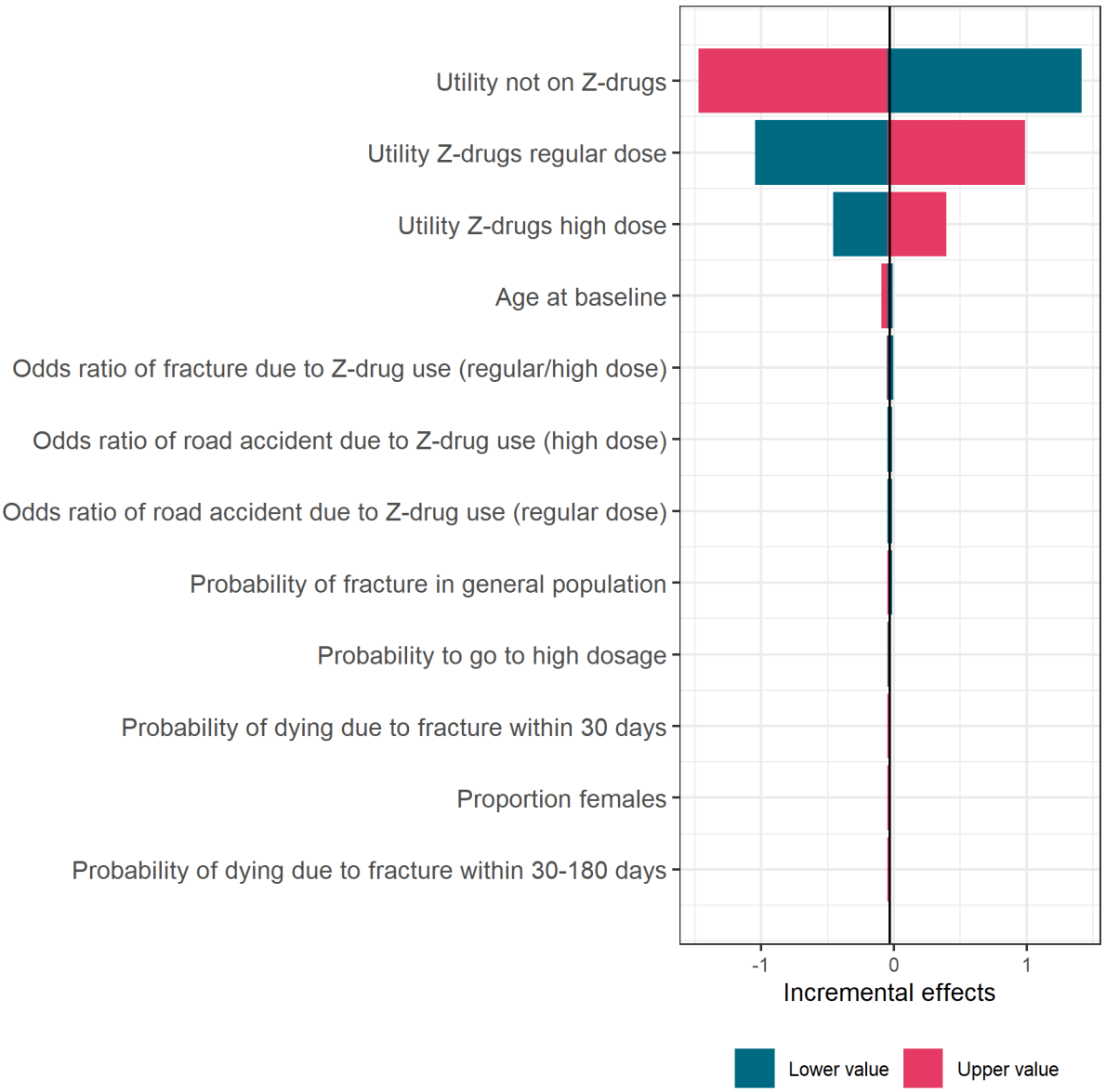


Figure 34 Tornado diagram of one-way sensitivity analysis for PICO 2b – incremental costs

Figure 35 Tornado diagram of one-way sensitivity analysis for PICO 2b – incremental effects