ThemenCheck Medizin

Extract of HTA report

Seasonal affective disorder[1]

Do non-drug interventions such as light and vitamin therapy lead to better results?

Health technology assessment commissioned by IQWiG

IQWiG Reports – Commission No. HT18-04

IQWiG

[1] Translation of Chapters 1 to 9 of the HTA report HT18-04 *Herbst-Winter-Depression: Führen nicht medikamentöse Verfahren wie Licht- und Vitamintherapie zu besseren Ergebnissen?* (Version 1.0; Status: 15 June 2020 [German original], 14 April 2021 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care (IQWiG)

Topic

Seasonal affective disorder: Do non-drug interventions such as light and vitamin therapy lead to better results?

HTA No.

HT18-04

Date of project start

4 October 2018

Address of publisher:

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Tel.: +49 221 35685-0
Fax: +49 221 35685-1
E-Mail: themencheck@iqwig.de
Internet: www.iqwig.de
www.themencheck-medizin.iqwig.de

Authors

- Barbara Nußbaumer-Streit, Danube University Krems, Department for Evidence-based Medicine and Evaluation, Cochrane Austria, Krems, Austria
- Viktoria Titscher, Danube University Krems, Department for Evidence-based Medicine and Evaluation, Krems, Austria
- Angela Kaminski-Hartenthaler, Danube University Krems, Department for Evidence-based Medicine and Evaluation, Krems, Austria
- Ingrid Zechmeister-Koss, Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria
- Christoph Strohmaier, Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria
- Michal Stanak, Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria
- Stephan Kallab, Niederösterreichische Landeskliniken-Holding, Legal and Human Resources Department, St. Pölten, Austria
- Kai Nitschke, University of Freiburg, Institute for Evidence in Medicine (for the Cochrane Germany Foundation), Freiburg, Germany

Clinical advisor

- Maximilian Huhn, Technical University of Munich, Germany

Reviewer

- Ursula Griebler, Danube University Krems, Department for Evidence-based Medicine and Evaluation, Krems, Austria

Author of HTA compact: The most important points clearly explained

- Jana Meixner, commissioned by the Danube University Krems, Krems, Austria

IQWiG coordinated the project and conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”.

Keywords: Phototherapy, Vitamin D, Seasonal Affective Disorder, Benefit Assessment, Systematic Review, Technology Assessment – Biomedical

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A12 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

For "ThemenCheck Medizin" (Topic Check Medicine), published by the Institute for Quality and Efficiency in Health Care (IQWiG), insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies. The assessment is done in the form of a health technology assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 topics are selected each year from among all submitted proposals. According to the legal mandate, these topics should be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In 2018, IQWiG commissioned a team of scientists from Danube University Krems to investigate the selected topic "Seasonal affective disorder: Do nondrug treatments such as phototherapy and vitamin therapy lead to better results?" The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal and organizational topics as well as a specialist in psychiatry and psychotherapy.

Why is the HTA report important?

People with seasonal affective disorder (SAD) suffer from seasonal symptoms such as depressed mood, loss of interest, lack of drive, extreme tiredness, or sudden hunger pangs, often associated with weight gain. Most patients experience episodes of mild to moderate depression, which can nevertheless adversely impact their professional and private lives. Annually, about 2.5% of the population in German-speaking countries is affected by SAD, and in the majority of patients, the disorder recurs in the subsequent year [2–4]. SAD is often diagnosed late or not at all, in part due to the prevailing societal perception of the associated symptoms being somewhat normal and a side effect of the darker months. It is not unusual to hear people say, "I have the winter blues."

After diagnosis, SAD is often treated with drugs (antidepressants) and/or psychotherapy. However, patients and treatment providers are also looking for alternatives: The reduced number of sunlight hours in autumn and winter is suspected to have physical effects which can be compensated by phototherapy. Since the body synthesizes less vitamin D in the winter

as a result of less intensive sunlight, the administration of vitamin D represents a potential treatment option.

This HTA report therefore aims to investigate the benefits and harms of phototherapy and vitamin D therapy in comparison with each other as well as in comparison with antidepressants, psychotherapy, placebo or no treatment in adults with SAD. Of particular interest were any effects on mortality, the extent of depression symptoms, and health-related quality of life as well as adverse events.

Which questions are answered – and which are not?

For the assessment of benefit and harm of phototherapy, the team of scientists from Danube University Krems included 21 relevant studies, most of them of moderate qualitative certainty of results. Sixteen studies compared phototherapy versus placebo, 3 studies phototherapy versus cognitive behavioural therapy, and 2 studies phototherapy versus the antidepressant fluoxetine.

After an intervention period of 2 to 8 weeks, there were indications suggesting that light box-based phototherapy resulting in greater improvements in symptoms of depression than placebo. This was the case for the patient-relevant aspects of response, remission of depression, and severity of depressive symptoms. In addition, for the comparison of light box therapy with fluoxetine, there was a hint of the antidepressant therapy being more likely to lead to AEs such as sleep disorders or tachycardia. The benefit of light box therapy was, however, comparable to the benefit of fluoxetine or cognitive behavioural therapy. For phototherapy with head-mounted units, there was no hint of greater effect than placebo.

Mortality-related treatment effects were not investigated in any study, and effects on health-related quality of life and cognitive functioning were each examined by only 1 study. Further, no long-term data on phototherapy were available since, except for a survey taken immediately following the 2 to 8 weeks of therapy, patients were not followed up for a longer time period. The external team of scientists did not find any studies on SAD treatment with vitamin D.

The costs of light box phototherapy include the device price and the cost of the associated consultations with a physician or psychotherapist and are similar to the costs of vitamin D or fluoxetine therapy for the respective minimum treatment durations. Only cognitive behavioural therapy – in group or individual setting – is far more cost-intensive. The treatment costs of fluoxetine and cognitive behavioural therapy are covered by SHI, while those of phototherapy and vitamin D therapy are typically not. However, some SHIs pay some of the costs of phototherapy if a diagnosis of SAD has been medically established. Two health economic studies comparing phototherapy with cognitive behavioural therapy were identified. According to the external team of scientists, the informative value of these studies

was very limited due to methodological limitations as well as lack of transferability from the U.S. to the German healthcare setting.

Generally, SAD patients represent a vulnerable group: About half of patients have a known family history of psychiatric disorders, and, alongside psychological stress some exhibit physical conditions such as excess weight or coronary heart disease. Although SAD patients are less stigmatized by society than people with different types of depression, societal acceptance of the disorder is poor. SAD is often perceived as a side effect of the darker months or as “winter fatigue”. Against this background, it comes as no surprise that both patients and physicians tend to discuss it as a disease caused by biological processes rather than a mental disorder.

Assuming SAD is due to a physical deficiency, phototherapy and vitamin D therapy might represent potential treatment options. However, due to a lack of studies, no conclusions can be drawn on the benefits and harms of vitamin D in SAD treatment. This is reflected by current healthcare practice: Vitamin D is currently not a recommended treatment option for SAD patients and is prescribed only to treat selected disorders or vitamin deficiencies which have been confirmed by laboratory testing. Currently, guidelines recommend antidepressants, phototherapy, or cognitive behavioural therapy [5,6]. Patients’ desire for a less invasive alternative to the commonly prescribed antidepressants also leads to greater acceptance of other measures, e.g. phototherapy or vitamin D therapy. This holds true at least in the experience of the external team of scientists.

In contrast to cognitive behavioural therapy, fluoxetine or vitamin D therapy as well as phototherapy can be applied by patients at their own homes, after consultation with a physician. If the light box is purchased by the patient, it can be used again in any further depressive episodes in autumn or winter without incurring any additional costs. Since few SHIs pay for all or part of phototherapy, access requirements differ. Patients who cannot afford to pay for phototherapy themselves and do not wish to switch to another SHI are forced to rely on the reimbursable drug and psychotherapeutic therapies. Nevertheless, every physician must inform patients about all treatment options, provided the latter are equally medically indicated, are part of standard medical practice, and are suitable for replacing treatments such as antidepressant therapy. From an organizational perspective, since consultation is provided by the same care provider, the use of phototherapy does not increase resource consumption or cause any shift in services.

IQWiG confirms the assessment from the Danube University Krems team of scientists, who found that light box therapy can indeed represent an alternative in the treatment of SAD. Published studies have shown that, after 2 to 8 weeks of intervention, light box therapy improved depression symptoms to a greater extent than did placebo. In addition, it was associated with fewer adverse events than the antidepressant fluoxetine. Light boxes can be

easily used at home at a convenient time and require only a one-time purchase. Due to a lack of relevant studies, no conclusions can be drawn on the benefits and harms associated with vitamin D therapy in SAD.

What's the next step?

To obtain a more comprehensive picture, it is desirable to have additional informative studies investigating the long-term benefits and harms of light box therapy, its effects on additional patient-relevant aspects such as health-related quality of life as well as light box therapy in comparison with other established therapies. Further, there is a general need for further research on SAD treatment with vitamin D. Apart from seeking to answer the question as to which therapy is safest and most effective, this HTA report is intended to help focus public attention on SAD and hence increase awareness of a disorder which can affect patients' social and professional functioning.

References

1. Bundesministerium der Justiz und für Verbraucherschutz. Sozialgesetzbuch (SGB) Fünftes Buch (V): Gesetzliche Krankenversicherung; (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477) [online]. 22.03.2020 [Accessed: 14.05.2020]. URL: http://www.gesetze-im-internet.de/sgb_5/SGB_5.pdf.

2. Wirz-Justice A, Graw P, Krauchi K, Wacker HR. Seasonality in affective disorders in Switzerland. Acta Psychiatr Scand Suppl 2003; (418): 92-95.

3. Pjrek E, Baldinger-Melich P, Spies M, Papageorgiou K, Kasper S, Winkler D. Epidemiology and socioeconomic impact of seasonal affective disorder in Austria. Eur Psychiatry 2016; 32: 28-33.

4. Schwartz PJ, Brown C, Wehr TA, Rosenthal NE. Winter seasonal affective disorder: a follow-up study of the first 59 patients of the National Institute of Mental Health Seasonal Studies Program. Am J Psychiatry 1996; 153(8): 1028-1036.

5. Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde. S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression: Langfassung; Version 5 [online]. 2015 [Accessed: 14.05.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/depression/depression-2aufl-vers5-lang.pdf.

6. National Institute for Health and Care Excellence. Depression in adults: recognition and management [online]. 28.10.2009 [Accessed: 20.08.2019]. (Clinical Guidelines; Volume 90). URL: https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742636741.

HTA key statements

Research questions of the HTA report

The aims of this investigation are to

- assess the benefit of treating seasonal affective disorder (SAD) patients with phototherapy or vitamin D therapy in comparison with each other, treatment with second-generation antidepressants, or psychotherapy (according to the Federal Joint Committee [G-BA] psychotherapy guideline plus systemic therapy), sham treatment, or no treatment (waiting list) with regard to patient-relevant outcomes
- assess costs (intervention costs) arising in the treatment of SAD patients with phototherapy or vitamin D therapy in comparison with no treatment, treatment with second-generation antidepressants, or psychotherapy
- assess the cost effectiveness of phototherapy or vitamin D therapy in comparison with no treatment, treatment with second-generation antidepressants, or psychotherapy in SAD patients as well as
- review ethical, social, legal, and organizational aspects associated with phototherapy or vitamin D therapy.

