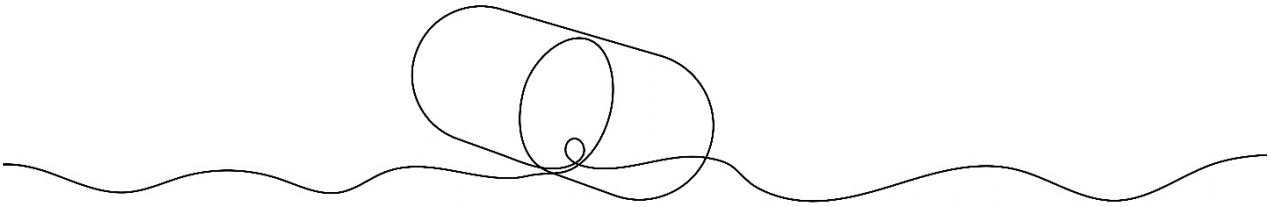
BE-SAFE

Implementing a patient-centred and evidence-based intervention to reduce **BE**nzodiazepine and sedative hypnotic use to improve patient **SAFE**ty and quality of care



Trustworthy guidelines to reduce BSHs

BE-SAFE public deliverable report **D2.1**

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Table of content

1. Introduction

Insomnia disorder or inability to sleep for more than three months is a common sleep disorder with an estimated prevalence of 10 to 30% of population and some even high as 50 to 60% which is seen in older adults, female gender and patients with co-morbid disorders such as anxiety, depression or sleep apnoea. Most of these patients are treated with benzodiazepines and sedative-hypnotic drugs (BSHs) that pose risks such as addiction, falls, fractures, confusion, daytime sleepiness and postural low blood pressure, particularly in vulnerable and older adults. Despite of a current recommendations to avoid using BSHs in older adults, it is still one of the commonly prescribed drugs for this sleep disorder.

This deliverable is related the work package 2 (WP2) of the BE-SAFE project. The scope of the WP2 of the BE-SAFE project is to develop guidelines and implement recommendations on BSHs reduction in six trial countries (Belgium, Greece, Poland, Norway, Spain, and Switzerland). The objectives of the WP2 are as follows:

1. Develop trustworthy clinical guidelines to reduce BSHs used for sleep problems in older adults, using the validated MAGIC process (T2.1)
2. To support adaptation into efficiently disseminated national or local versions through MAGICapp, ready for use and implementation by project participants (T2.2a)
   To evaluate the methods and process of guideline adaptation for local use (T2.2b)
3. To develop implementation recommendations to reduce BSHs (T2.3)

In this deliverable report, we have described the work related to the objective 1 and the preparatory work related to the other two objectives.

BE-SAFE WP2 which is led by MAGIC Evidence Ecosystem Foundation (www.magicevidence.org) has used rigorous standards and methodologies to produce trustworthy, accessible and timely guidelines to deprescribe BSHs medications in chronic insomnia patients. This work is being done by MAGIC and partners within the context of their BMJ Rapid Recommendations, as outlined below.

2. Work performed

2.1. Rationale

Previous guidelines on strategies for the implementation of deprescription of benzodiazepines and sedative-hypnotics (BSHs) medications, have suffered important limitations both in the comprehensiveness and rigor of the evidence synthesis supporting their recommendations and in meeting the current trustworthiness criteria for guideline standards and methods. There is a need of a comprehensive clinical practice guideline to deprescribe BSHs medications in chronic insomnia patients.

2.2. Description

We formed a guideline panel to draft recommendations to deprescribe BSHs medications. The panel consisted of 23 members including clinicians, methodologists and patient partners from Belgium, Canada, Greece, India, Norway, Spain, Sweden and Switzerland. These members had no conflicts of interest. We conducted a comprehensive evidence synthesis from the existing 41 clinical trials (43 reports) related to various methods (such as tapering, Cognitive behaviour therapy, education, medications and combination of these methods) used to deprescribe BSHs medications. This evidence was used by the panel to discuss the recommendations during the five panel meetings held between December 2022 and July 2023. Based on the experiences and expertise of panel members, certainty of

the evidence, benefits and harms of the deprescribing methods, values and preferences of patients, acceptability, feasibility, resource needs and equity issues, we drafted the recommendations.

We followed international standards for trustworthy guidelines and the GRADE (Grading of recommendations, assessment, development and evaluations) method for critically appraising research evidence and for developing guideline recommendations. The guidelines are authored and will also be published in MAGICapp (Annexure 1), ready for adaptation and implementation in the BE-SAFE project. The guidelines will also eventually be published as a scientific paper in BMJ, as with previous BMJ Rapid Recommendations developed by MAGIC.

To improve interpretation and readability, we drafted the recommendations in a layered format. The first layer was on whether deprescription is necessary or not. The second layer was on whether multi-component interventions should be preferred to single-component interventions for the implementation of deprescription. The third layer was on individual methods of deprescription such as education of patients, education of physicians, CBT, tapering and pharmacological agents.

The table provides a summary of the recommendations. Importantly, the guideline panel reached agreement concerning the direction and strength of recommendations, all being weak/ conditional in strength. This implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values. When there are weak recommendations, caregivers need to allocate more time to shared decision-making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient. For each recommendation, the guideline panel include remarks just below to outline key issues for health care professionals to consider when acting on these recommendations. The following figure shows one of the recommendations as they appear in MAGICapp.

Levels of recommendations	Recommendation	Remarks
First layer recommendation (Patient level)	For patients taking BSHs for insomnia disorder, we suggest offering deprescription rather than usual care. (GRADE weak recommendation)	• Either option (deprescription or continuing BSHs) is reasonable and depends on the patients' values and preferences as well as their clinical context. E.g., discontinuation may be particularly important for an older patient exposed to polypharmacy, and who are at high risk of harms from BSH, such as falls or confusion. On the other hand, a patient at lower risk of such adverse events, and facing other challenging health conditions, may not prioritize discontinuation of BSH in a given time and context. • Shared decision-making is needed for patients who are considering deprescription. • Clinicians need not feel obligated to systematically raise the issue of deprescription

Second layer recommendation	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest offering multi-component rather than single-component interventions. (GRADE weak recommendation)	• Either option is reasonable and depends on the patient's values and preferences as well as their clinical context. • In situations with limited clinician time available, or when multiple-component interventions may cause too high a burden for the patient, it may be preferable to offer single-component interventions rather than multi-component interventions. • See third layer recommendation for more guidance on what component to choose.
Third layer recommendations	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest including education for patients to usual care. (GRADE weak recommendation)	• The panel acknowledged that discontinuation rates are likely to be overestimated, and dropout rates under-estimated, for patients accepting to be enrolled in discontinuation trials. • The panel acknowledged that the feasibility of patient education for deprescribing BSHs may vary substantially, depending on the type, format, and content of the patient education.
	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest including education for physicians to usual care. (GRADE weak recommendation)	• The panel acknowledged that the feasibility of physicians' education for deprescribing BSHs may vary substantially, depending on the type, format and content of the education. Educational modules may not be available in all contexts, many are not adapted to physicians' information needs or level of experience or may not be informed by current best evidence.
	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest tapering of BHSs rather than usual care. (GRADE weak recommendation)	• Tapering as a single-component intervention may have little or no effect on discontinuation compared to usual care. It may be more effective as part of a multi-component intervention, particularly when combined with CBT. • The panel acknowledged the feasibility issues due to the clinicians' time-needed to taper.
	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest CBT - alone or with	• CBT used alone may have little or no effect on discontinuation compared to usual care. It may be more effective as part of a multi-

	tapering - rather than usual care. (GRADE weak recommendation)	component intervention, particularly when combined with tapering. • The panel acknowledged the feasibility issues due to the time-needed to treat.
	When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest NOT using any pharmacologically assisted interventions (including melatonin, paroxetine, ramelteon, dothiepin) (GRADE weak recommendation)	• None of the drugs tested in randomized trials to assist tapering of BSHs showed any substantial benefit in discontinuation of BSHs. Several of them are known to cause potential side effects, while other are well tolerated. • Regarding feasibility, we have limited information related to the availability of these pharmacological agents in all countries and the acceptability of these agents by physicians.

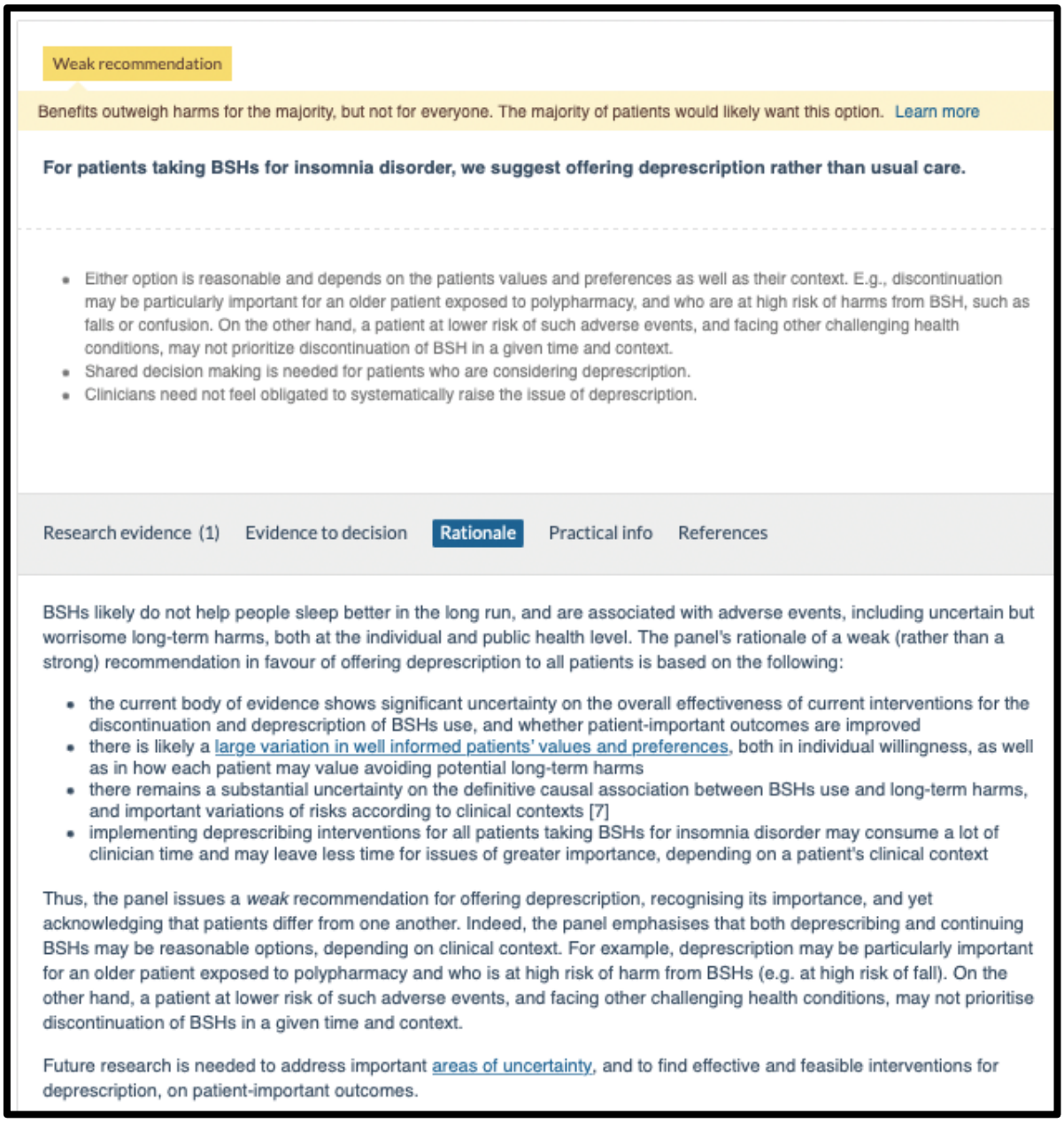

Figure: First layer recommendation as it appears in MAGICapp, with remarks visible and tabs giving more information at request (here showing rationale)

2.3. Partners involved

BE-SAFE partners from Belgium (Université catholique de Louvain), Greece (University of Athens), Poland (Institute of Psychiatry and Neurology), Norway (Oslo University Hospital), Spain (Fundació Salut i Envelliment) and Switzerland (University of Bern) along with researchers from McMaster University, Canada, BMJ Rapid Recommendations panel members and MAGIC Evidence Ecosystem Foundation, Norway are involved in drafting these recommendations.

3. Conclusion, next steps

We have drafted three layers of recommendations as a part of this BE-SAFE project to deprescribe BSHs medications in patients who are diagnosed with sleeplessness.