Conclusion of the HTA report

Twenty-one studies on SAD treatment with data on a total of 1441 adults were found. Sixteen studies compared phototherapy versus placebo, 3 versus cognitive behavioural therapy, and 2 versus the antidepressant fluoxetine. No studies were found which compared phototherapy versus other types of psychotherapy or different antidepressants. For phototherapy, 4 studies used a head-mounted unit (HMU), while the others used light boxes. Two studies investigated the effect of dawn simulation as well as light box therapy. No studies were found on SAD treatment with vitamin D. Therefore, no conclusions can be drawn on the effectiveness and safety of vitamin D therapy against SAD.

A joint analysis of all types of phototherapy versus placebo resulted in no hint of benefit for the outcomes of response, remission of depression, severity of depressive symptoms, functioning, or AEs. No data are available on the outcomes of mortality or health-related quality of life. Subgroup analyses evaluating light box therapy separately from phototherapy with HMUs differ in results. There are hints of a short-term benefit of light box therapy in comparison with placebo with regard to depression-related outcomes (response, remission, severity of depressive symptoms). There is no hint of any difference in the number of AEs or changes in cognitive functioning. For phototherapy with HMUs, in contrast, no hint of any

benefit can be derived with regard to response, remission, severity of depressive symptoms, or AEs. Regarding the outcome of functioning, no data are available for this comparison.

For dawn simulation versus placebo, there is a hint of benefit with regard to response, but none for remission, severity of depressive symptoms, or AEs. No data are available for this comparison regarding the outcomes of mortality, functioning, and health-related quality of life.

In general, long-term effects of phototherapy in comparison with placebo remain unknown since the outcomes were surveyed at the end of the intervention period of 2 to 8 weeks.

A direct comparison with other treatment options provides no hint of light box therapy being of greater benefit in SAD treatment than the antidepressant fluoxetine or cognitive behavioural therapy. After 5 to 8 weeks, all 3 interventions were associated with response or remission rates of about 50%, and the severity of depressive symptoms was comparable. Two studies additionally investigated the long-term effect of light box therapy versus cognitive behavioural therapy, showing similar remission rates after 1 year. There is a hint of fluoxetine causing more AEs during treatment than light box therapy. No such hint was found for cognitive behavioural therapy. Regarding mortality and functioning, no data were available for either the comparison of phototherapy versus fluoxetine nor for phototherapy versus cognitive behavioural therapy. Data on health-related quality of life are available only for the comparison of phototherapy versus fluoxetine, and these data do not provide any hint of greater benefit of phototherapy. No conclusions can be drawn on the benefit and harm of phototherapy in comparison with other antidepressants or other types of psychotherapy because no studies were found on these topics.

At a light box price of EUR100, the intervention costs for 4 weeks of light box therapy, including consultations, amounts to approximately EUR202. Hence, the costs are similar to those of 6 weeks of antidepressant therapy with fluoxetine (approx. EUR184.91 to EUR190.10), but lower than those of cognitive behavioural therapy. The total costs of 4 weeks of cognitive behavioural therapy, administered twice weekly, equal EUR834.67 in a group of 8 and EUR1359.92 for individual therapy. At about EUR182, vitamin D therapy is associated with the lowest intervention costs. In this context, it is worth noting that the cost of a phototherapy device is incurred only once, which is relevant in case of a recurrence of depressive episodes in subsequent winters.

The 2 identified health economic studies compared phototherapy versus cognitive behavioural therapy or no treatment. They were conducted in the United States and the informative value was considerably lower due to methodological limitations. Therefore, their results are not transferable to the German healthcare system.

Currently, German SHIs typically do not cover the costs of phototherapy or vitamin D therapy, while they do cover the costs of treatment with antidepressants and psychotherapy. Drug therapy with antidepressants is currently the most common treatment method for acute SAD. Lack of coverage of therapies can not only influence the choice of treatment, but also promote social inequalities.

Ethical and social challenges related to SAD particularly include societal doubts as to whether SAD is actually a clinical picture or represents a “normal” part of the dark season. In this context, physician awareness of SAD should be promoted in order to prevent its diagnosis or treatment from being delayed or missed. Physicians are also required by law to inform patients about all available treatment options for SAD and to obtain informed consent to treatment. From an organizational perspective, the implementation of phototherapy and vitamin D therapy does not require more personnel, because both therapies can be self-administered by the patient.

Table of contents

List of tables

List of abbreviations

Abbreviation	Meaning
AE	adverse event
AMG	Arzneimittelgesetz (Medicinal Products Act)
AMWF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (Association of the Scientific Medical Societies in Germany)
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOÄ	Gebührenordnung für Ärzte (German Medical Fee Schedule)
HeilM-RL	Heilmittel-Richtlinie (Guideline on Remedies)
HMU	head-mounted unit
HTA	health technology assessment
ICD	International Classification of Diseases
IGeL	Individuelle Gesundheitsleistung (individual out-of-pocket health service)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	International Unit
OR	odds ratio
QALY	quality-adjusted life year
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RCT	randomized controlled trial
RR	relative risk
SAD	seasonal affective disorder
SAE	serious adverse event
SHI	statutory health insurance
SMD	standardized mean difference
SSRI	selective serotonin reuptake inhibitors

HTA overview

1 Background

1.1 Health policy background and commission

According to § 139b (5) of Social Code Book V, Statutory Health Insurance, statutory health insurance members and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the ThemenCheck Medizin ("topic check medicine") website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about healthcare services and structures. The HTA report will be made available to the professional community through the ThemenCheck Medizin website (www.themencheck-medizin.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

1.2.1 Definition and epidemiology

SAD is a seasonal type of depression, typically causing symptoms in autumn and winter and subsiding in spring and summer [1]. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) lists SAD under F33 as a subtype of recurrent depressive disorder with a seasonal pattern [2]. The diagnostic criteria for SAD from the U.S. classification system Diagnostic and Statistical Manual of Mental Disorders (DSM-5) require at least 2 episodes of depressive disturbance occurring in consecutive years during the same season and not being able to be explained by other circumstances, such as loss of work for seasonal workers [3]. The most common type of SAD is the winter form, in which depressive symptoms develop in autumn and winter and do not resolve until spring. In the less common summer form, depressive symptoms occur only in summer [3]. This report focuses on the winter form

of SAD – also known as “autumn-winter depression”. Therefore, the terms SAD and autumn-winter depression are used synonymously in this report.

SAD patients suffer not only from typical symptoms of depression, such as a depressed, low mood, lack of drive or loss of interest, and joylessness, but often also from atypical symptoms such as a ravenous appetite for carbohydrates, increased need to sleep, or weight gain [4]. Most SAD patients experience episodes of mild to moderate depression; suicidal ideation is less common than in patients suffering from nonseasonal depression. Nevertheless, SAD patients exhibit impaired functioning in winter, and the disorder adversely impacts their private and professional lives [5,6].

The prevalence of SAD is higher in northern countries than in southern ones; in Europe and the United States, it is reported as between 1% and 10%. While no prevalence data are available for Germany, surveys from Austria and Switzerland report some 2.5% of the population being affected by SAD in these latitudes [7,8].

According to a German study, some 80% of patients diagnosed with SAD experienced a depressive episode in the subsequent year as well [9]. Long-term studies have shown that 5 to 11 years after diagnosis, 22% to 42% still suffered from SAD. In 33% to 44% of patients, SAD developed into nonseasonal depression, while in 14% to 18%, symptoms disappeared completely [9,10].

1.2.2 Treatment

Since the depressive episodes start in autumn or winter, SAD development is thought to be associated with fewer hours of sunlight. Lack of sunlight might affect the circadian rhythm as well as the hormone and neurotransmitter balance [11]. Since north of 40 degrees latitude, no vitamin D is synthesised from sunlight in winter, vitamin D deficiency might be a potential cause of the development of SAD [12]. Germany is located north of 40 degrees latitude: Munich, for instance, is at 48 degrees and Hamburg at 53 degrees latitude.

Phototherapy

According to the German National Disease Management Guideline for unipolar depression, phototherapy is a first-line therapy for SAD patients [13]. Typically, white fluorescent light similar to natural daylight is used, while filtering out ultraviolet radiation. Patients should receive phototherapy 30 to 45 minutes daily at a light intensity of 10 000 lux [14]; ideally, the sessions should be in the mornings as soon as possible after getting up [15]. Typically, phototherapy is administered with a light box placed at a distance of 50 to 80 cm from the patient. Other options are devices which are attached directly to the head – so-called head-mounted units (HMUs) [16] – or phototherapy rooms in which patients spend time. It is

important for patients to keep their eyes open during phototherapy since light is processed through a nerve tract referred to as retinopituitary tract [16].

Another form of phototherapy is dawn simulation, which involves gradually brightening the bedroom in which the patient is still sleeping from 0 to 300 lux in the mornings [17,18]. Dawn simulation is easier for patients to integrate into their daily routines, but existing studies have shown it to be less effective than phototherapy with a light box [19,20].

Phototherapy takes a few days or weeks to take effect. It should be continued throughout the winter months since discontinuing phototherapy can lead to a recurrence of depressive symptoms [5].

From the perspective of the general public, the relevant question is whether phototherapy is the effective and safe for the treatment of SAD. Therefore, the present report investigates the effectiveness and safety of phototherapy in comparison with no intervention or different interventions.

Vitamin D therapy

The body's vitamin D needs are in part met through diet, but most of the vitamin D is produced in the skin when exposed to the sun's ultraviolet B rays. A small study with 15 SAD patients showed better preliminary results for vitamin D supplements than for phototherapy after 1 week [21]. The National Disease Management Guideline for unipolar depression does not include any recommendations for or against vitamin D therapy in SAD [13]. However, given the importance of this issue to the German public, a systematic review of randomized controlled trials (RCTs) on the efficacy and safety of vitamin D therapy in SAD might provide insights on this topic. In the present report, the efficacy and safety of therapy with vitamin D_3 (cholecalciferol), i.e. the most important physiological form of vitamin D, was examined in different pharmaceutical forms (tablets, drops) and dosages.

Second-generation antidepressants

Disturbances of the neurotransmitter system are suspected as a potential cause of SAD [22]. Therefore, SAD is often treated with second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, selective noradrenaline reuptake inhibitors, or selective noradrenaline-dopamine reuptake inhibitors. According to the German National Disease Management Guideline for unipolar depression, SSRIs and phototherapy are recommended as the first-line treatment of SAD [13]. A Cochrane review on the effectiveness of second-generation antidepressants in the treatment of SAD identified 3 RCTs with the SSRI fluoxetine and found a numerical, but not statistically significant advantage of fluoxetine when compared to placebo [23]. This report does not rely on first-generation antidepressants

(tricyclics, tetracyclics, monoamine oxidase inhibitors) as comparators, because their adverse event (AE) profile is worse than that of second-generation antidepressants.

Psychotherapy

Psychological vulnerability can play a role in the development of SAD. Therefore, psychotherapeutic interventions are viewed as potential treatment methods as well [24]. Research focuses particularly on cognitive behavioural therapy [25].

According to the Federal Joint Committee (G-BA) guideline on the conduct of psychotherapy, German statutory health insurance (SHI) covers the cost of the following psychotherapeutic services because the latter are based on a comprehensive theory of pathogenesis and have been proven to be effective in studies: psychoanalytic procedures, behavioural therapy, and systemic therapy [26,27]. This HTA report therefore focuses on these forms of psychotherapy as the comparator intervention.

1.3 Utilization

A survey in psychiatric departments and hospitals in Germany, Austria, and Switzerland showed that among the 86 responding institutions, 99% prescribe SAD patients antidepressants for the treatment of acute episodes of depression, 87% prescribe phototherapy, and 85% psychotherapy. In isolated cases, vitamin D therapy was recommended as well [28]. It is unknown whether and to what extent physicians in private practice prescribe SAD patients phototherapy, vitamin D therapy, antidepressants, or psychotherapy.

1.4 Concerns of those proposing the topic

A member of the public asked about the benefit of nondrug methods like phototherapy and vitamin therapy for patients with mild depression, such as winter depression. She was particularly interested in any effective alternatives to pharmacological antidepressants as well as in their advantages and disadvantages.

The *ThemenCheck Medizin* staff at IQWiG developed an HTA research question on the basis of this suggestion.

2 Research questions

The aims of this investigation are to

- assess the benefit of treating SAD patients with phototherapy or vitamin D therapy in comparison with each other, treatment with second-generation antidepressants, or psychotherapy (according to the G-BA psychotherapy guideline plus systemic therapy), sham treatment, or no treatment (waiting list) with regard to patient-relevant outcomes
- assess costs (intervention costs) arising in the treatment of SAD patients with phototherapy or vitamin D therapy in comparison with no treatment, treatment with second-generation antidepressants, or psychotherapy
- assess the cost effectiveness of phototherapy or vitamin D therapy in comparison with no treatment, treatment with second-generation antidepressants, or psychotherapy in SAD patients as well as
- review ethical, social, legal, and organizational aspects associated with phototherapy or vitamin D therapy.

3 Methods

3.1 Methods for the benefit assessment

The target population of the benefit assessment was adult SAD patients (≥ 18 years). The experimental interventions were phototherapy and vitamin D therapy. The comparator intervention was the respective other intervention, a second-generation antidepressant, psychotherapy, placebo, or no treatment. For studies on phototherapy, "placebo" was defined as follows: light boxes with 0 to a maximum of 300 lux, infrared light, or light boxes classified as a placebo in the original study, as well as inactive negative ion generators. Phototherapy with less than 300 lux was considered a placebo even if it had been classified as active treatment in the study itself because no light-related effects can be expected at such low lux levels [29]. Dawn simulation was viewed as an active intervention even at light intensities below 300 lux. However, at less than 5 lux or a duration of less than 15 minutes, it was classified as sham dawn simulation [29].

Based on research conducted in advance and interviews with 2 patients (see 3.6), the following patient-relevant outcomes were examined for the investigation:

- Mortality
- Morbidity
  - Response
  - Remission of depression
  - Severity of depressive symptoms
  - Functioning
- Health-related quality of life
- AEs

Only RCTs were included in the benefit assessment. To eliminate any carry-over effects or impact of seasonal changes, only the first phase of any cross-over RCTs was used in the HTA. In addition, only studies with an intervention duration of at least 2 weeks were included since, according to the clinical expert acting as advisor for this HTA, no intervention-related effect can be expected from shorter studies. If studies used multiple scales to calculate depression scores, the HTA extracted the depression scores measured with the scale most commonly used in the included studies.

In the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and PsychINFO databases, a systematic search for primary literature was conducted. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane

Database of Systematic Reviews, HTA Database, and PsycINFO. In addition to the primary literature, the reference lists of the systematic reviews identified for the search of reference lists were viewed. The following additional sources of information and search techniques were additionally used: study registries, publicly available documents from regulatory authorities, and requests to authors. If additional relevant documents are identified in the commenting procedure for the preliminary HTA report, they will be taken into account before the report is finalized.

The present project is part of an IQWiG study investigating the efficiency of study selection [30]. Therefore, the study selection from the hits of the bibliographic search was conducted both on the title/abstract level and on the full-text level by 3 persons (2 external experts, 1 IQWiG employee) independently from one another, each using his or her own screening tool. The results of the selection were summarized after the full text assessment. Any discrepancies were solved by the external expert managing the project. The hits from the study registries were viewed by 2 people, while the search results from any further information sources were screened by 1 person and reviewed by a 2nd person.

One person extracted data into standardized tables, and a 2nd person reviewed them. To evaluate the qualitative certainty of results, 2 persons, independently of one another as per IQWiG procedure, assessed the risk of bias on the study and outcome levels and rated it as low or high in each case. Any discrepancies were resolved by discussion.

To the extent that the studies were comparable in terms of their research questions and relevant characteristics and no meaningful heterogeneity was observed, the individual results were quantitatively summarized in metaanalyses using the statistics software R [31–33]. If at least 5 studies were available, a model with random effects was calculated (Knapp-Hartung method including the Paule-Mandel estimator for the heterogeneity parameter τ). If 2 to 4 studies were pooled or subgroups calculated, a model with fixed effect was used. The originally planned subgroup analyses by age, sex, and severity of depression at baseline were omitted because the studies were similar in terms of the average severity of depression as well as sex and age distributions and the studies themselves did not report on such subgroups. Instead, a post-hoc subgroup analysis was conducted, which distinguished between phototherapy with a patient-facing light box versus phototherapy with a head-mounted unit (HMU). For any metaanalyses pooling data from at least 10 studies, an additional funnel plot was generated in order to assess the risk of publication bias.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above. The latter is the case if no data are available or the available data do not permit classification into one of the other categories. In that case, there is no hint of (greater)

benefit or (greater) harm. The evidence was rated following the standardized definitions of IQWiG.

3.2 Methods for the health economic assessment

3.2.1 Intervention costs

To calculate the intervention costs, the average resources directly required when performing the experimental and comparator interventions were determined. The services directly associated with performing the interventions were taken into account as well. The relevant regulated or negotiated prices of these services were used wherever possible and available. For any services which are not subject to clear regulations or price negotiations and whose costs could not be determined via database searches, queries were sent to service providers, and manufacturer websites were searched. Reimbursable and non-reimbursable costs were listed separately. Where prices and costs were not from the year in question, i.e., 2019, they were adjusted for inflation on the basis of the harmonized consumer price index of the German Federal Statistical Office [34].

3.2.2 Cost effectiveness

To assess health economic aspects, a systematic search for comparative studies – cost-effectiveness analyses, cost-utility analyses, or cost-benefit analyses – was conducted [35] and restricted to Germany and high-income countries as defined by the World Bank (gross national income per capita over USD12 235) [36].

As part of the focused information retrieval, the databases Embase, HTA database, and MEDLINE were searched. Three persons viewed references identified as relevant together while performing the benefit assessment. Systematic reviews and requests to authors were used as supplementary sources. Any additional relevant documents identified during the commenting procedure for the preliminary HTA were to be taken into account before the report was finalized.

One person extracted the data from the included studies into standardized tables, and a 2nd person reviewed them. The reporting quality of the included health economic studies was assessed following the criteria of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [37]. For the methodological assessment of health economic studies with decision-analytic models, use of the checklist “Assessing the Evidence for Health Care Decision Makers” from ISPOR (International Society for Pharmacoeconomics and Outcomes Research) was planned, but no such studies were identified over the course of the HTA [38]. The transferability of results was assessed based on the criteria of the European Network for Health Technology Assessment (EUnetHTA) HTA Adaptation Toolkit from the European Network for Health Technology Assessment [39]. The HTA report comparatively describes the results on the cost effectiveness reported in the studies as well as the authors’ conclusions.

3.3 Methods for evaluating ethical aspects

The evaluation of ethical aspects was based on the overarching questions of the simplified questionnaire from Hofmann et al. 2014 [40]. The scoping search was performed on the information sources of Belit, CINAHL, EthxWeb, ETHICSWEB, MEDLINE, PsycINFO, and Scopus. Additional sources were the studies included for the benefit and economical assessment as well as interest group-based information sources such as stakeholder websites were used.

The target population of the ethical evaluation was expanded to include patients with nonseasonal depression. This is a legitimate approach because the ethical challenges faced by SAD patients and those suffering from nonseasonal depression tend to be similar.

One person viewed information from all sources identified in the searches for conclusions on ethical arguments and aspects of the intervention to be investigated, extracted them into standardized tables, and also provided a narrative. The result was scrutinized for quality by a 2nd person.

3.4 Methods for evaluating social and organizational aspects

Scoping searches in MEDLINE, the AMWF (Association of the Scientific Medical Societies in Germany) guideline database, and on the internet (Google) focused on the evaluation of social and organizational aspects. In addition, both the studies included for the benefit assessment and health economic evaluation as well as the studies viewed for ethical aspects were screened for social and/or organizational aspects. Further, findings from patient interviews were integrated (see 3.6) and the “reflective thoughts” method was applied following INTEGRATE-HTA instructions [41].

The information processing on social aspects followed the conceptional framework proposed by Mozygemba et al. 2016 [42], while the information processing on organizational aspects followed the grid template proposed by Perleth 2014 [43] for the assessment of the organizational consequences of treatment methods.

One reviewer screened the information from all sources found in the scoping searches for conclusions on social and/or organizational arguments and aspects of the technologies to be investigated. The results were scrutinized for quality by a 2nd person. All arguments and aspects necessary for information processing were extracted into tables and summarized as a narrative.

3.5 Methods for evaluating legal aspects

The databases of the German Federal Court, the Federal Legal Information System, the Manz legal database, the Lexis Nexis legal database, and the EUR-Lex legal database of the European Union were searched for relevant literature. In addition, a Google search and a search on

websites of the Medical Service of the National Association of SHI Funds, the Bavarian Association of SHI Physicians, and the European Commission were conducted.

Information processing on legal aspects was based on the guideline developed by Brönneke 2016 [44] for the identification of legal aspects.

One person screened information for statements about legal aspects of the technologies to be investigated. The result was scrutinized for quality by a 2nd person. All arguments and aspects necessary for information processing were extracted into tables and summarized as a narrative.

3.6 Patient interviews

After obtaining a favourable opinion from the internal review board of Danube University Krems (EK GZ02/2018-2021), 2 interviews with SAD patients were conducted using a predefined interview guide, posing questions on the disorder, experiences with therapies (particularly phototherapy and vitamin D therapy), and on expectations for an ideal therapy. The interviews were intended to determine which aspects of the disorder are experienced as particularly burdensome and which outcomes are most important to patients.