The next steps to be taken are the following:

- to draft recommendations to treat sleeplessness using medications and other methods and the recommendations to implement the deprescription methods.
- to publish the guidelines as BMJ Rapid Recommendations, together with the related systematic reviews
- to support adaptation of the recommendations to six countries and conduct trials there. Based on the results of these trials, the guideline recommendations will be undergoing updating as needed for the final phase of BE-SAFE.

4. Annexes

The MAGICapp version of the recommendations can be found at:

https://app.magicapp.org/#/guideline/jDePyL

The PDF version of the recommendations are attached.

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BE-SAFE

Clinical guideline on deprescription of benzodiazepine and sedative hypnotics (BSHs) in insomnia disorder

Link to online interactive multilayered guideline in MagicApp:
https://app.magicapp.org/#/guideline/jDePyL

This guideline is one of the deliverables from BE-SAFE - Work Package 2 on “Clinical guidelines & implementation recommendations to reduce benzodiazepine and sedative hypnotics (BSHs) in patients diagnosed with insomnia disorder”

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Disclaimer

Sections

1. Guideline overview

This guideline is developed as a part of the **BE-SAFE project**, funded by the European Union's Horizon Europe research and innovation programme and the Swiss State Secretariat for Education, Research and Innovation (SERI)*[1]*. The overarching goal of BE-SAFE is to improve patient safety by addressing knowledge and practice gaps related to the reduction of **Benzodiazepines and Sedative-Hypnotics (BSHs)** used for sleep difficulties in Europe. The present recommendations are part of several clinical practice guidelines produced within the second work package of BE-SAFE, specifically on **strategies for implementing discontinuation and deprescription of BSHs in patients diagnosed with insomnia disorder**.

1.1 Why is the guideline needed?

Benzodiazepines and sedative-hypnotics (BSHs) are a class of medications often prescribed to treat sleep disorders. European guidelines recommend to start with non-pharmacological treatments, and pharmacological treatment only in the short-term (less than 4 weeks), since long-term treatment lacks evidence, and may expose patients to side-effects *[2]*. However, long-term BSHs use remains common among adult patients *[3]*, and in older adults across Europe *[4]*, despite their potential short and long-term harms - including risks of falls, fractures, or cognitive impairment (*[5] [6][7] [8]*) - as well as their associated healthcare costs. Some uncertainty remains regarding the causal link between long-term BSHs use and its potential long-termharms, mostly because the evidence of such association is based on observational studies with inherent limitations. However, the widespread use of BSHs probably translates in a substantial impact on public health, the overall burden and cost of care. As an example, the costs of care for fall injuries related to BSHs in hospital settings has been estimated to be 1.8 billion euros per year across Europe *[9]*.

Deprescription of BSHs in adult patients are therefore clinically meaningful to reduce potential harms and improve the quality of patient care. However, deprescription strategies are often challenging to achieve have often not been directly compared and require trustworthy guidelines based on the whole body of current best evidence. The goal of the present recommendations is to support physicians in the deprescription process of BSHs in patients who already use these drugs for insomnia disorder.

1.2 Navigate the guideline and related content

1. A three-layered guideline on strategies for implementing discontinuation and deprescription of BSHs:

The international panel followed the BMJ Rapid Recommendation methodology to issue a guideline with the three following layers of recommendations, each with a structured Summary of Findings (SoFs) synthesising the current body of evidence in the GRADE approach:

- The first layer relates to whether deprescription and discontinuation of BSHs, instead of its continued use, should be recommended in patients using BSHs for insomnia disorder.
- The second layer relates to whether multi-component interventions should be preferred to single-component interventions for the implementation of deprescription.
- The third layer lists specific recommendations on categories of interventions to implement the discontinuation and deprescription of BSHs among patients with insomnia disorder.

These three layers can be explored to inform clinicians and patients' decisions when they are considering discontinuation or deprescription. These recommendations can be useful either when approaching discontinuation or deprescription for an individual patient, or to implement a broader strategy in a given healthcare system (e.g. a specialized unit, an outpatient or inpatient clinic, or a hospital/institution).

The recommendations are preceded by key remarks regarding the scope and applicability, as well as the panels statements on patients' values and preferences. They are then followed by areas of uncertainties and avenues for future research.

2. Other sections of the guideline:

As a part of BE-SAFE project, some participating countries may adapt these recommendations: the adaptation section briefly outlines these next stages.

Then follows a section outlining our guideline development process and methods, including the list, affiliation and credentials of the panel members.

The final section lists the abbreviations, glossary of terminologies, contacts and funding details.

3. Interpretation of recommendations and the colour code:

Recommendation for (Green)
A strong recommendation is given when there is high-certainty evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)
A strong recommendation against the intervention is given when there is high-certainty evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)
A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when values and preferences of fully infomred patients vary.

Conditional Recommendation against (Orange)
A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when values and preferences of fully infomred patients vary.

4. Supporting information:

Click on the recommendation to learn more about the basis of the recommendation:

Research Evidence: Provides the overall effect estimates of effect of all key outcomes informing a given recommendations, along with the **Certainty of the evidence:**

- **High:** We are very sure that the true effect is close to the estimated effect.
- **Moderate:** We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.
- **Low:** We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
- **Very low:** We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Evidence to Decision: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.
Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.
Practical information: Practical information regarding the treatment and information on any special patient considerations, whenever relevant.
Decision Aids: Tools to assist shared decision making and patient participation in health care decisions.
References: Reference list for the recommendation.
Feedback: If you have a MAGICapp account, you can log in to comment on specific recommendations. To create a free account, click on the 'Account' button in the top right hand corner of the screen.

More information below on the Guideline development process, as well as the application of GRADE and the Evidence to Decision Framework.

1.3 What is new in this version and what is coming next?

This is the first set of BE-SAFE recommendations, and their **focus is solely on strategies for deprescription of BSHs in patients diagnosed with insomnia disorder**.

The panel believes that the recommendations to deprescribe BSHs is incomplete without knowing how to treat insomnia disorder from the start. **The next stages of BE-SAFE guidelines will therefore include recommendations on the pharmacological and non-pharmacological management of insomnia disorder**. This work will be based on two other very large systematic reviews and network meta-analysis (including >450 eligible trials).

Finally, the guideline will be enriched by **implementation recommendations** informed by all the recommendations, as well as the field work from other work packages in BE-SAFE. This next stage will also be informed by deeper analysis of the systematic review informing this guideline on strategies for deprescription, interpreting data from the perspective of existing implementation frameworks.

2. The recommendations

See section "**Navigate the guideline and related content**" to understand how the three-layered recommendations were issued by the panel and how they fit with the rest of the guideline.

Each recommendation(s) are provided with their specific GRADE Summary of Findings (estimates of effects for all key outcomes and their certainty of evidence), evidence to decision factors, a short rationale of the recommendations and other related content.

2.1 Key remarks

I. A three-layered-guideline to inform decision making on discontinuation and deprescription of BSHs

The panel issued a guideline in three layers to help clinicians and patients' decisions when they are considering a situation of discontinuation or deprescription of BSHs:

- The first layer relates to whether deprescription and discontinuation of BSHs, instead of its continued use, should be recommended in patients using BSHs for insomnia disorder.
- The second layer relates to whether multi-component interventions should be preferred to single-component interventions for the implementation of deprescription.
- The third layer lists specific recommendations on categories of interventions to implement the discontinuation and deprescription of BSHs among patients with insomnia disorder.

II. Scope and applicability of the recommendations

The recommendations apply to:

- Adult patients of all ages, taking BSHs for insomnia disorder.

These recommendations do NOT apply to:

- Patients with new onset insomnia disorder considering different options for pharmacological and non-pharmacological management.
- Patients with addiction who take doses of BSHs above those recommended.

III. Main areas of uncertainty (see more in the dedicated section below)

- The current body of evidence, consisting of 43 publications of 41 randomised trials remains very limited; most studies have not measured the outcomes that matter most to patients (such as quality of life and daytime functioning), the observed beneficial effects are in most cases uncertain (i.e., low to very low according to GRADE), and many studies investigate approaches focused on individuals - patients or clinicians, such as education of patients or cognitive behavioural therapy - while very few trials focus on system-oriented approaches to help implement deprescription at a broader level.
- The panel also acknowledges the lack of direct evidence to inform important practical questions, such as adverse events of deprescription, optimal tapering instructions, or optimal triggers for BSHs discontinuation.
- The panel took into consideration the variable percentage of patients who refused to participate in the trials while issuing the recommendations. They acknowledged that patients willing to enter deprescription trials, and not dropping out in the course of the tested intervention, may be more willing to discontinue their BSHs compared to any random patient from the general population. Thus, data from such randomised trials are likely to overestimate rates of deprescription, as well as underestimate dropout rates.

2.2 Values and preferences statement

The panel believes that there is likely a **large variation** in patients' values and preferences regarding:

1. their **willingness** to consider reducing or stopping BSHs medication, upon the suggestion of their healthcare providers
2. the importance given in **avoiding complications** of BSHs use, such as confusion, falls, dependence, or cognitive impairment
3. the need and value of **supportive approaches** (such as Cognitive Behavioral Therapy for Insomnia (CBT-I) or other psychotherapeutic approaches, counseling, or sleep hygiene protocols) when they consider reducing or stopping BSHs

Moreover, the panel believes that a majority of patients place **greater value** on how reducing or stopping BSHs could affect their **daytime functioning**, fatigue, overall mental health and quality of life, whereas they place **less value** on the effect on **how they actually sleep** (i.e., measures of sleep efficiency: hours of sleep, number of awakenings, time to fall asleep, etc).

Additional remarks:

- The present statements assume patients are **well-informed** in a manner adapted to their information needs and capacities.
- Patients are in **various stage of motivation** when considering the reduction of their BSHs use. Motivational approaches may further support strategies of deprescription.
- Differences in **age may matter.** For example, older patients might feel less bothered by daytime fatigue whereas younger patients who have heavier work or family demands, may put more value of daytime fatigue.
- The panel acknowledged that, on average, practicing **clinicians tended to be more concerned about the potential harms of BSHs use than their patients** who tended to be less concerned.

2.3 First layer recommendations: Deprescription vs. Usual care

Weak recommendation

For patients taking BSHs for insomnia disorder, we suggest offering deprescription rather than usual care.

- *Either option is reasonable and depends on the patients values and preferences as well as their context. E.g., discontinuation may be particularly important for an older patient exposed to polypharmacy, and who are at high risk of harms from BSH, such as falls or confusion. On the other hand, a patient at lower risk of such adverse events, and facing other challenging health conditions, may not prioritize discontinuation of BSH in a given time and context.*
- *Shared decision making is needed for patients who are considering deprescription.*
- *Clinicians need not feel obligated to systematically raise the issue of deprescription.*

Practical Info

Practical information on the delivery of education for patients or physicians, on tapering, and on CBT, can be found under 'Practical info' of the corresponding recommendations in the third layer.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

When taken together, the body of evidence from randomised trials suggests that interventions targeted at helping individuals discontinue BSHs may increase the proportion of patients who discontinue by about 14% compared to usual care (low certainty), with little or no effect on dropout rates from the intervention tested (low certainty). The panel acknowledged that discontinuation rates are likely to be overestimated, and dropout rates under estimated, for patients accepting to be enrolled in discontinuation trials (see Key remarks).

There may be little or no effect of discontinuation intervention on all the other outcomes of interests (all displaying low to very low certainty), including: daytime functioning, quality of life, mental health (depression or anxiety), sleep symptoms or sleep efficiency.

Certainty of the Evidence

Low

Although 11 studies reported evidence on discontinuation, and nine studies on drop-out rates, the certainty of the evidence remained low due to serious risk of bias and serious imprecision. Evidence for all other outcomes originated from only one to two studies, and resulted in low to very low certainty (see Summary of Findings). Thus, future research is very likely to have an important impact on the certainty and magnitude of the estimate of effects across all outcomes.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

Interventions for deprescription vary greatly in the resources their require for implementation, their feasibility and accessibility. This may impact an equitable allocation of health care resources, particularly in primary care settings (see also second and third layer recommendations on more specific interventions).

Implementing interventions for the deprescription for all patients taking BSHs for insomnia disorder may consume a lot of clinician time and may leave less time for other medical issues that would need to be prioritized, depending on the patient's clinical context. Adapting to this context, and engaging in shared decision making whenever relevant, is likely to be more efficient both at the individual and system level.