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

The information retrieval found a total of 658 hits, of which 21 RCTs published in 29 documents were deemed relevant for the research question of the benefit assessment and were included in it. In addition, 1 ongoing study and 2 completed studies without reported results were identified, all of which investigated phototherapy. No relevant study was found on vitamin D therapy.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 9 January 2019.

Table 1: Study pool of the benefit assessment

Study			
	Full publication (in professional journals)	**Results report from the study registries**	**Study registry**
Anderson 2009	Yes [45]		
Avery 2001	Yes [46]		
Desan 2007	Yes [47]		Yes [48]
Eastman 1992	Yes [49]		
Eastman 1998	Yes [50]		
Glickmann 2006	Yes [51]		
Joffe 1993/Levitt 1993	Yes [52] Yes [53]		
Lam 2006/Michalak 2007	Yes [54] Yes [55]		
Levitt 1994	Yes [56]		
Levitt 1996	Yes [57]		
Michalon 1997	Yes [58]		
Rohan 2004	Yes [59]		
Rohan 2007	Yes [60]		Yes [61]
Rohan 2015	Yes [62] 2015 Yes [63] 2013 Yes [64] 2016		Yes [65]
Ruhrmann 1998	Yes [66]		
Spezzano 2007	Yes [67]		
Spies 2018	Yes [68]		Yes [69]
Teicher 1995	Yes [70]		
Terman 2006	Yes [71]		
Wileman 2001	Yes [72]		
NCT00809523, 2013		Yes [73]	

4.2 Characteristics of the studies included in the assessment

The 21 included RCTs investigated **phototherapy** for SAD in a total of 1441 adults [45–47,49–60,62,66–73]. The population in Spezzano 2007 [67] was the youngest, at a mean age of 19.7 years, while the population of Rohan et al. 2004 [59] was the oldest, at a mean age of 50.5 years. All studies included more women than men, with women representing 60% to 91% of participants. The interventions lasted between 2 and 8 weeks. In the studies comparing phototherapy versus cognitive behavioural therapy, unlike participants, outcome collectors were blinded [59,60,62]. The other studies blinded participants, but the blinding status of outcome collectors remained unclear in 5 studies [53,56–58,73].

Eleven studies were conducted in the United States [45,46,49–51,59,60,62,67,70,71], 4 in Canada [54–58], 1 in the United Kingdom [72], 1 in Germany [66], and 1 in Austria [68]. Three studies were carried out in multiple countries: 2 in the United States, Canada, and the Netherlands [47,73] and 1 in the United States and Canada [52,53]. The oldest study was published in 1992 [49], while the most recent study was from 2018 [68].

Four studies performed phototherapy using HMUs [52,53,56,57,70], while the other studies used light boxes in front of which participants were to sit for 30 to 120 minutes daily (depending on the study) [45–47,49–51,54,55,58–60,62,66–68,71–73]. Two studies investigated dawn simulation in addition to light box therapy [46,71]. Phototherapy was administered for 2 to 8 weeks each, typically in the morning. In 2 studies, phototherapy was conducted in the mornings and evenings [59,60]. Two further studies allowed participants to freely choose the timing of phototherapy during the daytime [50,72]. All but 1 study had phototherapy self-administered by patients at their homes. Only 1 study lacked information on the location where it was performed [73].

Sixteen studies compared phototherapy versus placebo, with 6 studies using negative ion generators as placebo [47,49,50,67,71,73] and 10 studies using placebo lamps with insufficient or no light intensity [45,46,51–53,56–58,68,70,72]. One study compared phototherapy versus a waiting list group and cognitive behavioural therapy [60]. Two further studies investigated phototherapy in comparison with cognitive behavioural therapy [59,60,62], while 2 others compared it against treatment with the antidepressant fluoxetine and additional placebo control, with the phototherapy group additionally receiving placebo tablets and the fluoxetine group additional inactive phototherapy [55,54,66]. No RCTs were found which compared phototherapy versus other second-generation antidepressants, other forms of psychotherapy, or vitamin D therapy and met the inclusion criteria.

For **vitamin D** therapy of SAD, no RCT meeting the inclusion criteria was found.

4.3 Overview of patient-relevant outcomes

For **phototherapy**, data were extracted from 21 studies. Table 2 presents an overview of the data on patient-relevant outcomes available from the included studies. Metaanalyses were generated on the outcomes “response”, “remission of depression”, and “severity of depressive symptoms”. Not all studies reporting these outcomes were included in the metaanalyses, however, because either necessary information was missing or, as in the case of Spezzano 2007 [67], the population excessively differed in age (18 to 22 years) from the other studies (mean age: 31.6 to 50.5 years) [45–66,68–73]. The results of these studies are presented as supplementary information in the corresponding results sections of the HTA overview and can be found in the tables (Table 15 to Table 17) of the full report.

Although many studies provide data on AEs, the reporting was too heterogeneous for a metaanalysis.

Functioning and quality of life were reported by 1 study each; these results are summarized as a narrative.

No study reported data on the outcome of mortality.

For **vitamin D** therapy, no data are available on any patient-relevant outcome because no study meeting the inclusion criteria was found.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Mortality	Morbidity				HRQoL	AE
	Mortality	Response	Remission of depression	Severity of depressive symptoms	Functioning	Health-related quality of life	Adverse events
Phototherapy versus placebo or waiting list							
Anderson 2009	-	-	●	●	-	-	-
Avery 2001	-	○	○	-	-	-	○
Desan 2007	-	-	●	●	-	-	○
Eastman 1992	-	○	-	●	-	-	-
Eastman 1998	-	●	●	-	-	-	-
Glickmann 2006	-	-	●	-	-	-	-
Joffe 1993/Levitt 1993	-	●	●	●	-	-	-
Levitt 1994	-	●	●	●	-	-	-
Levitt 1996	-	●	-	●	-	-	○
Michalon 1997	-	-	●	○	○	-	-
Rohan 2007	-	-	○	○	-	-	-
Spezzano 2007	-	○	-	○	-	-	○
Spies 2018	-	-	-	●	-	-	-
Teicher 1995	-	●	●	●	-	-	-
Terman 2006	-	●	●	●	-	-	○
Wileman 2001	-	●	●	○	-	-	-
NCT00809523 2013	-	-	-	●	-	-	○
Phototherapy versus antidepressants (fluoxetine)							
Lam 2006/ Michalak 2007	-	●	●	●	-	○	○
Ruhrmann 1998	-	●	●	●	-	-	○

(continued)

Table 2: Matrix of patient-relevant outcomes (continued)

Study	Outcomes						
	Mortality	Morbidity				HRQoL	AE
	Mortality	Response	Remission of depression	Severity of depressive symptoms	Functioning	Health-related quality of life	Adverse events
Phototherapy versus psychotherapy (cognitive behavioural therapy)							
Rohan 2004	-	-	●	-	-	-	-
Rohan 2007	-	-	●	●	-	-	-
Rohan 2015	-	-	●	●	-	-	○
Vitamin D therapy versus placebo, no treatment, or treatment with phototherapy, antidepressants, or psychotherapy							
No studies found							

● Data were reported and were suitable for being summarized in metaanalyses.
○ Data were reported and presented in tabular and narrative form, but not suitable for integration in metaanalyses.
- No data were reported (no further information) / The outcome was not surveyed.
Abbreviations: AE = adverse event; HRQoL = health-related quality of life

4.4 Assessment of the risk of bias at study and outcome levels

The risk of bias at study level was rated as low for 2 studies [45,54,55] and as high for the remaining 19 studies [46,47,49–53,56–60,62,66–68,70–73]. High risk of bias was typically due to unclear randomization and group allocation. In the absence of study protocols, it was also unclear whether some studies reported all of their results. Except in Lam/Michalak [54,55], the risk of bias at outcome level was high for all outcomes. Details on the risk of bias at study and outcome levels for each study are found in Section A3.2.2 of the full report.

4.5 Results on patient-relevant outcomes

Hereinbelow, the results are briefly presented by outcome. For each of them, the comparison of phototherapy versus placebo or waiting list is discussed first, with subgroup results on phototherapy with light boxes versus HMU being presented as supplementary information. This is followed by the presentation of results on the comparison of dawn simulation versus placebo. Dawn simulation is a special type of phototherapy which relies on very low lux levels and long light exposure periods before waking; in practice, it is therefore too dissimilar from

therapy with light boxes and HMUs to allow a metaanalytical summary. Thereupon, the comparison of light box therapy versus antidepressants is discussed, followed by the comparison of light box therapy versus psychotherapy. Detailed results are found in the tables and metaanalyses in Section A3.3 of the full report.

4.5.1 Mortality

No studies were found on this outcome.

4.5.2 Response

The studies defined response as a 50% reduction in the respective depression score from baseline to the end of the intervention.

- **Phototherapy versus placebo**

The metaanalysis shows that within 2 to 4 weeks, patients who received phototherapy were 1.23 times more likely to exhibit a response than those in the placebo group. Some 47% of those in the placebo group met the response criteria, compared to 61% in the phototherapy group. However, this difference was not statistically significant (relative risk [RR]: 1.23, 95% confidence interval [CI] 0.99 to 1.52, n = 429, 7 RCTs) [50,52,53,56,57,70–72]. Even the 2 studies which did not report any specific response rates and were therefore impossible to integrate into the metaanalyses reported not statistically significant differences between phototherapy and placebo in a total of 96 patients [46,49]. Spezzano 2007 [67], in contrast, observed very large effects of phototherapy in students aged 18 to 22 years (response with phototherapy: 80%; placebo: 0%; RR: 33, 95% CI 2.11 to 515.05, n = 40). Therefore, there is no hint of benefit for phototherapy in general.

A subgroup analysis which analysed studies with light boxes separately from those with HMUs showed a statistically significant favourable effect of light box therapy (response with light box: 65%; placebo: 43%; RR: 1.38, 95% CI 1.05 to 1.82, n = 202, 4 RCTs) [50,57,71,72]. For HMUs, there was no hint of any benefit (response with HMU: 58%; placebo: 50%; RR: 1.11, 95% CI 0.86 to 1.43, n = 227, 4 RCTs) [52,53,56,57,70]. Hence, a hint of benefit can be derived for phototherapy with light boxes, but not HMUs.

- **Dawn simulation versus placebo**

Two studies investigated dawn simulation versus placebo, but due to a lack of reported data, it was impossible to perform a metaanalysis. According to both studies, patients using dawn simulation were statistically significantly more likely to achieve a response than those in the placebo group (Avery et al. 2001 [46]: odds ratio [OR] 1.73, 95% CI 1.32 to 2.27, n = 62; Terman et al. 2006 [71]: RR: 3.71, 95% CI 1.25 to 11.00, n = 39). This results in a hint of benefit of dawn simulation.