Rationale

BSHs likely do not help people sleep better in the long run, and are associated with adverse events, including uncertain but worrisome long-term harms, both at the individual and public health level. The panel's rationale of a weak (rather than a strong) recommendation in favour of offering deprescription to all patients is based on the following:

- the current body of evidence shows significant uncertainty on the overall effectiveness of current interventions for the discontinuation and deprescription of BSHs use, and whether patient-important outcomes are improved
- there is likely a large variation in well informed patients' values and preferences, both in individual willingness, as well as in how each patient may value avoiding potential long-term harms
- there remains a substantial uncertainty on the definitive causal association between BSHs use and long-term harms, and important variations of risks according to clinical contexts *[7]*
- implementing deprescribing interventions for all patients taking BSHs for insomnia disorder may consume a lot of clinician time and may leave less time for issues of greater importance, depending on a patient's clinical context

Thus, the panel issues a *weak* recommendation for offering deprescription, recognising its importance, and yet acknowledging that patients differ from one another. Indeed, the panel emphasises that both deprescribing and continuing BSHs may be reasonable options, depending on clinical context. For example, deprescription may be particularly important for an older patient exposed to polypharmacy and who is at high risk of harm from BSHs (e.g. at high risk of fall). On the other hand, a patient at lower risk of such adverse events, and facing other challenging health conditions, may not prioritise discontinuation of BSHs in a given time and context.

Future research is needed to address important areas of uncertainty, and to find effective and feasible interventions for deprescription, on patient-important outcomes.

Clinical Question/ PICO

Population: Patients using benzodiazepines and closely related sedative hypnotics
Intervention: Interventions to help individual patients discontinue BSHs
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Interventions to help individual patients discontinue BSHs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 2.49 (CI 95% 1.62 — 3.84) Based on data from 3,270 participants in 11 studies. (Randomized controlled)	**130** per 1000 Difference:	**271** per 1000 **141 more per 1000** (CI 95% 65 more — 235 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics may increase the proportion of patients who discontinue compared to usual care.
Dropouts During Intervention	Odds ratio 1.25 (CI 95% 0.95 — 1.65) Based on data from 4,528 participants in 9 studies. (Randomized controlled)	**110** per 1000 Difference:	**134** per 1000 **24 more per 1000** (CI 95% 5 fewer — 59 more)	**Low** Due to serious risk of bias, Due to serious indirectness [2]	Interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics may not affect the proportion of patients who dropout during the intervention.
Mental Health (HADS-A)	Scale: 0 — 21 Lower	Difference:	**MD 0 higher** (CI 95% 0.87	**Low** Due to serious	Interventions targeted at helping individual

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Interventions to help individual patients discontinue BSHs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	better Based on data from 506 participants in 1 studies. (Randomized controlled)		lower — 0.87 higher)	risk of bias, Due to serious indirectness [3]	patients discontinue benzodiazepines/ sedative hypnotics may not affect mental health (anxiety) compared to usual care.
Mental Health (Hamilton Rating Scale for Depression)	Scale: 0 — 52 Lower better Based on data from 66 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.75 lower** (CI 95% 2.69 lower — 1.19 higher)	**Low** Due to serious risk of bias, Due to serious indirectness [4]	Interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics may not effect mental health (depression) compared to usual care.
Physical Function (SF-36-Physical Functioning Scale)	Scale: 0 — 100 High better Based on data from 268 participants in 2 studies. (Randomized controlled)	Difference:	**MD 1.51 higher** (CI 95% 10.88 lower — 13.9 higher)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [5]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on physical function compared to usual care.
Quality of Life (Health Utility Index)	Scale: 0 — 1 High better Based on data from 121 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.06 lower** (CI 95% 0.19 lower — 0.07 higher)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [6]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on quality of life compared to usual care.
Cognitive Function (Delayed Recall 15 Words Test)	Scale: 0 — 15 High better Based on data from 180 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.02 lower** (CI 95% 1 lower — 0.96 higher)	**Low** Due to serious risk of bias, , Due to serious indirectness [7]	Interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics may have little or no effect on cognitive function compared to usual care.
Mental Health (Hamilton Rating Scale for Anxiety)	Scale: 0 — 56 Lower better Based on data from 66 participants in 1 studies. (Randomized controlled)	Difference:	**MD 3.94 higher** (CI 95% 0.46 higher — 7.42 higher)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [8]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on mental health (anxiety) compared to usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Interventions to help individual patients discontinue BSHs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mental Health (SF-36 Mental Health Scale)	Scale: 0 — 100 High better Based on data from 268 participants in 2 studies. (Randomized controlled)	Difference:	**MD 0.23 higher** (CI 95% 17.07 lower — 17.53 higher)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [9]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on mental health compared to usual care.
Mental Health (HADS-D)	Scale: 0 — 21 Lower better Based on data from 506 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0 higher** (CI 95% 0.62 lower — 0.62 higher)	Low Due to serious risk of bias, Due to serious indirectness [10]	Interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics may not effect mental health (depression) compared to usual care.
Sleep Symptoms and Sleep Efficiency (Pittsburgh Sleep Quality Index)	Scale: 0 — 21 Lower better Based on data from 122 participants in 1 studies. (Randomized controlled)	Difference:	**MD 3.3 higher** (CI 95% 0.18 higher — 6.42 higher)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [11]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on sleep symptoms and sleep efficiency compared to usual care.
Signs and Symptoms of Insomnia (Insomnia Severity Index)	Scale: 0 — 28 Lower better Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**MD 4.82 lower** (CI 95% 7.87 lower — 1.77 lower)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [12]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on signs and symptoms of insomnia compared to usual care.
Total Sleep Time (Hours)	High better Based on data from 122 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.5 lower** (CI 95% 1.23 lower — 0.23 higher)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [13]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on total sleep time compared to usual care.
Sleep Onset Latency (Minutes)	Lower better Based on data from 167 participants in 2 studies. (Randomized controlled)	Difference:	**MD 12.12 higher** (CI 95% 15.77 lower — 40 higher)	Very low Due to serious risk of bias, Due to serious inconsistency,	We are uncertain of the effects of interventions targeted at helping individual patients discontinue

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Interventions to help individual patients discontinue BSHs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
				Due to serious imprecision [14]	benzodiazepines/ sedative hypnotics on sleep onset latency compared to usual care.
Number of Prescriptions 6 months	Lower better Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.9 lower** (CI 95% 1.44 lower — 0.36 lower)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [15]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on number of prescriptions compared to usual care.
Drug Free Nights 7 nights	High better Based on data from 124 participants in 1 studies. (Randomized controlled)	Difference:	**MD 2.2 lower** (CI 95% 3.48 lower — 0.92 lower)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [16]	We are uncertain of the effects of interventions targeted at helping individual patients discontinue benzodiazepines/ sedative hypnotics on drug-free nights compared to usual care.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Indirectness: serious.**
3. **Risk of Bias: serious. Indirectness: serious.**
4. **Risk of Bias: serious. Indirectness: serious.**
5. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
6. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
7. **Risk of Bias: serious. Indirectness: serious. Imprecision: no serious.**
8. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
9. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
10. **Risk of Bias: serious. Indirectness: serious.**
11. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
12. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
13. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
14. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
15. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
16. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**

Attached Images

2.4 Second layer recommendations: Multi- vs. Single-component interventions for BSHs deprescription

Weak recommendation

When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest offering multi-component rather than single-component interventions.

- *Either option is reasonable and depends on the patient's values and preferences as well as their clinical context.*
- *In situations with limited clinician time available, or when multiple-component interventions may cause too high a burden for the patient, it may be preferable to offer single-component interventions rather than multi-component interventions.*
- *See third layer recommendation for more guidance on what component to choose.*
- *See areas of uncertainty regarding alternative components that have not yet been tested, and that may be candidates for future research.*

Practical Info

Practical information on the delivery of education for patients or physicians, on tapering, and on CBT, can be found under 'Practical info' of the corresponding recommendations in the third layer.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

When taken together, the body of evidence from randomised trials suggests that multi-component interventions may increase the proportion of patients who discontinue BSHs by about 24% compared to usual care (low certainty), with little or no effect on dropout rates from the intervention tested (low certainty).

These findings are consistent with the trials comparing multi-component vs. usual care, and single-component vs. usual care, respectively showing a 28% increase (moderate certainty) and a 16% increase (low certainty) in discontinuation rates (see the two additional summary of findings linked to this recommendation).

There may be little or no effect of discontinuation interventions on all the other outcomes of interests (all displaying low to very low certainty), including: daytime functioning, quality of life, mental health (depression or anxiety), sleep symptoms or sleep efficiency.

Certainty of the Evidence

Low

Although eight studies reported evidence on discontinuation, and six studies reported evidence on drop-out rates, certainty of the evidence remained low due to serious risk of bias and serious imprecision. Reassuringly, the certainty of the evidence directly comparing multi-component to usual care was moderate (PICO 2.4.2), providing support to the effect on discontinuation.

Evidence for all other outcomes originated from only one to two studies and resulted in low to very low certainty (see Summary of Findings). Thus, future research is very likely to have an important impact on the certainty and magnitude of the estimate of effects across all outcomes.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

The more component added, the more challenging their implementation may be, particularly in settings where resources are limited. For multi-component interventions, Time Needed to Treat (TNT) may be a concern both at the physician-level and

healthcare system-level. In such healthcare settings, single interventions may be opted. See third layer recommendation for more guidance on what component to choose. Furthermore, working on potential barriers and facilitators may help implementing multi-component interventions.

Rationale

Multi-component interventions may be more effective than single-component interventions in helping patients and their clinicians discontinue BSHs (PICO 2.4.1). However, the evidence to support this remains uncertain. Furthermore, multi-component interventions, particularly when engaging very different approaches and resources, are likely to consume more time for both clinicians and patients than single-component interventions. Thus, both multi-component and and single-component interventions may be reasonable options, but the choice of interventions is paramount. See third layer recommendation for more guidance on what component to choose.

Future research is needed to address important areas of uncertainty, and to find effective and feasible interventions for deprescription, on patient-important outcomes. Furthermore, working on potential barriers and facilitators may help implement multi-component interventions.

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Multi-component
Comparator: Single-component

Outcome Timeframe	**Study results and measurements**	**Comparator** Single Component	**Intervention** Multi-component	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 2.7 (CI 95% 0.95 — 7.72) Based on data from 19,852 participants in 8 studies. (Randomized controlled)	**390** per 1000 Difference:	**633** per 1000 **243 more per 1000** (CI 95% 12 fewer — 442 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Multicomponent interventions may increase the proportion of patients who discontinue benzodiazepines/ sedative hypnotics compared to single component interventions.
Dropouts During Intervention	Odds ratio 1.02 (CI 95% 0.44 — 2.36) Based on data from 393 participants in 6 studies. (Randomized controlled)	**170** per 1000 Difference:	**173** per 1000 **3 more per 1000** (CI 95% 87 fewer — 156 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Multicomponent interventions may have little or no effect on dropouts during intervention compared to single component interventions.
Quality of Life (Health Utility Index)	Scale: 0 — 1 High better Based on data from 102 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.08 higher** (CI 95% 0.02 lower — 0.18 higher)	**Very low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision [3]	We are uncertain of the effects of multicomponent interventions on quality of life compared to single component interventions.
Cognitive Function	Scale: 0 — 15 High	Difference:	**MD 0.9 higher** (CI 95% 0.13	**Very low** Due to serious	We are uncertain of the effects of

Outcome Timeframe	**Study results and measurements**	**Comparator** Single Component	**Intervention** Multi-component	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
(Delayed Recall 15 Words Test)	better Based on data from 146 participants in 1 studies. (Randomized controlled)		lower — 1.93 higher)	indirectness, Due to serious risk of bias, Due to serious imprecision [4]	multicomponent interventions on cognitive function compared to single component interventions.
Physical Function (SF-36-Physical Health Component Score)	Scale: 0 — 100 High better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 8.32 lower** (CI 95% 19.6 lower — 2.96 higher)	**Very low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision [5]	We are uncertain of the effects of multicomponent interventions on physical function compared to single component interventions.
Mental Health (Beck Depression Inventory)	Scale: 0 — 63 Lower better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.43 lower** (CI 95% 2.82 lower — 1.96 higher)	**Low** Due to serious indirectness, Due to serious risk of bias [6]	Multicomponent interventions may have little or no effect on mental health compared to single component interventions.
Physical Function (SF-36-Physical Functioning Scale)	Scale: 0 — 100 High better Based on data from 117 participants in 1 studies. (Randomized controlled)	Difference:	**MD 3 higher** (CI 95% 6.42 lower — 12.42 higher)	**Very low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision [7]	We are uncertain of the effects of multicomponent interventions on physical function compared to single component interventions.
Mental Health (SF-36 Mental Health Scale)	Scale: 0 — 100 High better Based on data from 117 participants in 1 studies. (Randomized controlled)	Difference:	**MD 5 lower** (CI 95% 15.87 lower — 5.87 higher)	**Very low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision [8]	We are uncertain of the effects of multicomponent interventions on mental health compared to single component interventions.
Sleep Symptoms and Sleep Efficiency (Pittsburgh Sleep Quality Index)	Scale: 0 — 21 Lower better Based on data from 49 participants in 1 studies. (Randomized controlled)	Difference:	**MD 2.4 lower** (CI 95% 4.12 lower — 0.68 lower)	**Very low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision [9]	We are uncertain of the effects of multicomponent interventions on sleep symptoms and sleep efficiency compared to single component interventions.
Sleep Efficiency	Scale: 0 — 100 High better Based on data from 119	Difference:	**MD 0.88 higher** (CI 95% 3.46 lower — 5.23 higher)	**Low** Due to serious risk of bias and serious	Multicomponent interventions probably do not affect sleep efficiency compared to