- **Phototherapy versus antidepressants**

The metaanalysis comparing phototherapy using a light box versus the SSRI fluoxetine (20 mg daily) fails to show to which of the treatments patients respond better after 5 to 8 weeks. The 95% CI was broad and included favourable effects for both phototherapy and fluoxetine (response with phototherapy: 54%, fluoxetine: 53%; RR: 1.04, 95% CI 0.77 to 1.40, n = 136, 2 RCTs) [54,55,66]. Hence, there is no hint of a greater benefit of phototherapy.

- **Phototherapy versus psychotherapy**

For this comparison, no data on the outcome of response were found.

4.5.3 Remission of depression

The studies defined remission as a 50% reduction in the employed depression score in addition to reaching of a predefined depression score by the end of the intervention. The defined upper limits varied based on the scale used to measure depression, but overall, they were comparable across studies. Details on the specific definitions and scales used in each of the studies are found in Table 16 of the full report.

- **Phototherapy versus placebo or waiting list**

A metaanalysis showed that, within 2 to 6 weeks, patients receiving phototherapy were 1.32 times more successful in achieving remission than those in the placebo group. However, the difference was not statistically significant (remission on phototherapy: 52%; placebo: 39%; RR: 1.32, 95% CI 0.88 to 2.00, n = 479, 10 RCTs) [45,47,50–53,56,58,70-72]. Likewise, Avery 2001 [46], which was impossible to include in the metaanalysis for lack of data on specific remission rates, showed no statistically significant difference between groups (OR: 0.92, 95% CI 0.69 to 1.33, n = 64). The funnel plot suggested publication bias since small studies more frequently showed results in favour of phototherapy. Therefore, there is no hint of benefit for phototherapy in general.

A subgroup analysis on the employed type of phototherapy revealed a favourable effect for light box therapy (remission with light box: 46%; placebo: 25%; RR: 1.48, 95% CI 1.05 to 2.09, n = 275, 7 RCTs) [45,47,50,51,58,71,72], but not with HMUs (remission with HMU: 58%;

placebo: 58%; RR: 0.95, 95% CI 0.75 to 1.18, n = 204, 3 RCTs) [52,53,56,70]. Hence, a hint of benefit of light box therapy can be derived for this outcome as well, but not for phototherapy with HMUs.

A study by Rohan et al. 2007 [60] compared phototherapy versus a waiting list group, showing a numerical, but not statistically significant, advantage of phototherapy (RR: 2.50, 95% CI 0.81 to 7.70, n = 31). Since the waiting list group is not equivalent to the placebo groups, this study was not integrated in the metaanalysis.

- **Dawn simulation versus placebo**

One study showed that dawn simulation was statistically significantly more successful in leading to remission than placebo (Avery et al. 2001 [46]: OR: 1.51, 95% CI 1.07 to 2.13, n = 62). Due to a broad CI, however, no conclusion on the effectiveness of dawn simulations can be derived from the second study (Terman et al. 2006 [71]: RR: 0.89, 95% CI 0.38 to 2.06, n = 39). Hence, there is no hint of benefit of dawn simulation.

- **Phototherapy versus antidepressants**

The comparison of light box therapy versus antidepressant therapy with fluoxetine (20 mg daily) was inconclusive as to the intervention under which patients were more successful in achieving remission within 5 to 8 weeks. The CI was broad and included favourable effects for both phototherapy and fluoxetine (remission on phototherapy: 50%, fluoxetine: 46%; RR: 1.05, 95% CI 0.74 to 1.49, n = 136, 2 RCTs) [54,55,66]. This results in no hint of greater benefit of phototherapy.

- **Phototherapy versus psychotherapy**

The comparison of phototherapy with a light box versus cognitive behavioural therapy after 6 weeks of treatment was inconclusive in terms of the superiority of either intervention: The CI included both an advantage for persons who received phototherapy as well as an advantage for those on cognitive behavioural therapy (remission on phototherapy: 48%, psychotherapy 46%, RR: 1.04, 95% CI 0.79 to 1.38, n = 220, 3 RCTs) [59,60,62]. In the subsequent winter, no statistically significant differences in remission were found between people treated with phototherapy versus cognitive behavioural therapy (Rohan et al. 2004 [59]: remission on phototherapy: 38%, psychotherapy: 43%, RR 0.88, 95% CI 0.25 to 3.02, n = 15; Rohan et al. 2015 [62]: remission on phototherapy 36%, psychotherapy: 32%; RR: 0.95, 95% CI 0.64 to 1.41, n = 169). Therefore, there is no hint of greater benefit of phototherapy.

4.5.4 Severity of depressive symptoms

- **Phototherapy versus placebo or waiting list**

At the end of the intervention, which lasted 2 to 6 weeks depending on the study, persons who received phototherapy had less pronounced depressive symptoms than those in the placebo group. However, the difference was not statistically significant (standardized mean difference [SMD]: -0.20, 95% CI -0.47 to 0.06, n = 495, 10 RCTs) [45,47,49,52,53,56,57,68,70,71,73]. The funnel plot showed no evidence of publication bias. Therefore, there is no hint of benefit for phototherapy in general.

Among the studies excluded from the metaanalysis, Michalon et al. 1997 [58] observed that 15 patients who had received 2 weeks of phototherapy scored an average of 12 points on a scale of 0–89 points on the SIGH-SAD (Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder) scale. In comparison, the 15 patients in the placebo group had a mean of 24. At the beginning of the intervention, both groups had a mean of 31 points on the SIGH-SAD scale. SAD studies typically specify a cut-off for SAD on this scale at between 20 and 22 points, although no threshold has been officially defined. Since no standard deviations were reported, it was not possible to include this study in the metaanalysis. Spezzano 2007 [67], a study which was excluded from the metaanalysis due to its young population, also observed a statistically significantly lower depression score in the 20 patients on phototherapy (SIGH-SAD: 12.6 [± 12.4]) compared with the 20 patients in the placebo group (SIGH-SAD: 35.7 [± 6.9]) after 3 weeks of treatment (p = 0.0). At the beginning of the study, the participants in both groups had mean values of about 39. Rohan 2007 [60], which compared phototherapy versus a waiting list group, arrived at similar results: After 6 weeks of the intervention, the 16 patients in the phototherapy group had a mean of 12.7 (± 6.9) points on the SIGH-SAD scale, while those in the waiting list group had a mean of 23.1 (± 8.8) points. Due to excessive differences between the waiting list and placebo groups, this study was not integrated in the metaanalysis.

A separate analysis of light-box-based and HMU-based phototherapy revealed a moderately favourable effect for light boxes (SMD: -0.33, 95% CI -0.58 to -0.09, n = 268, 7 RCTs) [45,47,49,57,68,71,73], but not for HMUs (SMD: -0.11, 95% CI -0.38 to 0.16, n = 227, 4 RCTs) [52,53,56,57,70]. This result is confirmed by 2 studies which were excluded from the metaanalysis and likewise showed a favourable effect of light box therapy in comparison with placebo [58,67]. Therefore, an indication of benefit of light box therapy in comparison with placebo can be derived. However, there is no hint of benefit of phototherapy with HMUs.

- **Dawn simulation versus placebo**

A study with 42 participants surveyed the severity of depressive symptoms after 3 weeks [71]. Patients using dawn simulation scored an average of 5.2 fewer points on the SIGH-SAD scale than those in the placebo group (MD: -5.20, 95% CI -10.61 to 0.21), but the difference between groups was not statistically significant. Hence, there is no hint of benefit of dawn simulation.

- **Phototherapy versus antidepressants**

The comparison of phototherapy versus the antidepressant fluoxetine (20 mg daily) was inconclusive as to the intervention under which patients had less severe symptoms after 5 to 8 weeks. The CI was broad and included favourable effects for both phototherapy and fluoxetine treatment (SMD: -0.05, 95% CI -0.39 to 0.29, n = 136, 2 RCTs) [54,55,66]. Hence, there is no hint of greater benefit of phototherapy.

- **Phototherapy versus psychotherapy**

The comparison of phototherapy versus cognitive behavioural therapy after 6 weeks of treatment showed a numerically greater reduction in the phototherapy group, but the difference was not statistically significant (SMD: -0.18, 95% CI -0.45 to 0.10, n = 204, 2 RCTs) [60,62]. Therefore, there is no hint of greater benefit of phototherapy.

4.5.5 Functioning

- **Phototherapy versus placebo**

A study which surveyed cognitive functioning in a total of 32 patients found no statistically significant differences between phototherapy and placebo after 2 weeks of phototherapy when using any of 7 neuropsychological tests [58]. In some subcategories of the tests, such as logical memory – delayed recall; recognition memory for faces; and Rey complex figure recall, statistically significant improvements were measured between baseline and post-intervention. However, these improvements were found in both groups and might also be chance results due to multiple testing. Hence, no hint of benefit of phototherapy can be derived.

- **Dawn simulation versus placebo**

No evidence on the outcome of functioning was found for this comparison.

- **Phototherapy versus antidepressants**

No evidence on the outcome of functioning was found for this comparison.

- **Phototherapy versus psychotherapy**

No evidence on the outcome of functioning was found for this comparison.

4.5.6 Health-related quality of life

- **Phototherapy versus placebo**

No evidence on the outcome of health-related quality of life was found for this comparison.

- **Dawn simulation versus placebo**

No evidence on the outcome of health-related quality of life was found for this comparison.

- **Phototherapy versus antidepressants**

After 8 weeks of intervention, a study with 96 patients surveyed health-related quality of life using 2 standardized instruments [54,55]. Both the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the health status questionnaire SF-20 showed similar values after phototherapy or treatment with the antidepressant fluoxetine (Q-LES-Q: phototherapy: 20.56 [± 13.11], fluoxetine: 21.77 [± 17.04], SF-20: phototherapy 7.82 [± 15.49], fluoxetine: 9.38 [± 14.39]). No information is available on statistically significant differences between the groups at the end of the intervention. Hence, there is no hint of a greater benefit of phototherapy.

- **Phototherapy versus psychotherapy**

No evidence on the outcome of health-related quality of life was found for this comparison.

4.5.7 Adverse events

- **Phototherapy versus placebo**

Six studies with a total of 334 patients surveyed AEs [46,47,57,67,71,73]. Overall, AEs occurred in isolated cases both in the phototherapy group and in the placebo group. One study with 40 patients observed no AEs in either group [67]. Terman et al. 2006 [71] do not mention any AEs in the phototherapy group either. In each of 2 studies with a total of 87 patients, 1 patient on phototherapy reported headache, nausea, insomnia, or dry mouth, while none in the placebo group were affected by these AEs [46,47]. In Levitt et al. 1996 [57], which examined a total of 43 patients for AEs, they were observed only in isolated cases. Patients receiving phototherapy with HMUs most frequently complained of eye pain (3 of 12 persons) and headaches (also 3 of 12 persons). Interestingly, however, 4 (of 10) patients in the placebo HMU group reported eye pain as well. Another study with a total of 106 patients showed that 3 of 52 patients receiving phototherapy had eye pain, and 5 had headaches. In the placebo group, 1 of 54 patients had headaches. Since AEs were reported only in isolated cases and were similarly rare in both groups, there is no hint of harm from phototherapy.