Outcome Timeframe	**Study results and measurements**	**Comparator** Single Component	**Intervention** Multi-component	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	participants in 2 studies. (Randomized controlled)			imprecision. [10]	single component interventions.
Mental Health (SF-36-Mental Health Component Score)	Scale: 0 — 100 High better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 1.09 lower** (CI 95% 10.9 lower — 8.72 higher)	Very low Due to serious indirectness, Due to very serious imprecision, Due to serious imprecision, Due to serious risk of bias [11]	We are uncertain of the effects of multicomponent interventions on mental health compared to single component interventions.
Signs and Symptoms of Insomnia (Insomnia Severity Index)	Scale: 0 — 28 Lower better Based on data from 168 participants in 3 studies. (Randomized controlled)	Difference:	**MD 1.17 lower** (CI 95% 4.54 lower — 2.19 higher)	Low Due to serious risk of bias and serious imprecision. [12]	Multicomponent interventions probably have little or no effect on signs and symptoms of insomnia compared to single component interventions.
Total Sleep Time (Hours)	High better Based on data from 180 participants in 3 studies. (Randomized controlled)	Difference:	**MD 0.22 lower** (CI 95% 1.07 lower — 0.62 higher)	Low Due to serious risk of bias, Due to serious imprecision [13]	Multicomponent interventions may reduce total sleep time compared to single component interventions..

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
4. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
5. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
6. **Risk of Bias: serious. Indirectness: serious.**
7. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
8. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
9. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
10. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.
11. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
12. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.
13. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Multi-component Intervention
Comparator: Usual care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Multi-component	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 4.67 (CI 95% 2.88 — 7.57) Based on data from 380 participants in 2 studies. (Randomized controlled)	130 per 1000 Difference:	411 per 1000 **281 more per 1000** (CI 95% 171 more — 401 more)	**Moderate** Due to serious risk of bias [1]	Multi-component intervention probably increases the proportion of patients who discontinue BSH compared to usual care

1. **Risk of Bias: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Single-component Intervention
Comparator: Usual care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Single-component	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 2.72 (CI 95% 1.75 — 4.22) Based on data from 3,321 participants in 12 studies. (Randomized controlled)	130 per 1000 Difference:	289 per 1000 **159 more per 1000** (CI 95% 77 more — 257 more)	**Low** Due to serious risk of bias, and serious imprecision [1]	Single-component intervention may increase the proportion of patients who discontinue BSH compared to usual care

1. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

2.5 Third layer recommendations on each main type of interventions tested in trials

The third layer consists of five recommendations on the following categories of interventions for deprescription, assessed in randomised trials:

1. Education of patients vs usual care.
2. Education of physicians vs usual care.
3. Tapering.
4. CBT (alone or with tapering) vs usual care.
5. Pharmacologically assisted interventions, including the following molecules: melatonin, paroxetine, dothiepin, and ramelteon (several different BSHs were also used in deprescription interventions, but were not included in this guideline, as it specifically aimed at deprescription of any BSHs).

2.5.1 Education of patients vs. Usual care

Weak recommendation

When implementing strategies for deprescribing BSHs for insomnia disorder, we suggest including education for patients to usual care.

Practical Info

Current best evidence from randomized trials cannot yet identify the optimal education strategy for patients regarding deprescription. Seven trials reported on education for patients. Educational interventions varied widely across trials and included letters from physicians or pharmacists, educational brochures and self-help booklets, access to educational websites, and counseling by physicians. Mailed or written educational materials were sometimes reinforced by telephone calls by physicians or pharmacists. Education almost always entailed advising patients on tapering or cessation of benzodiazepines and many interventions also included self-assessment components, peer testimonies to enhance self-efficacy, education on drug interactions, visual tapering guidelines, and guidance on alternatives to benzodiazepines. Future research may help identify optimal education strategies for patients considering deprescription.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Education of patients may increase the proportion of patients who discontinue BSHs by 17% compared to usual care (low certainty), with little or no effect on dropout rates from the intervention tested, as well as on the number of prescriptions (low certainty). The panel acknowledged that discontinuation rates are likely to be over-estimated, and dropout rates under-estimated, for patients accepting to be enrolled in discontinuation trials (see Key remarks).

No data was reported on other outcomes of interests including: daytime functioning, quality of life, mental health (depression or anxiety), sleep symptoms or sleep efficiency.

There may not be any harms related to education of patients about BSHs, assuming this is done accurately based on the current body of evidence.

Certainty of the Evidence

Low

Although six studies reported evidence on discontinuation, and four studies reported evidence on drop-out rates, the certainty of the evidence remained low due to serious risk of bias and serious imprecision. Thus, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimates.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

Feasibility

The panel acknowledged that the feasibility of patient education for deprescribing BSHs may vary substantially, depending on the type, format and content of the patient education. The following section attempts to estimate the time needed to implement patient education for deprescription of BSHs. The estimates only consider the direct time needed to implement the intervention, and not any potential time savings in the long run that may follow from successful deprescription of BSHs. The estimates should be considered as a template which could be adapted for specific contexts. For example, we herein assume that the patient education would be provided by the patients general

practitioner. If the patient education would instead be provided by a pharmacist the time assessments would instead apply to this profession.

Time Needed to Treat (TNT) Assumptions:

- Patient education consists of either:
  - a letter (with or without educational materials) sent from a general practitioner, which take 5 minutes per patient
  - or a face-to-face consultation with a general practitioner, which take 15 minutes per patient
- 20% of people (based on discontinuation rates in the trials) who receive patient education will reach out to their general practitioner for help to quit BSHs, and will thus have additional follow-up, which take 15 minutes per patient
- Each general practitioner work 47 weeks a year, 40 hours a week, of which 60% is spent in face-to-face patient care, which means a total time for direct patient care of 1128 hours per year for each general practitioner
- Each general practitioner serves 1500 adults
- 10% of the adult population are taking BSHs for insomnia
- People who undergo “patient education” but continue BSHs are eligible for repeated intervention once a year

If patient education was fully implemented (i.e., 5 minutes per patient for the letter-approach and 15 minutes per patient for the face-to-face-approach, and additional 15 minutes for the 30 people who reach out to their general practitioner for help to quit) for all adults taking BSHs (i.e., 10% of 1500 adults = 150 adults per general practitioner) over one year, it would require 20 hours of clinician time with the letter-approach (150 x 5 minutes = 12.5 hours, plus 30 x 15 minutes = 7.5 hours, 12.5 + 7.5 = 20 hours), and 37.5 hours of clinician time with the face-to-face-approach (150 x 15 minutes = 37.5 hours, plus 30 x 15 minutes = 7.5 hours, 37.5 + 7.5 = 45 hours), of the 1128 hours available in the assumed context. This corresponds to 2% (for the letter-approach) and 4% (for the face-to-face-approach) of the available general practitioner time in the assumed context.

If patient education was fully implemented to all eligible patients, these rough estimates (built on the assumptions listed above) suggest it would **require 20-45 hours of clinician time per year in a practice of 1500 adults (depending on whether the intervention consist of a letter only, or a face-to-face meeting). This corresponds to approximately 2-4% of the available general practitioner time in the assumed context.** These estimates are rough and may not apply to contexts where these assumptions do not hold.

Rationale

The panel issued a weak recommendation in favour of education of patients on deprescription of BSHs, as it may increase the proportion of patients who discontinue, albeit with low certainty or even lack of evidence on many patient-important outcomes. Offering such education to all patients using BSHs may also be time consuming. However, a minority of the panel also believed that most patients may be willing to be educated, and some of the educational methods might need less time. Overall, patient education may have more impact as a part of a multi-component intervention.

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Education (Patients)
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Education (Patients)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 2.88 (CI 95% 1.8 — 4.61)	130	301	Low Due to serious	Education (patients) may increase the

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Education (Patients)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	Based on data from 1,481 participants in 6 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **171 more per 1000** (CI 95% 82 more — 278 more)	risk of bias, Due to serious imprecision [1]	proportion of patients who discontinue benzodiazepines/ sedative hypnotics compared to usual care.
Dropouts During Intervention	Odds ratio 1.41 (CI 95% 0.76 — 2.63) Based on data from 2,746 participants in 4 studies. (Randomized controlled)	**110** per 1000 Difference:	**148** per 1000 **38 more per 1000** (CI 95% 24 fewer — 135 more)	**Low** Due to serious imprecision, Due to serious risk of bias [2]	Education (patients) may have little or no effect on dropouts during intervention compared to usual care.
Number of Prescriptions 6 months	Lower better Based on data from 149 participants in 1 studies. (Randomized controlled)	**1.9** (Mean) Difference:	**1** (Mean) **MD 0.9 lower** (CI 95% 1.44 lower — 0.36 lower)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Education (patients) may have little or no effect on number of prescriptions compared to usual care.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

2.5.2 Education of physicians vs. Usual care

Weak recommendation

When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest including education for physicians to usual care.

Practical Info

Current best evidence from randomised trials cannot yet identify the optimal education strategy for physicians regarding deprescription. Six trials reported on education for physicians. These interventions involved letters from regulatory authority bodies, phone calls from pharmacists, other physicians, or researchers, and educational visits or workshops from pharmacists or other medical staff. Education of physicians was often combined with audit & feedback interventions that involved providing physicians with their prescription profiles detailing potentially harmful prescriptions in comparison to their peers.

Our panel also identified that clinicians may need less information about potential harms related to BSHs use, and more information on how to successfully engage patients on discontinuing BSH, or tutorials on optimal tapering instructions and follow-up. Future research may help identify optimal education strategies for patients considering deprescription.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Education of physicians may increase the proportion of patients who discontinue BSHs by as much as 60% compared to usual care (low certainty).

No data was reported on other outcomes of interests including: dropout rates from the intervention tested, daytime functioning, quality of life, mental health (depression or anxiety), sleep symptoms or sleep efficiency.

There may not be any harms related to educating physicians on BSHs, assuming this is done accurately based on the current body of evidence.

Certainty of the Evidence

Very low

Only one study reported the discontinuation outcome and the certainty of evidence was assessed as very low due to serious risk of bias, serious imprecision and serious indirectness, which means that we are very uncertain about the estimates.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

Feasibility & Accessibility

The panel acknowledged that the feasibility of physicians' education for deprescribing BSHs may vary substantially, depending on the type, format and content of the education. Educational modules may not be available in all contexts, many not be adapted to physicians' information needs or level of experience or may not be informed by current best evidence.

Rationale

The panel issued a weak recommendation in favor of education of physicians on deprescription of BSHs, despited very low certainty on discontinuation, or even lack of evidence on many patient-important outcomes, as this may be an important

prerequisite for any deprescription intervention to actually succeed. Overall, education of physicians as a single-component is likely to have limited effect on deprescription and discontinuation, although it may have more impact as part of multi-component intervention. The panel also acknowledged that the content of education may play an important role, yet to be determined. For example, clinicians may need less information about potential harms related to BSHs use, and more information on how to successfully engage patients on discontinuing BSHs, or tutorials on optimal tapering instructions and follow-up. There also may be other key areas of uncertainty, still unanswered by current best evidence.

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Education (Physicians)
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Education (Patients)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 18.78 (CI 95% 2.31 — 152.69) Based on data from 109 participants in 1 studies. (Randomized controlled)	130 per 1000 Difference:	737 per 1000 **607 more per 1000** (CI 95% 127 more — 828 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [1]	Education (physicians) may increase the proportion of patients who discontinue benzodiazepines/ sedative hypnotics compared to usual care.

1. **Risk of Bias: serious. Indirectness: serious.** The single trial was from 1990s and probably the education of physicians tested may not be applicable now. . **Imprecision: serious.**

Attached Images

2.5.3 Tapering

Weak recommendation

When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest tapering of BSHs rather than usual care.

Tapering as a single-component intervention may have little or no effect on discontinuation compared to usual care. It may be more effective as part of a multi-component intervention, particularly when combined with CBT.

Practical Info

In this recommendation related to tapering of BSH medications, usual care should **NOT** be interpreted as 'encouraging continuation of BSHs medications'. Current best evidence from randomised trials cannot yet identify the optimal tapering strategy and follow-up. Thirteen trials reported on tapering, either alone or in combination with other interventions. Most trials tapered doses by 25% at 1 or 2-week intervals, though tapering regimens varied and could be as gradual as 10% reduction at 2-to-3-week intervals or as aggressive as 50% reduction at a 1-week interval. In nearly all trials, tapering was overseen by physicians. One trial compared tapering with GP follow-up (which involved education, reassurance, and dose reduction agreements) with tapering using only written instructions. Some trials adjusted tapering based on patient readiness. Future research may help identify which elements of tapering strategy are optimal for patients.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Although thirteen trials reported on tapering, 11 included it in combination with other interventions and do not contribute to estimate the effect of tapering itself. Therefore, the direct evidence informing this recommendation includes only 2 studies, whose results are presented in the two summary of findings of this section. One trial compared tapering with GP follow-up (which involved education, reassurance, and dose reduction agreements) with tapering using only written instructions (see Summary of Findings 2.5.3.1). This GP follow-up for tapering may result in little to no increase in the proportion of patients who discontinue BSHs, nearly by about 7% compared to usual care (low certainty). It also showed little or no effect on other reported outcomes of interests including: daytime functioning, mental health (depression or anxiety), sleep symptoms or sleep efficiency.

However, a second study assessed tapering combined with CBT vs. CBT(see Summary of Findings 2.5.3.2). Findings showed tapering combined with CVT may increase the proportion of patients who discontinue BSHs, between 9 to 70% compared to CBT (low certainty due to risk of bias and serious imprecision in the effect). This combined intervention had little or no effect on drop-out rates (low certainty), and probably results in no changes in sleep efficiency (moderate certainty).

Certainty of the Evidence

Low

Certainty of the evidence remained low for most outcomes, or moderate for some, showing little or no effect on outcomes related to mental health. This was mostly due to serious risk of bias and serious imprecision. By contrast, the combination of tapering and CBT showed moderate certainty of no worsening of sleep efficiency while tapering.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

Feasibility

The following section attempts to estimate the time needed to implement **tapering with follow-up from clinicians, without CBT**. The estimates only consider the direct time needed to implement the intervention, and not any potential time savings in the long run that may follow from successful deprescription of BSHs. The estimates should be considered as a template which could be adapted for specific contexts.

Time Needed to Treat (TNT) Assumptions:

- Tapering with follow-up consists of telephone calls with a general practitioner (or primary care nurse) every other week for 10 weeks, which take 10 minutes each, in total 50 minutes per patient.
- Each general practitioner (or primary care nurse) work 47 weeks a year, 40 hours a week, of which 60% is spent in face-to-face patient care, which means a total time for direct patient care of 1128 hours per year for each general practitioner/primary care nurse.
- Each general practitioner/primary care nurse serves 1500 adults.
- 10% of the adult population are taking BSHs for insomnia.
- People who undergo tapering with follow-up but continue BSHs are eligible for repeated intervention once a year.

If a tapering intervention was fully implemented (i.e., 50 minutes per patient) for all adults taking BSHs (i.e., 10% of 1500 adults = 150 adults per general practitioner or primary care nurse) over one year, it would require 125 hours of clinician time (150 x 50 minutes = 125 hours) of the 1128 hours available in the assumed context. This corresponds to 11% of the available time for general practitioners (or primary care nurses) in the assumed context.

If tapering with follow-up was fully implemented to all eligible, our rough estimates (built on the assumptions listed above) suggest it would require 125 hours of clinician time per year in a practice of 1500 adults which corresponds to approximately 11% of the available time for general practitioners (or primary care nurses) in the assumed context. These estimates are rough and may not apply to contexts where these assumptions do not hold.

Rationale

The panel issued a weak recommendation in favour of tapering of BSHs use, despite very low certainty on discontinuation, or even lack of evidence on many patient-important outcomes, as tapering may be an important prerequisite for any deprescription intervention to actually succeed.

However, tapering as a single component intervention is likely to have limited effect on deprescription and discontinuation, although it may have more impact as part of a multi-component intervention, showing more positive potentials when combined with CBT.

Offering tapering with follow-up to all patients using BSHs may also be time consuming and resource demanding, even more so when combined with CBT. Indeed, it is estimated it would require 125 hours of clinician time per year in a practice of 1500 adults, which corresponds to approximately 11% of the available time for general practitioners (or primary care nurses).

Furthermore many practical questions remain essentially unanswered by current best evidence, such as which are the optimal triggers for BSHs discontinuation, the optimal tapering instructions and follow-up, or other key areas of uncertainty.

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Taper
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Taper	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Relative risk 1.56 (CI 95% 1.14 — 2.13) Based on data from 532 participants in 1 studies. (Randomized controlled)	130 per 1000 Difference:	203 per 1000 **73 more per 1000** (CI 95% 18 more — 147 more)	Low Due to serious risk of bias, Due to serious imprecision [1]	Tapering may have little or no effecton discontinuation compared to usual care.
Dropouts During Intervention	Odds ratio 1.28 (CI 95% 0.36 — 4.56) Based on data from 587 participants in 2 studies. (Randomized controlled)	110 per 1000 Difference:	137 per 1000 **27 more per 1000** (CI 95% 67 fewer — 250 more)	Low Due to serious imprecision, Due to serious risk of bias [2]	Tapering may have little or no effects on dropouts during intervention compared to usual care.
Function (SF-36 Physical Functioning Scale)	Scale: 0 — 100 High better Based on data from 85 participants in 1 studies. (Randomized controlled)	Difference:	**MD 7 lower** (CI 95% 19 lower — 5 higher)	Low Due to serious risk of bias, Due to serious imprecision [3]	Tapering may worsen function compared to usual care.
Mental Health (SF-36 Mental Health Scale)	Scale: 0 — 100 High better Based on data from 85 participants in 1 studies. (Randomized controlled)	Difference:	**MD 5 lower** (CI 95% 19.94 lower — 9.94 higher)	Low Due to serious risk of bias, Due to serious imprecision [4]	Tapering may worsen mental health compared to usual care.
Mental Health (Hamilton Rating Scale for Anxiety)	Scale: 0 — 56 Lower better Based on data from 44 participants in 1 studies. (Randomized controlled)	Difference:	**MD 5.4 higher** (CI 95% 1.67 higher — 9.13 higher)	Low Due to serious risk of bias, Due to serious imprecision [5]	Tapering may worsen mental health (anxiety) compared to usual care.
Mental Health (Hamilton Rating Scale for Depression)	Scale: 0 — 52 Lower better Based on data from 44 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.1 higher** (CI 95% 1.95 lower — 2.15 higher)	Moderate Due to serious risk of bias [6]	Tapering probably has little or no effect on mental health (depression) compared to usual care.
Mental Health (HADS-A)	Scale: 0 — 21 Lower better Based on data from 506 participants in 1 studies.	Difference:	**MD 0 higher** (CI 95% 0.87 lower — 0.87 higher)	Moderate Due to serious risk of bias [7]	Tapering probably has little or no difference on mental health (anxiety) compared to usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Taper	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Randomized controlled)				
Cognitive Function (Delayed Recall 15-words Test)	Scale: 0 — 15 High better Based on data from 107 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.4 lower** (CI 95% 1.47 lower — 0.67 higher)	**Low** Due to serious risk of bias, Due to serious imprecision [8]	Tapering may have little or no effect on cognitive function compared to usual care.
Mental Health (HADS-D)	Scale: 0 — 21 Lower better Based on data from 506 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0 higher** (CI 95% 0.62 lower — 0.62 higher)	**Moderate** Due to serious risk of bias [9]	Tapering probably has little or no difference on mental health (depression) compared to usual care.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Imprecision: serious.**
4. **Risk of Bias: serious. Imprecision: serious.**
5. **Risk of Bias: serious. Imprecision: serious.**
6. **Risk of Bias: serious.**
7. **Risk of Bias: serious.**
8. **Risk of Bias: serious. Imprecision: serious.**
9. **Risk of Bias: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Cognitive Behavioural Therapy, Taper
Comparator: Cognitive Behavioural Therapy

Outcome Timeframe	**Study results and measurements**	**Comparator** CBT	**Intervention** CBT, Taper	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 20 (CI 95% 0.47 — 100) Based on data from 66 participants in 1 studies. (Randomized controlled)	186 per 1000 Difference:	820 per 1000 **634 more per 1000** (CI 95% 89 fewer — 772 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	CBT, taper may increase the proportion of patients who discontinue benzodiazepines/ sedative hypnotics compared to CBT alone.

Outcome Timeframe	**Study results and measurements**	**Comparator** CBT	**Intervention** CBT, Taper	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Dropouts During Intervention	Odds ratio 1.25 (CI 95% 0.46 — 3.45) Based on data from 78 participants in 1 studies. (Randomized controlled)	123 per 1000 Difference:	149 per 1000 **26 more per 1000** (CI 95% 62 fewer — 203 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	CBT, taper may have little or no effect on dropouts during intervention compared to CBT alone.
Sleep Efficiency	Scale: 0 — 100 High better Based on data from 51 participants in 1 studies. (Randomized controlled)	Difference:	**MD 2.31 higher** (CI 95% 3.07 lower — 7.69 higher)	**Moderate** Due to serious risk of bias [3]	CBT, taper probably has little or no effect on sleep efficiency compared to CBT alone.
Signs and Symptoms of Insomnia (Insomnia Severity Index)	High better Based on data from 51 participants in 1 studies. (Randomized controlled)	Difference:	**MD 1.62 higher** (CI 95% 1.56 lower — 4.8 higher)		
Sleep Onset Latency (Minutes)	High better Based on data from 51 participants in 1 studies. (Randomized controlled)	Difference:	**MD 8.88 lower** (CI 95% 17.86 lower — 0.1 higher)		
Total Sleep Time (Hours)	High better Based on data from 51 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.36 higher** (CI 95% 0.07 lower — 0.79 higher)		

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious.**

Attached Images

2.5.4 CBT vs. Usual care

Weak recommendation

When implementing strategies for deprescribing BSHs for insomnia disorder, we suggest CBT - alone or with tapering - rather than usual care.

CBT used alone may have little or no effect on discontinuation compared to usual care. It may be more effective as part of a multi-component intervention on deprescription, particularly when combined with tapering. It may be reasonable to offer CBT in selected cases only, since offering CBT to all patients eligible may consume a substantial proportion of the therapist time available and thus not be feasible to implement.

Practical Info

Ten trials reported on CBT. Seven trials reported on CBT combined with tapering and five trials reported on CBT alone. This evidence from randomized trials cannot yet identify the optimal way to deliver CBT: four trials used in-person group sessions; four trials used individual sessions; one trial provided CBT through written materials; and another exclusively used an interactive E-learning platform. Typically, trained psychologists or counselors delivered the CBT. In one trial psychology graduate students delivered CBT. The number of CBT sessions ranged between 4 and 10, were between 1 and 2 hours long, and were most often delivered weekly. Trials sometimes reinforced in-person CBT sessions with educational materials. CBT content emphasized topics such as sleep hygiene, stimulus control, cognitive restructuring to counter negative sleep beliefs, relaxation techniques, and education about sleep disorders. Future research may help identify which elements of CBT are optimal for patients considering deprescription.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

CBT, when used alone, may result in little to no increase in the proportion of patients who discontinue BSHs, nearly by about 5.6% compared to usual care (low certainty). In a sensitivity analysis excluding the trial from Coteur et al. *[13]* - a trial criticised for a suboptimal delivery of CBT online - discontinuation only increased by 7.5% (95% CI: 2.6% to 23.5%). CBT also showed little or no effect on other reported outcomes of interest including: daytime functioning, mental health (depression or anxiety), and probably no aggravation of sleep efficiency.

However, tapering combined with CBT may increase the proportion of patients who discontinue BSHs, between 9 to 70% compared to CBT (low certainty due to risk of bias and serious imprecision in the effect). This combined intervention had little or no effect on dropout rates (low certainty), and probably results in no changes in sleep efficiency (moderate certainty).

Certainty of the Evidence

Low

Certainty of the evidence remained very low to low for most outcomes, and moderate for some outcomes. This was mostly due to serious risk of bias,serious imprecision and serious indirectness. Regarding indirectness, patients willing to engage in CBT in study context already show a rather high degree of willingness to discontinue BSH. This may also influence the effect size and may not be representative to a larger public. By contrast, the combination of tapering and CBT showed moderate certainty of no worsening of sleep efficiency while tapering.