- **Dawn simulation versus placebo**

According to a study, no AEs occurred within 2.5 to 3.5 weeks in 21 patients receiving dawn simulation. In the placebo group, in contrast, 3 of 18 patients complained of headaches and sleep disorders [71]. Hence, there is no hint of harm from dawn simulation.

- **Phototherapy versus antidepressants**

A study with 96 patients who received either phototherapy or fluoxetine for 8 weeks surveyed AEs in a standardized manner. While the number of persons who reported at least 1 AE was

similar in both groups (phototherapy: 33%, fluoxetine: 35%), there were differences in the types of AEs they experienced: Statistically significantly more patients on fluoxetine therapy reported agitation (pathological restlessness with an increased urge to move) (0% versus 13%, $p < 0.01$), insomnia (2% versus 29%, $p < 0.01$), and tachycardia (0% versus 10%, $p < 0.01$), while for all other surveyed AEs, no statistically significant differences were observed [54,55]. In another study with 40 patients, 1 person on phototherapy experienced a manic episode [66]. There is a hint suggesting that, compared with fluoxetine, phototherapy causes fewer cases of agitation, insomnia, and tachycardia.

- **Phototherapy versus psychotherapy**

During 6 weeks of treatment, Rohan et al. 2015 [62] observed no AEs in any of the 177 patients receiving phototherapy or cognitive behavioural therapy. Hence, there is no hint of harm from phototherapy.

4.6 Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

	Mortality	Morbidity				Health-related quality of life	AEs
		Response	Remission	Severity of depressive symptoms	Functioning		
Phototherapy vs. placebo	-	⇔	⇔	⇔	⇔	-	⇔
Subgroup Light box vs. placebo	-	⇑	⇑	⇑	⇔	-	⇔
Subgroup HMU vs. placebo	-	⇔	⇔	⇔	-	-	⇔
Dawn simulation vs. placebo	-	⇗	⇔	⇔	-	-	⇔
Light box vs. fluoxetine	-	⇔	⇔	⇔	-	⇔	⇗
Light box vs. cognitive behavioural therapy	-	-	⇔	⇔	-	-	⇔
Vitamin D therapy vs. placebo or another therapy	-	-	-	-	-	-	-

⇑: indication of (greater) benefit or indication of lesser harm
⇗: hint of (greater) benefit or hint of lesser harm
⇔: no hint, indication, or proof; homogeneous result
-: no data reported
Abbreviations: HMU = head-mounted unit

4.7 Discussion

With regard to response, remission, and severity of depressive symptoms, a comparison of phototherapy versus placebo showed numerical, but not statistically significant, advantages of phototherapy. However, a post-hoc subgroup analysis which considered various phototherapy devices separately revealed indications of the effectiveness of phototherapy with patient-facing light boxes. However, no hint of benefit can be derived for phototherapy with HMUs. Three of 4 studies using light boxes had an intervention period of 3 to 4 weeks [50,71,72], while all studies with HMUs conducted phototherapy for only 2 weeks [52,53,56,57,70]. The longer intervention period for light boxes might have increased

effectiveness. Other influencing factors might have been the lux level, duration of phototherapy, or time of day exposed, but due to the insufficient number of similar studies, no subgroup analyses were calculated for these factors.

For the outcome of severity of depressive symptoms, depression scores from the intervention and control groups, but not the change in scores, were compared at the end of the intervention. This approach requires that initial values be similar in both groups. In virtually all studies, the initial difference in depression scores between the two groups was less than half of the standard deviation of the placebo group. Studies in which this difference was slightly larger were nevertheless included in the metaanalysis because the placebo group had a lower initial score, and therefore, the effect of phototherapy was underestimated rather than overestimated.

All told, AEs such as headache or eye pain were reported to develop during the intervention only in isolated cases. There is no hint of phototherapy being more likely to lead to AEs than placebo. However, because the studies surveyed AEs only to the end of the intervention, any long-term harm of phototherapy cannot be assessed.

Two studies which compared phototherapy with behavioural therapy investigated remission and severity of depressive symptoms after 1 year; both groups had similar results [59,62]. All other included studies surveyed the outcomes at the end of the intervention, which, depending on the study, lasted between 2 and 8 weeks. Therefore, it remains unclear whether phototherapy has any effect beyond the treatment period.

The funnel plot suggested publication bias for the outcome of remission of depression, but not for the outcome of severity of depressive symptoms. No funnel plots were generated for the other outcomes because they would be of limited informative value given that fewer than 10 studies are available. All things considered, it is therefore conceivable that studies not showing any favourable effect of phototherapy remained unpublished.

5 Results: Health economic assessment

5.1 Intervention costs

In SAD treatment, it is essential to take into account patients' individual circumstances. Therefore, the intervention costs detailed below might differ from those incurred in the clinical routine, or additional costs might arise. Also, it was assumed that SAD F33 according to ICD-10 had already been diagnosed, regardless of the treatment form. This means that the costs of all pretherapeutic diagnostics for SAD were disregarded. The treatment of recurrent depression can stretch over an extended time period. The National Disease Management Guideline for depression recommends regularly checking treatment response and evaluating effectiveness no later than 3 to 4 weeks after the start of acute therapy in order to monitor treatment progress [13]. Therefore, further diagnostics required over the course of disease are included in the estimate of the intervention costs. This includes initial consultations, trial sessions to determine which therapy is appropriate in the individual case, interim consultations, and final consultations. Adjustment for inflation using the Harmonized Consumer Price Index for Germany for the year in question (2019) was required only for the 2012 cost data from the IGeL Monitor. The other costs and prices were based on current sources. A detailed description and list of treatments, their treatment paths, and cost items is found in Section A4.1.1 of the full report.

5.1.1 Phototherapy

Generally, 2 treatment modes are distinguished: Treatment administered at a hospital or physician's office versus treatment at home. The choice of treatment mode affects the phototherapy-related costs.

On the basis of the National Disease Management Guideline for unipolar depression [13] and a clinical treatment plan [74], the calculations in this report assume that therapy at a physician's office or hospital is administered in the form of 40-minute sessions for 4 weeks or 28 days. If therapy is performed at a physician's office or hospital, the time required per patient to obtain informed consent is about 10 minutes (done once by the physician), for nurse instructions during the first session about 10 minutes (done once by the physician), and for nurse work during each subsequent session about 5 minutes.

Hence, costs arise for device acquisition, instruction on the treatment procedure and use of the device as well as for the continued monitoring of the patient's psychiatric status. Phototherapy is billed as an individual out-of-pocket health service (IGeL) at between EUR7.50 and EUR13.94. Assuming that phototherapy is a non-reimbursable, private service, 28 sessions cost a total of EUR210 to EUR390.32 per person.

A few SHIs cover the cost of phototherapy. In those cases, the patient is responsible only for a copayment of EUR10 per prescription as per SGB V [75] and the German Guideline on Remedies (HeilM-RL) [76], and EUR299 to EUR380.32 is reimbursed.

The alternative is to perform the treatment in the home environment after purchasing a phototherapy device. The cost associated with therapy at home using the patient's own device primarily consist of the purchase price of a phototherapy device, which is to be paid out of the patient's own pocket and equals between EUR59.99 and EUR430 [77–79]. Some SHIs offer (partial) reimbursement [79], or patients might be responsible only for a copayment in accordance with HeilM-RL [76] and SGB V [75]. For instance, 1 health insurer covers 80% of the purchase price, including VAT, up to EUR150 – hence, the patient is responsible for 20% of the device cost or its price minus EUR150. At a device price of EUR100, for instance, the patient is responsible for EUR20.

Even treatment at home requires an initial consultation, and the patient has to be instructed on how to use the device. Therefore, costs of EUR102 for an initial consultation and informed consent (40 minutes) and a final consultation (30 minutes) must be added to the device cost. At a device price of EUR100 and provided the SHI covers the device cost, this results in intervention costs of EUR202, of which the patient must pay out of pocket EUR122 for the initial consultation and informed consent in accordance with the German Medical Fee Schedule (GOÄ) (EUR102) and the copayment for the device (EUR20). For the initial and final consultation, 3.5 times the fee rate stipulated by the GOÄ (EUR51 per consultation) was used since they include a determination of the patient's psychiatric status for treatment monitoring as well as instructions regarding the device. A detailed breakdown of the cost items is found in the full report (see A4.1.1.1).

5.1.2 Vitamin D therapy

According to the G-BA's Pharmaceutical Guideline, vitamin D is not reimbursable for this indication [80]. Before starting vitamin D therapy – focusing on vitamin D3 – the 25-hydroxycholecalciferol level must be quantitatively measured by immunoassay to initially determine whether vitamin D3 therapy is necessary or a depression-associated deficiency exists and, if so, to then determine the correct dosage. The optimal dose-effectiveness relationship of vitamin D cannot be derived from the literature.

In consultation with a clinician (Dr Maximilian Huhn) [81], a weekly vitamin D dose of 20 000 International Units (IUs) over an 8-week period was assumed for this calculation of intervention costs. The pharmacy retail price for 50 vitamin D soft capsules at 20 000 IU each is EUR36.95 (0.74 per capsule). One ligand-binding assay per examination can be privately billed at EUR27.98 as per GOÄ. Due to its 8-week duration, vitamin D therapy as well should include an interim consultation in addition to the initial and concluding consultations to

monitor the course of SAD. Since vitamin D therapy is a privately paid service, the GOÄ fee rate was used for the consultations in this case as well. Consequently, private costs of EUR116.57 arise for the consultations (initial consultation [30 minutes]: EUR51 or 3.5 times the fee rate; interim consultation [15 minutes]: EUR14.57 or simple fee rate; concluding consultation [30 minutes]: EUR51 or 3.5 times the fee rate). For the initial and concluding consultations, a higher fee rate was used because in addition to the general evaluation and psychiatric examination, they include a discussion of the correct use and mode of action of the vitamin D preparation. In total, the intervention costs over 8 weeks equal EUR181.50.

5.1.3 Second- generation antidepressants or SSRIs: fluoxetine

Treatment recommendations for SAD include phototherapy as well as treatment with SSRIs such as fluoxetine [13,82]. The guideline lists antidepressants broken down by drug classes, with information provided on dosage, plasma levels, and monitoring. The cost breakdown includes only the cost of the acute treatment and regular monitoring for effectiveness, which is particularly important in the acute care phase. An exact description of the treatment pathway and cost data is found in Section A4.1.1 of the full report. Depending on the manufacturer, 6 weeks of treatment (2-week up-titration phase + 4 weeks of standard dose) results in a total reimbursable cost of between EUR184.91 and EUR185.10 (preparation containing 20 mg fluoxetine, 100 count) after deducting copayments and the mandatory pharmacy discount. Of this total, EUR20.25 to EUR20.44 are attributable to fluoxetine and the remainder to the initial consultation (30 minutes), the monitoring units or interim consultations (15 minutes each), complete blood count, electrocardiogram (ECG), and the final consultation (30 minutes). When including the patient copayment, the total cost equals EUR184.91 to EUR190.10.