Values and preferences

Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations

Important issues, or potential issues not investigated

Feasibility

The panel acknowledged that the feasibility of CBT for deprescribing BSHs may vary substantially, depending on the type, format and content of the CBT.The following section attempts to estimated the time needed to implement CBT. The estimates only consider the direct time needed to implement the intervention, and not any potential time savings in the long run that may follow from successful deprescription of BSHs. The estimates should be considered as a template which could be adapted for specific contexts. For example, we herein assume that the patient education would be provided by a primary care therapist. If CBT was instead provided by other specialists (e.g. cognitive-behavioral therapists), the time assessments would instead apply to this profession, and impact feasibility differently.

Time Needed to Treat (TNT) Assumptions:

- CBT consists of eight one-hour sessions and is performed by a primary care therapist
- Each primary care therapist work 47 weeks a year, 40 hours a week, of which 60% is spent in face-to-face patient care, which means a total time for direct patient care of 1128 hours per year for each primary care therapist
- Each primary care therapists serves 3000 adults
- 10% of the adult population are taking BSHs for insomnia
- People who undergo CBT but continue BSHs are not eligible for repeated CBT within 10 years
- Each year, 13% of people taking BSHs stop even without a deprescribing intervention, and the same number of people (i.e., 1.3% of the total adult population) start taking BSHs

If CBT was fully implemented (i.e., 8 hours per patient) for all adults taking BSH (i.e., 10% of 3000 adults = 300 adults per primary care psychologist) over one year, it would require 2400 hours of primary care therapist time (300 x 8 = 2400), of the 1128 hours available in the assumed context. This corresponds to 213% of the available primary care therapistt time in the assumed context.

If CBT was fully implemented over 10 years for all adults taking BSH, it would require:

- 8 hours each for 300 patients = 2400 hours over 10 years = 240 hours per year
- Each year, 39 new people will start taking BSHs and thus be eligible for CBT = 312 hours per year
- 240 hours + 312 hours = 552 hours of the 1128 hours available per year

If CBT was fully implemented to all eligible, our rough estimates (built on the assumptions listed above) suggest it would require 552 hours of primary care therapist time per year in a general population of 3000 adults, which corresponds to approximately 50% of the available primary care therapist time in the assumed context. These estimates are rough and may not apply to contexts where these assumptions do not hold.

Rationale

The panel issued a weak recommendation in favor of CBT for deprescribing BSH, despite very low certainty on discontinuation, or even lack of evidence on many patient-important outcomes. CBT used alone is likely to have limited effect on deprescription and discontinuation, but it may have more impact as part of multi-component intervention, showing more positive potentials when combined with tapering.

Offering CBT to all patients using BSH may also be time consuming and resource demanding. Indeed, it is estimated it would require 552 hours of primary care therapist time per year in a general population of 3000 adults which corresponds to approximately 50% of the available time for primary care therapists in the assumed context (see subheading “evidence to decision”).

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Cognitive Behavioral Therapy
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Cognitive Behavioral Therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation (excluding Coteur et al.)	Odds ratio 1.73 (CI 95% 0.78 — 3.84) Based on data from 681 participants in 6 studies. (Randomized controlled)	130 per 1000 Difference:	205 per 1000 **75 more per 1000** (CI 95% 26 fewer — 235 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [1]	CBT (combined) may have little or no effect on the proportion of patients who discontinue benzodiazepines/ related hypnotics compared to usual care.
Discontinuation (all studies)	Odds ratio 1.53 (CI 95% 0.78 — 2.99) Based on data from 1,408 participants in 7 studies. (Randomized controlled)	130 per 1000 Difference:	186 per 1000 **56 more per 1000** (CI 95% 26 fewer — 179 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2]	CBT (combined) may have little or no effect on the proportion of patients who discontinue benzodiazepines/ related hypnotics compared to usual care.
Dropouts During Intervention	Odds ratio 1.14 (CI 95% 0.82 — 1.58) Based on data from 1,417 participants in 7 studies. (Randomized controlled)	110 per 1000 Difference:	123 per 1000 **13 more per 1000** (CI 95% 18 fewer — 53 more)	**Moderate** Due to serious risk of bias [3]	CBT (combined) probably has little or no effect on dropouts during intervention compared to usual care.
Physical Function (SF-36-Physical Health Component Score)	Scale: 0 — 100 High better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 8.32 lower** (CI 95% 19.6 lower — 2.96 higher)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	CBT (combined) may worsen physical function compared to usual care.
Physical Function (SF-36-Physical Functioning Scale)	Scale: 0 — 100 High better Based on data from 268 participants in 2 studies. (Randomized controlled)	Difference:	**MD 4.4 higher** (CI 95% 1.77 lower — 10.57 higher)	**Low** Due to serious risk of bias, Due to serious imprecision [5]	CBT (combined) may have little or no effect on physical function compared to usual care.
Cognitive Function (Delayed Recall 15 Words Test)	Scale: 0 — 15 High better Based on data from 180 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.75 higher** (CI 95% 0.19 lower — 1.68 higher)	**Low** Due to serious imprecision, Due to serious risk of bias [6]	CBT (combined) may have little or no effect on cognitive function compared to usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Cognitive Behavioral Therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Quality of Life (Health Utility Index)	Scale: 0 — 1 High better Based on data from 121 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.04 higher** (CI 95% 0.05 lower — 0.14 higher)	Low Due to serious risk of bias, Due to serious imprecision [7]	CBT (combined) may improve quality of life compared to usual care.
Mental Health (SF-36-Mental Health Component Score)	High better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 1.09 lower** (CI 95% 10.9 lower — 8.72 higher)	Low Due to serious risk of bias, Due to serious imprecision [8]	CBT (combined) may have little or no difference on mental health compared to usual care.
Mental Health (SF-36 Mental Health Scale)	Scale: 0 — 100 High better Based on data from 268 participants in 2 studies. (Randomized controlled)	Difference:	**MD 0.74 higher** (CI 95% 14.66 lower — 16.15 higher)	Low Due to serious risk of bias, Due to serious imprecision [9]	CBT (combined) may have little or no effect on mental health compared to usual care.
Mental Health (Beck Depression Inventory)	Scale: 0 — 63 Lower better Based on data from 43 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.43 lower** (CI 95% 2.82 lower — 1.96 higher)	Moderate Due to serious risk of bias [10]	CBT (combined) probably has little or no effect on mental health (depression) compared to usual care.
Sleep Symptoms and Sleep Efficiency (Pittsburgh Sleep Quality Index)	Scale: 0 — 21 Lower better Based on data from 171 participants in 2 studies. (Randomized controlled)	Difference:	**MD 0.3 higher** (CI 95% 5.28 lower — 5.87 higher)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [11]	We are uncertain whether CBT (combined) improves or worsens sleep symptoms and sleep efficiency compared to usual care.
Sleep Efficiency	Scale: 0 — 100 High better Based on data from 119 participants in 2 studies. (Randomized controlled)	Difference:	**MD 1.13 lower** (CI 95% 7.79 lower — 5.52 higher)	Moderate Due to serious risk of bias [12]	CBT (combined) probably has little or no effect on sleep efficiency compared to usual care.
Signs and Symptoms of Insomnia (Insomnia Severity Index)	Scale: 0 — 28 Lower better Based on data from 168 participants in 3 studies. (Randomized controlled)	Difference:	**MD 1.56 lower** (CI 95% 4.41 lower — 1.29 higher)	Moderate Due to serious risk of bias [13]	CBT (combined) probably has little or no difference on signs and symptoms of insomnia compared to usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Cognitive Behavioral Therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Total Sleep Time (Hours)	High better Based on data from 281 participants in 4 studies. (Randomized controlled)	Difference:	**MD 0.51 lower** (CI 95% 1.18 lower — 0.16 higher)	Low Due to serious risk of bias, Due to serious imprecision [14]	CBT (combined) may have little or no effect on total sleep time compared to usual care.
Sleep Onset Latency (Minutes)	High better Based on data from 238 participants in 3 studies. (Randomized controlled)	Difference:	**MD 8.56 higher** (CI 95% 7.34 lower — 24.47 higher)	Moderate Due to serious risk of bias [15]	CBT (combined) probably has little or no effect on sleep onset latency compared to usual care.
Drug Free Nights 7 days	High better Based on data from 124 participants in 1 studies. (Randomized controlled)	Difference:	**MD 2.2 lower** (CI 95% 3.48 lower — 0.92 lower)	Low Due to serious risk of bias, Due to serious imprecision [16]	CBT (combined) may reduce drug-free nights over 7 days compared to usual care.

1. **Risk of Bias: serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.**
2. **Risk of Bias: serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.**
3. **Risk of Bias: serious.**
4. **Risk of Bias: serious. Imprecision: serious.**
5. **Risk of Bias: serious. Imprecision: serious.**
6. **Risk of Bias: serious. Imprecision: serious.**
7. **Risk of Bias: serious. Imprecision: serious.**
8. **Risk of Bias: serious. Imprecision: serious.**
9. **Risk of Bias: serious. Imprecision: serious.**
10. **Risk of Bias: serious.**
11. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
12. **Risk of Bias: serious.**
13. **Risk of Bias: serious.**
14. **Risk of Bias: serious. Imprecision: serious.**
15. **Risk of Bias: serious.**
16. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

2.5.5 Pharmacologically-assisted interventions

Weak recommendation against

When implementing strategies for deprescribing BSHs for insomnia disorder, we suggest NOT using any pharmacologically assisted interventions (including melatonin, paroxetine, ramelteon, or dothiepin).

Other drugs may be used in practice but were not assessed in randomized trials. Therefore, the caution implied in this recommendation would also apply to them.

Practical Info

The panel acknowledges that some patients ask for alternative medication to BSHs when attempting deprescription.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

None of the molecules tested in randomised trials to assist tapering of BSHs showed any substantial benefit in discontinuation of BSHs. Several of them are known to cause potential side-effects, while other are well tolerated.

Certainty of the Evidence — Low

Each molecule was tested in only one trial (two trials for paroxetine), resulting in either low certainty of effect, or moderate certainty of little or no effect.

Values and preferences — Substantial variability is expected or uncertain

See overall values and preferences statement.

Resources and other considerations — Important issues, or potential issues not investigated

Regarding feasibility, we have limited information related to the availability of these pharmacological agents in all countries and the acceptability of these agents by physicians.

Rationale

The panel issued weak recommendation against the use of any of these molecules to assist BSHs discontinuation, in light of the absence of benefits, and the risk of potential side effects. As a reminder, these recommendations do not apply to the pharmacological management of patients with new onset insomnia disorder (see key remarks).

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Melatonin
Comparator: Taper

Outcome Timeframe	**Study results and measurements**	**Comparator** Taper	**Intervention** Melatonin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 0.58 (CI 95% 0.25 — 1.39) Based on data from 89 participants in 1 studies. (Randomized controlled)	203 per 1000 Difference:	129 per 1000 **74 fewer per 1000** (CI 95% 143 fewer — 58 more)	Moderate Due to serious imprecision [1]	Melatonin along with tapering probably has little or no effect on discontinuation of benzodiazepines/ sedative hypnotics compared to tapering alone.
Dropouts During Intervention	Odds ratio 1 (CI 95% 0.06 — 16.48) Based on data from 92 participants in 1 studies. (Randomized controlled)	137 per 1000 Difference:	137 per 1000 **0 fewer per 1000** (CI 95% 128 fewer — 586 more)	Moderate Due to serious imprecision [2]	Melatonin along with tapering probably has little or no effect on dropouts during intervention compared to tapering alone.

1. **Imprecision: serious.**
2. **Imprecision: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Paroxetine
Comparator: Usual Care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Paroxetine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mental Health (Hamilton Rating Scale for Depression)	Scale: 0 — 52 Lower better Based on data from 43 participants in 1 studies. (Randomized controlled)	8.8 (Mean) Difference:	5.7 (Mean) **MD 3.1 lower** (CI 95% 5.79 lower — 0.41 lower)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Paroxetine may improve mental health (depression) compared to usual care.
Mental Health (Hamilton Rating Scale for Anxiety)	Scale: 0 — 56 Lower better Based on data from 43 participants in 1 studies. (Randomized controlled)	10.1 (Mean) Difference:	10.2 (Mean) **MD 0.2 higher** (CI 95% 4.69 lower — 5.09 higher)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Paroxetine may have little or no effect on mental health (anxiety) compared to usual care.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Paroxetine
Comparator: Taper

Outcome Timeframe	**Study results and measurements**	**Comparator** Taper	**Intervention** Paroxetine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 3.96 (CI 95% 1.01 — 15.52) Based on data from 45 participants in 1 studies. (Randomized controlled)	203 per 1000 Difference:	502 per 1000 **299 more per 1000** (CI 95% 2 more — 595 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Paroxetine may increase the proportion of patients who discontinue benzodiazepine/related hypnotics compared to paring alone.
Mental Health (Hamilton Rating Scale for Depression)	Scale: 0 — 53 Lower better Based on data from 45 participants in 1 studies. (Randomized controlled)	Difference:	**MD 3.2 lower** (CI 95% 5.74 lower — 0.66 lower)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Paroxetine may improve mental health (depression) compared to tapering alone.