5.1.4 Psychotherapy/cognitive behavioural therapy

Cognitive behavioural therapy uses cognitive and behavioural approaches and elements. Cognitive behavioural therapy is recommended for the treatment of SAD after all first-line therapies have been exhausted or no response to these forms of therapy is detected [83]. According to the G-BA guidelines for psychotherapy, cognitive behavioural therapy can be billed to the SHI [26]. For twelve 90-minute sessions (group therapy with 4 or 8 patients) or twelve 50-minute sessions (individual therapy) over a period of 6 weeks, EUR1002.6 can be billed in case of groups of 4, EUR722.04 in groups of 8, or EUR1197.36 for individual therapy. Billable services also include a trial session dedicated to evaluating the initiation of psychotherapy, which is subject to approval. An application for coverage must be written before initiating short-term therapy. In addition to the treatment units, a 15-minute interim consultation and a 30-minute concluding consultation are necessary. The total cost per person for cognitive behavioural therapy equals EUR1115.23 in a group of 4, EUR834.67 in a group of 8, and EUR1359.92 for individual therapy.

5.2 Cost effectiveness

5.2.1 Results of the information retrieval

In the information retrieval, a total of 2 studies [84,85] (2 dissertations) were found to be relevant on the basis of the inclusion criteria and were included in the assessment. Three other studies which were also viewed [86–88] were not comparative health economic evaluations and therefore did not meet the inclusion criterion of economy 1 (IE1). Search queries did not find any further or ongoing health economic studies. There were no requests to authors.

Comparative health economic studies on vitamin D therapy were not found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 9 January 2019.

Table 4: Study pool of the health economic assessment

Study	Available documents [reference]
Ross, 2017	American University, Washington, D.C. [84]
Freed, 2005	American University, Washington, D.C. [85]

5.2.2 Characteristics and cost effectiveness results of the studies included in the assessment

For assessing cost effectiveness, 2 studies [84,85] were analysed on the basis of the inclusion criteria; both of them were conducted in the United States for a period of about 2 years (winter 2012/13 to 2014/15 [84] and winter 2000/01 to the end of 2003 [85]). Both studies investigated the question of whether SAD-specific cognitive behavioural therapy is cost effective. The Ross study compared this cognitive behavioural therapy in a group setting (4–8 persons) to light box therapy or a hypothetical untreated group [84]. The Freed study compared cognitive behavioural therapy with phototherapy, combination therapy (cognitive behavioural therapy + phototherapy), and a waiting list group [85].

In the Ross study, the economic assessment included a cost-utility analysis, which related the difference in treatment costs to differences in quality-adjusted life years (QALYs) gained. An additional cost-benefit analysis compared costs to benefit in monetary terms and contrasted the results with those for a hypothetical untreated group [84]. In the other Freed study, a cost-effectiveness analysis was reportedly conducted, relating costs to clinical health parameters to generate a cost-utility analysis [85].

Both health economic studies are based on RCTs with data on 59 SAD patients [59] and 177 SAD patients [63,64,89]. The economic data were surveyed retrospectively.

Both studies used the results from 2 different questionnaires for measuring the depression score (Beck Depression Inventory II [BDI-II] and SIGH-SAD), which were obtained from the clinical studies, used the results to project the utility values and subsequently the QALYs, and compared the resulting QALYs. However, their presentation is misleading and departs from the reporting standards for health economic evaluations [90]. In particular, the estimated utility values used in both studies [91] cannot be fully generalized to patients with different types of depression or to different treatment approaches [92]. Mapping disease-specific instruments to generic instruments is generally discouraged because common standards such as proof of objectivity reliability, validity, and sensitivity to change must be met when implementing corresponding procedures [93]. A detailed description of the derivation of QALYs is found in A4.2.2 of the full report.

Neither of the two economic studies calculated the present discounted value of the interventions' benefits and costs. Additionally, no explicit threshold was used in the assessment of the cost effectiveness results, although the discussion in the Freed study [85] implied a threshold of USD20 000 per QALY gained. Only the Freed study [85] conducted a sensitivity analysis, varying the rates of remuneration for phototherapy and cognitive behavioural therapy, omitting SIGH-SAD assessments, and reducing monitoring units from 6 to 2 for phototherapy. Additionally, the author performed another calculation to reportedly adjust costs to where they reflect those arising in clinical routine rather than in a study environment.

Since both studies were conducted in the United States, the cost calculation was generated from the perspective of U.S. service providers and patients. From the service provider perspective, relevant costs are those billed to the patient. They result from human resources costs for diagnostics and treatment (psychiatric or psychological treatment), material costs (manuals, worksheets), device costs (only in the Freed study [85]) as well as overhead costs (e.g. room rental, staff costs). In the Ross study [84], however, the cost of the light device in the phototherapy index treatment (initial treatment) as well as the follow-up cost of cognitive behavioural therapy were not billed; the reason for this was the voluntary nature of study participation and random allocation to the respective treatment arms. Overall, the cost calculation is incomplete and includes only part of the costs which actually arise.

In the Ross study [84], the cost of the index treatment per patient (in 2012 dollars) from the service provider perspective is USD229.35 for group cognitive behavioural therapy (disregarding any follow-up costs) and USD121.06 for phototherapy, excluding the phototherapy lamp. The Freed study [85] estimated costs for the entire treatment period (about 2 years) from the service provider perspective, at USD995 for group cognitive behavioural therapy, USD1552 for phototherapy including a phototherapy lamp, USD1930 for

combination therapy including a phototherapy lamp, and USD617 for a waiting list group (minimal contact for follow-up, admission and discharge consultation).

The estimates from the patient perspective also included costs due to the time spent on treatment and travel (based on the median income). Fees from older studies [94] were adjusted for inflation [84] or Medicaid data (data from the U.S. healthcare programme for people of limited income, children, older people and people with disabilities) and data from a real estate database [84] were used for this purpose. Taking into account the patient perspective, the Freed [85] study calculated higher average costs for all 3 interventions: USD1177 for cognitive behavioural therapy, USD1618 for phototherapy, USD2033 for combination therapy, and USD702.15 for the waiting list group. The differences in costs between the groups were statistically significant ($p < 0.001$).

In the sensitivity analysis of the Freed study [85] – which varied the rate of remuneration for cognitive behavioural therapy, omitted the SIGH-SAD assessments as described above, and reduced the monitoring units for phototherapy from 6 to 2 – the costs from the service provider perspective increased to USD1373 for cognitive behavioural therapy and dropped to USD1223 for phototherapy. Combination therapy (cognitive behavioural therapy + phototherapy) became more expensive, at USD1979, and the cost of the waiting list group dropped to USD0.

With regard to the utility values analysed from study start to follow-up, improvements were found in all treatment groups when compared to baseline (Freed) [85] or to the hypothetical untreated group (Ross) [84]. Only the Freed study [85], however, found significant differences between groups, with significantly more QALYs gained in cognitive behavioural therapy than in phototherapy ($p < 0.05$). No incremental benefit (difference between the treatment groups) was reported.

Both studies presented the results of the health economic evaluation as average cost-effectiveness ratios – rather than incremental cost-effectiveness ratios as is typically done in health economic evaluations [90] – or as a net benefit. The average cost-effectiveness ratios listed below are based only on Freed [85] since the calculations in the other study [84] are not transparent.

The cost per QALY gained or the average cost-effectiveness ratio for cognitive behavioural therapy versus no intervention was USD24 731 (calculated from all study participants) or USD6155 (disregarding cost outliers). Hence, a QALY gained in comparison to no intervention would cost USD24 731 or USD6155. The average cost-effectiveness ratio equalled USD15 898 for phototherapy and USD12 849 for a combination of cognitive behavioural therapy and phototherapy. In the Freed study, there was a statistically significant intergroup difference in

cost per QALY gained, but this difference was no longer demonstrable in the sensitivity analysis [85].

From the service provider perspective, the Ross study reported a net benefit (monetized benefit minus cost in monetary units) of USD169.34 for phototherapy and a negative net benefit of USD87.06 for cognitive behavioural therapy. This means that costs exceeded benefits in the latter case [84].

5.2.3 Reporting and methodological quality

The reporting quality of the included health economic studies was assessed based on the CHEERS criteria [37].

Both studies aimed to determine whether cognitive behavioural therapy is cost effective when compared with phototherapy using a light box and with a hypothetical untreated group [84] or when compared with phototherapy, combination therapy (cognitive behavioural therapy + phototherapy), and a waiting list group [85]. However, both reports suffer from some limitations in terms of their reporting quality (for a detailed description, please refer to A4.2.4 of the full report):

- They failed to report on potential SAD treatment alternatives, such as second-generation antidepressants or vitamin D therapy.
- In both studies, some of the cost calculations from the various perspectives are inadequate. For instance, the cost-offset analysis method in the Ross study [84] is associated with conceptional problems since it risks discriminating against certain indication groups or patient subgroups [95].
- Both studies' chosen time horizons – 2 consecutive winters after treatment start [84] or index treatment including 1-year follow-up [85] – are problematic in that a longer-term perspective would seem relevant for the clinical picture of depression. No rationale was provided for the chosen time horizon, but the discussion section of 1 study mentioned the need for a longer follow-up [84].
- Only the Freed study [85] mentioned a threshold with reference to a criteria catalogue from a 1992 guideline for economic evaluations [96].
- However, the presentation of QALYs is misleading and departs from the reporting standards for health economic evaluations [90]. Consequently, results cannot be generalized to patients with different types of depression and cannot be fully transferred to different treatment approaches [92].

- Instead of incremental QALYs for the treatment alternatives, the simple difference in QALYs gained (QALYG) between a hypothetical untreated group and the treatment alternatives was reported. Mortality rates, interpersonal and social functioning, or the number of AEs were not reported. This calls into question the validity of the presented QALYs since QALYs are calculated on the basis of quality of life and mortality. In addition, due to inadequate blinding techniques, the underlying effectiveness studies [59,63,64,89] are subject to a very high risk of bias regarding treatment benefit.

- Both studies also discussed the conducted statistical tests. Instead of confidence intervals, standard deviations were reported. Only 1 study conducted a sensitivity analysis [85], which was, however, a simplified form of a univariate sensitivity analysis. The choice of variables was not justified in detail, and the discussion of the variation range was rudimentary.

- Instead of incremental cost-effectiveness ratios, both studies reported only average cost-effectiveness ratios. This approach departs from the reporting standards for health economic studies [90].

- Both studies reported and discussed limitations. However, some limitations are not listed in the included studies, such as a discussion on sensitivity analyses or uncertainties in the Ross study [84], discount rates [84,85], subgroup analyses [84,85], listing of optional comparators [84,85], potential considerations regarding a decision analytical model [84,85], or a discussion of different outcomes [84,85].