Outcome Timeframe	**Study results and measurements**	**Comparator** Taper	**Intervention** Paroxetine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mental Health (Hamilton Rating Scale for Anxiety)	Scale: 0 — 56 Lower better Based on data from 45 participants in 1 studies. (Randomized controlled)	Difference:	**MD 5.2 lower** (CI 95% 9.98 lower — 0.42 lower)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Paroxetine may improve mental health (anxiety) compared to tapering alone.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Dothiepin
Comparator: Taper

Outcome Timeframe	**Study results and measurements**	**Comparator** Taper	**Intervention** Dothiepin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Dropouts During Intervention	Odds ratio 0.78 (CI 95% 0.34 — 1.82) Based on data from 87 participants in 1 studies. (Randomized controlled)	203 per 1000 Difference:	166 per 1000 **37 fewer per 1000** (CI 95% 123 fewer — 114 more)	**Moderate** Due to serious imprecision [1]	Dothiepin probably has little or no effect on dropouts during intervention compared to tapering alone.

1. **Imprecision: serious.**

Attached Images

Clinical Question/ PICO

Population: Patients using Benzodiazepines and closely related sedative hypnotics
Intervention: Ramelteon
Comparator: Taper

Outcome Timeframe	**Study results and measurements**	**Comparator** Taper	**Intervention** Ramelteon	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation	Odds ratio 0.84 (CI 95% 0.36 — 1.95) Based on data from 101 participants in 1 studies. (Randomized controlled)	203 per 1000 Difference:	176 per 1000 **27 fewer per 1000** (CI 95% 119 fewer — 129 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Ramelteon may have little or no effect on the proportion of patients who discontinue benzodiazepines/ sedative hypnotics compared to tapering alone.
Dropouts During Intervention	Odds ratio 0.69 (CI 95% 0.33 — 1.43) Based on data from 135 participants in 1 studies. (Randomized controlled)	137 per 1000 Difference:	99 per 1000 **38 fewer per 1000** (CI 95% 87 fewer — 48 more)	**High**	Ramelteon has little or no effect on the proportion of patients who dropout during intervention compared to tapering alone.

1. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

2.6 Areas of uncertainties

I. Uncertainties of the effects estimates of the interventions tested.

The current body of evidence highlights a lot of uncertainties on estimates of effects, including on deprescription itself. The certainty of evidence ranged from low to very low. Thus, the estimates may change with future research, which may modify our certainty in these effects.

II. Unanswered questions of clinical relevance.

The evidence synthesis did not provide full answers to the following aspects of deprescription strategies:

- optimal triggers for BSHs discontinuation;
- contraindications for the BSHs deprescription;
- optimal tapering instructions;
- optimal follow-up / monitoring of tapering;
- adaptation of tapering schedule in case of adverse effects (such as withdrawal symptoms);
- expected benefits of BSHs discontinuation;
- possible risks of BSHs discontinuation, such as withdrawal symptoms;
- optimal withdrawal assessment tool;
- optimal communication between healthcare providers in the course of deprescription;
- potential subgroup effects of the interventions, such as between older and younger patients.

Part of these questions will be further addressed in next stages of BE-SAFE project, particularly when developing implementation recommendations (see above section: “What is new in this version and what is coming next”)

III. Untested interventions and other implementation aspects.

In the 41 included studies (43 reports) summarised in the research evidence, we found only specific types of implementation aspects of deprescription. Many types of interventions remain largely untested in randomised trials, although they may have been tried out in practice.

There are many frameworks to assess these implementation aspects, and the evidence synthesis team opted to use one of these: the Effective Practice and Organisation of Care which is commonly known as Cochrane EPOC framework *[39]*. This framework includes main four domains of interventions which are:

- **delivery arrangements** (changes in how, when and where healthcare is organized and delivered, and who delivers healthcare);
- **financial arrangements** (changes in how funds are collected, insurance schemes, how services are purchased, and the use of targeted financial incentives or disincentives);
- **governance arrangements** (rules or processes that affect the way in which powers are exercised, particularly with regard to authority, accountability, openness, participation, and coherence);
- **implementation strategies** (interventions designed to bring about changes in healthcare organizations, the behaviour of healthcare professionals or the use of health services by healthcare recipients).

Two pairs of authors extracted EPOC factors data in duplicate. The factors reported per arm in the studies are mentioned as numbers next to each factor and are highlighted in yellow colour. We have reported the relevant data under these four domains from the included studies and are illustrated in the following tables:

Delivery arrangements - categories and sub-categories

Some, but largely not all type of intervention from this domain were tested in randomised trials:

How and when care is delivered?	Where care is provided and changes to the healthcare environment?	Who provides care and how the healthcare workforce is managed?	Coordination of care and management of care processes	Information and communication technology
Group versus individual care - 2	Environment	Role expansion or task shifting - 2	Care pathways	Health information systems
Queuing strategies	Outreach services	Self-management - 5	Case management	The use of information and communication technology - 1
Co-ordination of care amongst different provider	Site of service delivery	Length of consultation - 2	Communication between providers - 3	Smart home technologies
Quality and safety systems	Size of organizations	Staffing models	Continuity of care	Telemedicine
Triage	Transportation services	Exit interviews	Discharge planning	
		Movement of health workers between public and private care	Disease management	
		Pre-licensure education	Integration	
		Recruitment and retention strategies for underserved areas	Packages of care - 3	
		Recruitment and retention strategies for district health managers - LMIC	Patient-initiated appointment systems	

Coordination of care and management of care processes
Procurement and distribution of supplies
Referral systems
Shared care
Shared decision-making
Teams - 1
Transition of Care

Financial arrangements - categories and sub-categories

All but one type of interventions from this domain was tested in a single randomised trial:

Collection of funds	Insurance schemes	Mechanisms for the payment of health services	Targeted financial incentives for health professionals and healthcare organisations
User fees or out of pocket payments	Social health insurance	Method of paying healthcare organisations	Pay for performance – target payments - 1
Caps and co-payments for drugs of health services	Community based health insurance	Payment methods for health workers	Fund holding
Prepaid funding	Private health insurance	Contracting out health services	Incentives for career choices
Community loan funds		Voucher schemes	
Health savings accounts		Conditional cash transfers	
External funding		Pricing and purchasing policies	

Governance arrangements - categories and sub-categories

None of the included trials reported on any of the Governance factors:

Authority and accountability for health policies	Authority and accountability for organisations	Authority and accountability for commercial products	Authority and accountability for health professionals
Decentralisation and centralisation	Ownership	Registration	Training and licensing
Stakeholder involvement in policy decisions	Insurance	Patents and profits	Prescribing
Community mobilization	Accreditation	Marketing regulations	Scope of practice
Patients' rights	Multi-institutional arrangements	Sales and dispensing	Emigration and immigration policies
Stewardship of private health services	Liability of healthcare organisations	Liability for commercial products	Dual practice
Decision-making about what or who is covered			Authority and accountability for quality of practice
Policies to reduce corruption			Professional competence
Policies to manage absenteeism			Professional liability

Shaw et also have narratively summarized the comparative effectiveness of policies for deprescribing BSH for insomnia or opioids for chronic non-cancer pain.*[83]* Financial deterrents through insurance scheme, or pay-for-performance incentives to prescribers, had little to no impact. Prescription monitoring resulted to higher rates of discontinuation yet triggering inappropriate substitutions.

Implementation strategies - categories and sub-categories

This domain was the most widely tested in the current body of evidence, and yet focused on educational aspects, missing out several other types of interventions:

Interventions targeted at healthcare organisations	Interventions targeted at healthcare workers		Interventions targeted at specific types of practice, conditions or settings
Organisational culture - 1	Audit and feedback - 14	Clinical incident reporting	Health conditions
	Monitoring the performance of the delivery of healthcare - 3	Communities of practice	Practice and setting
	Continuous quality	Improvement	
	Educational games	Educational materials - 33	
	Educational meetings - 21	Educational outreach visits or academic detailing - 2	
	Clinical practice guidelines - 1	Inter-professional education	
	Local consensus processes	Local opinion leaders	
	Managerial supervision	Patient-mediated interventions	
	Public release of performance data	Reminders	
	Routine patient-reported outcome measures	Tailored interventions – 38 (Mostly tapering schedules)	

3. Adaptation and implementation of the guideline

The guidelines for deprescription of BSHs drugs maybe adapted by some of the adaptation groups of Belgium, Greece, Norway, Poland, Spain and Switzerland based on the local regulations, national/ regional/ local clinical practice guidelines. This adaptation process will be guided and supported by BE-SAFE Adaptation support Core group and Adaptation core group.

This guideline as well as further analysis of the implementation data abstracted from the accompanying systematic review will also inform recommendations for implementation in BE-SAFE, along with field work from other work packages in BE-SAFE. This next stage will also be informed by deeper analysis of the implementation aspects of deprescription.

4. Guideline development process

This guideline was supported by the MAGIC Evidence Ecosystem Foundation as a part of the second work package in the BE-SAFE. MAGIC is a non-for-profit foundation that provides MAGICapp, an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices. MAGIC co-founded the BMJ Rapid Recommendations (BMJ RR) since 2015, and help apply the same rigorous and trustworthy methodology for all steps of this guideline development, recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels. These recommendations will be later published as BMJ RR which will be an open access publication. We outline below the main steps of the guideline development as well as supporting evidence synthesis.

4.1 Panel members

The BE-SAFE BMJ RR panel consists of 23 members. There are two clinical co-chairs (one female and one male), one methods co-chair (male), one methods co-chair trainee (male), two systematic reviewers (one female and one male), two senior methodologists (males), one implementation lead (male), one implementation trainee (female), eight clinical experts (two females and six males), one social worker (female), one epidemiologist (male) and three patient partners (two females and one male).

Five members are from Norway, five from Belgium, five from Switzerland, three from Canada, two from Spain, one from Greece, one from Sweden and one from India. Panel members from Poland could not be included due to potential COI after careful and independent assessment.

Sl. No.	Name	Affiliation/ Healthcare profession	BE-SAFE Role/ Expertise	Professional role	Country
Panel chairs					
1	Dr. Minna Johansson (Female)	Director of Cochrane Sustainable Healthcare at Cochrane Sweden	Advisory board member; Systematic reviews, knowledge translation	General Practitioner (GP)	Sweden
2.	Dr Enrico Callegari (Male)	Postdoc researcher at the Geriatric department, Oslo University Hospital. Attending Physician at the department of old age psychiatry, Østfold Hospital trust	Cooperating partner, Research interests in psychotropic polypharmacy in older people and methods to optimize psychotropic drug prescriptions in older persons	Gerontopsychiatrist	Norway
3.	Prof. Thomas Agoritsas (Male)	University Hospital of Geneva. MAGIC Evidence Ecosystem Foundation McMaster University	Board member; Chair and Deputy CEO of the MAGIC Evidence Ecosystem Foundation, Clinical guideline expert (co-founder of the BMJ Rapid Recs)	Senior methodologist and general internist	Switzerland
Panel methodologists					
4.	Sumanth Kumbargere Nagraj (Male)	MAGIC Evidence Ecosystem Foundation Honorary Research Fellow, UCL, UK Adjunct Professor, Manipal University College Malaysia	Senior Researcher, Co-ordinating BMJ RR for BE-SAFE	Systematic Reviewer	Norway

5.	Prof Per Olav Vandvik (Male)	MAGIC Evidence Ecosystem Foundation	CEO, WP2 Lead	Senior methodologist and general internist	Norway
6.	Dr Liam Yao (Male)	Post doc at McMaster University	No role in BE-SAFE	Systematic reviews and NMA	Canada
7.	Dr.Dena Zeraatkar (Female)	Assistant Professor, Department of Anaesthesia, Department of Health Research Methods, Evidence, and Impact, McMaster University	No role in BE-SAFE	Anaesthetist	Canada
8.	Dr Siri Seterelv (Female)	MAGIC Evidence Ecosystem Foundation	PhD researcher, adaptability and implementability perspective	Public health physician	Norway
9.	Stijn Van de Velde (Male)	MAGIC Evidence Ecosystem Foundation	Project Manager & Senior Researcher	Physiotherapist	Norway
10.	Prof Jeremy Grimshaw (Male)	Senior Scientist, Clinical Epidemiology Program Ottawa Hospital Research Institute	Implementation scientist, advisor and WP4 member	Epidemiologist	Canada
Clinical Experts (content expertise and front-line clinician perspective).					
11.	Prof Anne Spinewine (Female)	Louvain Drug Research Institute, et Faculté de Pharmacie et Sciences Biomédicales Clinical Pharmacy Research Group (LDRI/CLIP)	Coordinator BE-SAFE	Clinical pharmacist	Belgium
12.	Nicolas Delvaux (Male)	Guideline developer, Commission for guideline development, Antwerpen, Belgium Assistant professor and general practitioner, Department of Public Health and Primary Care, KU Leuven, Belgium	No role in BE-SAFE	GP	Belgium
13.	Dr Antoine Christiaens (Male)	Postdoctoral research fellow at Louvain Drug Research Institute, UCLouvain, Belgium; Invited researcher at Institute Pierre Louis of Epidemiology and Public Health, Sorbonne Université, Pars, France; Visiting Lecturer, Faculty of Public Health faculty, UCLouvain, Belgium	WP2 (guidelines) and WP3 (systematic review)	Geriatrician, Pharmaco-epidemiologist	Belgium
14.	Dr. Antoni Salvà Casanovas (Male)	Director of Fundació Salut I Envelliment UAB. Associate professor Department of	Internal leadership and coordination of	Geriatric Medicine	Spain

		Medicine, Universitat Autonoma de Barcelona, Spain	the Barcelona team		
15.	Prof.Nicolas Rodondi (Male)	Director of the Institute of Primary Health Care (BIHAM) University of Bern, Switzerland	PI Bern, Overall supervision	Primary care and General Internal Medicine	Switzerland
16.	Prof Thomas Berger (Male)	Director of clinical psychology & psychotherapy, University of Bern Expert in CBT and technology enhanced learning	Co-operating partner	Psychologist	Switzerland
17.	Dr. Amandine Berner (Female)	University Hospitals of Geneva	No role in BE-SAFE	Attending physician in general internal medicine	Switzerland
18.	Dr.A. Raghukanth (Male)	Pulmonologist, KIMS Hospital, Gachibowli, Hyderabad, India	No role in BE-SAFE	General internist	India
19.	Vagioula Tsoutsi (Female)	Researcher, MSc, PhD, Sleep Research Unit, First Department of Psychiatry, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece	No role in BE-SAFE	Social worker	Greece
20.	Xavier Rojano i Luque (Male)	Epidemiologist Fundació Salut i Envelliment UAB.	No role in BE-SAFE	Epidemiologist	Spain
Patient partners					
21.	Jacqueline Clodong Austin (Female)	-	No role in BE-SAFE	-	Belgium
22.	Voula (Paraskevi) Iliadou (Female)	-	No role in BE-SAFE	-	Greece
23.	Roger Bertozzi (Male)	-	No role in BE-SAFE	-	Switzerland

4.2 Methods

We followed the methods as described in the British Medical Journal Rapid Recommendations (BMJ RR)*[40]*.

4.2.1 Recruitment of panel members and conflicts of interests

Panel members were chosen from the BE-SAFE partner lists based on their expertise either in clinical field or methods aspect. Additional panel members outside of the BE-SAFE were approached as well for their additional expertise. We contacted potential panel members from low-and middle-income countries (LMICs) such as South Africa, Brazil and India. We sought help from the BE-SAFE members to recruit patient partners. We requested patient organisations from European Union, USA and Malaysia. We also contacted ASENARCO (the association in Spain which is aggregating patients with sleep problems) and requested the members of the Greek Patient Advisory Council (PAC) to help us in patient partner recruitment. We also posted flyers for patient recruitment in social media such as Facebook, Twitter and Instagram.

We used the conflict of interest (COI) template of BMJ RapidRecs and circulated the online link to all the potential panel members. All COI was examined as per rigorous standards of the RapidRecs, with a separate assessment from the MAGIC RapidRecs leadership and the British Medical Journal. Only panel members with no financial COI were included, and any potential intellectual COI was balanced among panel members.

4.2.2 Systematic review informing the recommendations

Search strategy

In collaboration with an experienced research librarian, we searched MEDLINE, EMBASE, CINAHL, and CENTRAL from inception to February 2023. We supplemented our search by reviewing references of similar systematic reviews *[41][42][43][44][45][46]*.

Eligibility criteria

We include parallel, cluster, or crossover-by-cluster randomised trials that compared interventions aimed at facilitating discontinuation or deprescription of one or more BSHs in patients with insomnia disorder. We included trials, however, even if the primary reason for BSHs use was not clear.

We excluded trials if 60% or more patients were using BSHs for conditions other than insomnia disorder (e.g., epilepsy), trials with interventions targeted at deprescription of drugs other than BSHs or all potentially inappropriate medications, and systematic or scoping or narrative reviews. We also excluded trials with fewer than 20 patients per arm.

We did not restrict trial eligibility based on date or language of publication.

Screening

Two reviewers, working independently and in duplicate, reviewed the titles and abstracts of search records and subsequently the full texts of records deemed eligible at the title and abstract screening stage. Reviewers resolved discrepancies by discussion or in consultation with a third reviewer.

Data collection

We included 41 trials (43 reports) *[10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][47][48][49][* Following training and calibration to ensure sufficient agreement, pairs of reviewers, working independently and in duplicate, extracted data from eligible trials. We extracted data on trial and patient characteristics, intervention characteristics (e.g., type, duration, intensity), contextual factors, and outcomes of interest at the longest point of follow-up. A formal outcome prioritisation exercise with the parallel *BMJ Rapid Recommendations* panel directed our selection of outcomes *[62][63]*.

A group of core content experts, with feedback from the wider guideline panel, developed a framework to characterise and classify interventions, according to the type of the intervention, duration, and intensity of delivery, among other variables. The framework drew from and combined existing frameworks, including the template for intervention description and replication (TIDieR) checklist *[64]*, principles of deprescription *[65]*, and the Effective Practice and Organisation of Care (EPOC) taxonomy *[39]* . The core group of content experts worked independently and in duplicate to classify interventions according to the framework.

Reviewers resolved discrepancies by discussion or by consultation with a third reviewer.

Risk of bias assessments

Following training and calibration to ensure sufficient agreement, reviewers, worked independently and in duplicate, to assess risk of bias using a modified Cochrane RoB 2.0 tool*[66] [67]*. For each trial, we rated each outcome as either 'low risk of bias', 'some concerns–probably low risk of bias', 'some concerns–probably high risk of bias', and 'high risk of bias' across the following domains: bias arising from the randomisation process, bias due to departures from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. For cluster trials and crossover-by-cluster trials, we additionally made judgements about risk of bias due to carryover and period effects and risk of bias due to identification/recruitment of patients into clusters. Reviewers resolved discrepancies by discussion and if necessary, by adjudication with a third reviewer.

Data synthesis and analysis

For each comparison and outcome, we performed frequentist random-effects meta-analysis using the restricted maximum likelihood (REML) estimator. To facilitate interpretation, we report dichotomous outcomes as number of events per 1,000 patients, using the median risk in trial arms receiving usual care as the assumed risk.

For cluster trials that appropriately accounted for correlations within clusters, we used results as reported in the analysis. Otherwise, we adjusted trial results by the design effect to calculate an effective sample size using either the intraclass correlation coefficient reported in the trial or, if one was not reported, the median intraclass correlation coefficient across all

included trials *[68]*. For crossover-by-cluster trials that appropriately accounted for within cluster correlations and the paired nature of the data, we used the results as presented in the trial report for analysis. Otherwise, we used data from the first period of the trial before crossover and adjusted results by the design effect as described above *[68]*.

When trials reported on multiple arms addressing the same type of intervention, we pooled the arms together, using the approximate method described by Rucker et al. *[69]*.

We performed all analyses using the *meta* and *metafor* packages in R (version 4.1.2) *[70][71]*.

Certainty of evidence

We assessed the certainty of evidence using the GRADE approach *[72]*.

For each comparison and outcome, we rated the certainty as either high, moderate, low, or very low based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias. We made judgements of imprecision using the minimally contextualised approach, which considers only whether confidence intervals include the null effect and thus does not consider whether plausible effects, captured by confidence intervals, include both important and trivial effects *[73]*. The final assessment of certainty was then fully contextualised by the guideline panel, as they reviewed the evidence to issue their recommendations.

4.2.3 Panel surveys

We conducted two surveys involving all the panel members. The first survey was to rate the outcomes and the subgroups which were used in the systematic reviews. The second survey was to choose the appropriate Values and Preferences statement. Panel surveys were used internally to structure the discussion and help elaborate rationale and reach consensus.

4.2.4 GRADE and Evidence to Decision framework

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *[72] [78]*. Methods and clinical co-chairs facilitated deliberations to reach final recommendations.

The following key factors informed transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) *[79]*;
- quality/certainty of the evidence *[72] [80]*;
- values and preferences of patients *[81]*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *[81]*;
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables.
- recommendations are rated as either weak or strong, as defined by GRADE.

The grading of evidence quality and recommendation strength is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For a quick and informative introduction to GRADE, the article 'Understanding GRADE: an introduction by Goldet & Howick' is recommended (J Evid Based Med 2013;6(1):50-4). See also http://www.gradeworkinggroup.org.

4.2.5 Panel meetings

We held a total of five virtual panel meetings from 12th December 2022 to 11th July 2023. The summary of each of these panel meetings is presented here:

Panel meeting (Date)	Summary of the proceedings
Panel meeting 1 (12 December 2022)	All panel members were introduced to the ground rules of the panel, BE-SAFE work packages, objectives of the panel, timeline, SR and NMA plan and introduction to GRADE.
Panel meeting 2 (24 March 2023)	We presented results of the first survey on outcomes and subgroups rating. Based on the discussion, we finalised the outcomes and subgroups for both the ongoing SRs.
Panel meeting 3 (26 June 2023)	We presented the results of the second survey on values and preferences statements, findings from SRs on long-term adverse events, time-needed-to treat (TNT) concept and the results of the SR on deprescription and implementation strategies.
Panel meeting 4 (6 July 2023)	We reviewed the Summary of findings regarding strategies to implement deprescription of BSHs and issued first layer recommendations.
Panel meeting 5 (11 July 2023)	We reviewed the Summary of findings regarding strategies to implement deprescription of BSHs and issued second and third layer recommendations along with other recommendations.

5. Other information

5.1 Abbreviations used

BE-SAFE	BEnzodiazepine and sedative-hypnotic use to improve patient SAFEty
BSHs	Benzodiazepines and sedative hypnotics
CPG	Clinical practice guidelines
TNT	Time-needed to treat
SoF	Summary of findings
SR	Systematic review
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
EtD	Evidence to decision
BMJ	British Medical Journal
BMJ RR	British Medical Journal Rapid Recommendations
MEDLINE	Medical Literature Analysis and Retrieval System Online
EMBASE	Excerpta Medica Database
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CENTRAL	Cochrane Central register of controlled trials
TiDiER	Template for intervention description and replication
EPOC	Effective Practice and Organisation of Care
RoB	Risk of Bias
REML	Restricted maximum likelihood
NMA	Network Meta-analysis
CBT	Cognitive Behavioural Therapy
CBT-I	Cognitive Behavioural Therapy - Insomnia
SERI	Swiss State Secretariat for Education, Research and Innovation
HCP	Healthcare provider

5.2 Glossary

a. Chronic insomnia disorder: is defined as "inadequate quantity or quality of sleep characterised by a subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs at least three nights a week, despite adequate opportunity for sleep, and that results in some form of daytime impairment and has persisted for at least one month".*[74]*

b. Deprescription: Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.*[75]*

c. Cognitive behavioural therapy: is a psycho-social intervention that focuses on challenging and changing cognitive distortions (such as thoughts, beliefs, and attitudes) and their associated behaviours to improve emotional regulation and develop personal coping strategies that target solving current problems.*[76]*

d. Medication tapering: The gradual discontinuation or reduction of a therapeutic dose of a particular drug required by a patient over a prolonged period of time.*[77]*

5.3 Get in touch

For any queries related to the clinical aspects of the guidelines, please contact the clinical co-chairs: Enrico Callegari: enrico.callegari@so-hf.no & Minna Johansson: minna.johansson@vgregion.se

For methodological queries, please contact the guideline methods chair, Thomas Agoritsas: thomas@magicevidence.org

For any other queries or comments, please contact Sumanth Kumbargere Nagraj: sumanth@magicevidence.org

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