- Conclusions were discussed and justified in both studies. They did not list any conflicts of interest, although both might suffer from some indirect ones: In one case (Ross) [84], the author of the clinical study and of a manual for cognitive behavioural therapy [63,64,89], was a member of the dissertation committee. In the second study [85], the data were based on an ongoing randomized study conducted by a member of the committee board [59]. Only 1 study [58] disclosed data on its funding.

5.2.4 Transferability

The 2 included studies compared only 2 interventions – cognitive behavioural therapy and phototherapy – and a hypothetical untreated group and a delayed-treatment group, respectively. Therefore, the research questions of the available studies reflected the research questions of the HTA report only in part.

Further limitations with regard to transferability are due to the populations of both studies not being representative: Both of them are small populations from the United States, with epidemiological, demographic, and socioeconomic characteristics which differ from those of the German population. The employed conversion methods for utility and QALYs as well as

the underlying evidence are unclear, and, due to differences between the German and U.S. healthcare systems, transferability to Germany is not warranted. On account of these limitations, transferring these study results to the German healthcare context is not recommended.

5.2.5 Discussion

This systematic health economic review presents the health economic evidence on nondrug treatment methods for SAD patients. Only 2 studies were found, but they, firstly, failed to meet central methodological standards and, secondly, are of very limited informative value due to a lack of relevant comparisons and lack of transferability between the U.S. and German healthcare settings. The health economic evidence available on this topic is therefore limited. In light of excessive differences between the U.S. and German healthcare systems, the studies were not directly transferable. It is not recommended to use the studies as a basis for making health economic decisions in Germany.

6 Results: Ethical, social, legal, and organizational aspects

6.1 Results on ethical aspects

Thirty-three publications were included for the evaluation of ethical aspects. No studies were found explicitly discussing ethical aspects related to phototherapy and vitamin D therapy in SAD. Ethical challenges related to SAD, phototherapy, and vitamin D therapy as well as the assessment thereof were analysed on the basis of the revised Socratic method according to Hofmann et al. 2014 [40]. Since the interventions were not associated with any major ethical challenges, the challenges which were identified were mostly related to the disease and to target groups. No studies specifically investigating ethics and SAD were found. Since SAD is a type of depression, SAD-related challenges were deemed equivalent to those associated with depression in general. Accordingly, the greatest ethical challenges relate to patients (vulnerability and prevention of harm), the disorder (SAD as a disease, stigma, underdiagnosis, medicalization, loss of autonomy), interventions, and comparator therapies (benefit-harm ratios).

6.1.1 Ethical challenges related to target patients

Many patients with SAD exhibit greater vulnerability: About half of them have a family history of psychiatric disorders, and many of them are prone to serotonergic comorbidities such as premenstrual syndrome, alcohol abuse, or excess weight [97,98]. Untreated depression is not only associated with psychological stress but can also jeopardize physical health. For instance, depression is associated with stress-related cerebral impairment [99,100] or coronary heart disease such as heart attacks [101]. Offering support to depression patients is therefore particularly important to prevent future harm and sequelae.

6.1.2 Ethical challenges related to the disorder

Is SAD a clinical picture or rather a “normal” part of winter? No societal consensus has been reached about this question due to common experiences with “winter fatigue” and biases against “ill-humoured individuals”, for which people with depression are often mistaken [102,103]. Patients reported healthcare providers’ lack of awareness as well as stigmatization as barriers to the recognition of SAD as a disorder (and possibly to its correct diagnosis) [104]. However, even patients expressed doubts as to whether listlessness, social withdrawal, and depressive moods might simply be part of winter, whether they actually represent a clinical picture or are unnecessarily medicalized [104]. When symptoms of depression become pathological, the patient’s autonomy and authentic personality are harmed due to a decrease in “energy, enthusiasm, concentration, hope, optimism, self-esteem, and self-respect” [102,105].

6.1.3 Ethical challenges related to the interventions

Although phototherapy and vitamin D therapy are associated with only minimal normative challenges, some ethical issues exist. Given a lack of data on the benefit and harm of vitamin D therapy, the benefit-harm ratio cannot be assessed. For phototherapy, any AEs must be taken into account alongside the indications of benefit, which are supported by metaanalyses [14]. Lack of SHI coverage of the service also promotes social inequality; both treatments require patient copayments [104]. Regarding comparator therapies, no conclusion can be drawn on the effectiveness of antidepressants when compared with placebo [23]. However, the benefit assessment showed a hint of fluoxetine being associated with more AEs than phototherapy. Patients also reported a dislike for taking antidepressants [104]. In the comparison of phototherapy versus cognitive behavioural therapy, neither was found to be superior. Both therapies require some time, but particularly the longer time period associated with cognitive behavioural therapy might represent an obstacle to patients experiencing an improvement in symptoms on time [104,106].

6.1.4 Ethical challenges related to the assessment

Ethical challenges related to this HTA include (1) disregarded comparator therapies, such as dietary changes or physical exercise, and (2) problems associated with the health economic analyses, e.g. their U.S.-centric perspective and the non-use of discounting and reference values. Any overestimates or underestimates of costs and cost effectiveness or any inappropriate transfer to the German healthcare context may affect price calculations, coverage decisions, and general treatment decisions in practice [84,85].

6.2 Results on social aspects

The information processing on social aspects was based on the comprehensive conceptional framework proposed by Mozygemba et al. 2016 [42]. Social aspects were evaluated based on 17 publications (studies, stakeholder websites) as well as insights gained from 2 patient interviews.

6.2.1 Social construct / perception of SAD

Both patients and psychiatrists typically perceive SAD as a biological rather than a psychological disorder [104]. This view also explains the idea of treating SAD with phototherapy and vitamin D therapy. Both measures aim to counteract lack of sunlight and its consequences. Psychological disorders such as depression are still less accepted in society than physical disorders and are often perceived as a personal weakness [107]. The focus on its biological causes could explain the lower stigmatization of SAD in society. Although diagnostic criteria have been established for SAD as a subtype of depression, doubts are widespread in society as to whether SAD actually represents a clinical picture or rather a

"normal" aspect of winter [103]. Patients view physicians as lacking awareness of SAD, a fact which can result in delayed or missed diagnosis and treatment of SAD [104].

6.2.2 Social image / perception of the intervention

Phototherapy: Patients expect phototherapy to alleviate or eliminate depressive symptoms, increase functioning in the private and professional environment, and improve their quality of life [104]. The phototherapy device is to replace lack of sunlight in the winter and eliminate any deficiencies.

Among physicians, knowledge about SAD and phototherapy as a potential treatment option seems to vary. While in the clinical setting, specialists often recommend phototherapy against SAD [28], patients paint a different picture for the general care setting. They themselves reportedly know little about treatment options such as phototherapy, expecting physicians to provide more information as well as support and consultation in the selection of phototherapy devices [104].

Patient acceptance of phototherapy is likely high, particularly since many people have a negative attitude toward drug therapies, while phototherapy represents a nondrug alternative. Patients expect fewer AEs from phototherapy than, for instance, from a regularly taken antidepressant. However, the application of phototherapy is time-intensive and, for some, difficult to incorporate into daily life. This might lead to low treatment adherence or even treatment discontinuation and reduce the acceptance of phototherapy [9,108].

Vitamin D therapy: Patients expect vitamin D therapy to reduce depressive symptoms. Vitamin D, which is not synthesized in the skin in winter, can be taken as a supplement to compensate for any deficiencies.

Specialists apparently do not consider vitamin D a treatment option for SAD. This is in line with the current recommendations of the National Disease Management Guideline for unipolar depression, which does not list vitamin D as a treatment option for SAD [13]. Only 3 of 100 surveyed hospitals in German-speaking countries reported recommending vitamin D to treat SAD [28]. According to patients, vitamin D was more often recommended due to an identified deficiency rather than due to SAD [104].

Vitamin D therapy is easily integrated into daily life, but the lack of evidence of its effectiveness against SAD represents a barrier to its being prescribed by physicians [104]. Even so, given the high sales figures of vitamin D preparations in Germany, the use of vitamin D as a nutritional supplement (regardless of the indication) is likely widespread in the population [109].

6.2.3 Sociocultural aspects of the use of the intervention

Phototherapy: Long-term use of phototherapy requires its integration into patients' daily routines. Potential problems mentioned by patients were lack of time in the mornings due to family obligations and conflicts with their work schedules, for instance due to shift work [92]. The fact that not all SHIs cover the cost of phototherapy might lead to social inequality since only individuals who can afford to pay for this intervention will use it [110,111].

Joint decision making by patients and physicians requires comprehensive knowledge about the disorder and the various treatment options. No cooperation between different healthcare professions is necessary, however, since phototherapy is typically self-administered by patients at home or independently at hospitals or physician's offices following a short briefing.

Vitamin D therapy: The use of vitamin D therapy can likely be implemented in the target group without any sociocultural influences. However, some individuals might conceivably dislike vitamin supplements. SHIs do not cover any costs for the use of vitamin D in SAD, which might lead to inequalities in utilization. Cooperation between healthcare professionals is necessary if blood work for vitamin D deficiency is performed in external laboratories. Vitamin D is taken by patients at home.

6.3 Results on legal aspects

Information processing on legal aspects was based on the guideline developed by Brönneke et al. 2016 [44] for the identification of legal aspects and drew upon 17 documents.

6.3.1 Informed consent to treatment and duty to provide information on phototherapy and vitamin D therapy as treatment alternatives

According to Section 630e clause 3 German Civil Code [112], the informed consent discussion must include alternatives to the suggested measure if multiple methods which are equally medically indicated and commonly used might lead to substantially different burdens, risks, or chances of healing. Therefore, every physician must inform patients about phototherapy and vitamin D therapy if they are equally medically indicated, are part of standard medical practice, and represent less "invasive" methods, e.g. by replacing antidepressants. This applies even more so if physicians offer phototherapy or work at a facility that offers phototherapy or vitamin D treatment as alternatives to antidepressants.

6.3.2 Medical confidentiality and data protection

Medical confidentiality is important in general and particularly in such a sensitive area. In addition, data protection regulations must be observed [113].

6.3.3 Market approval

According to applicable law, phototherapy devices are considered medical devices within the meaning of the Medical Devices Act and are subject to the corresponding rules [114].

The dosage of vitamin D preparations determines whether they are considered nutritional supplements or medicinal products: An expert committee established for this purpose concluded that up to a daily dose of 20 µg, vitamin D likely has a nutrition-specific and physiological effect. Therefore, preparations with a daily vitamin D dose of up to 20 µg can be classified as nutritional supplements – but only if they meet all food law requirements and if the recommended therapeutic indications do not justify their classification as medicinal products. Higher-dose preparations are considered medicinal products. Exceptions may apply to foods for special medical purposes in compliance with the associated directive [115,116]. If they serve to restore, correct, or modify physiological functions, provided such impact is substantial, vitamin D preparations are classified as medicinal products by presentation within the meaning of Section 2 (1) line 2a AMG (German Medicinal Products Act). If they are intended for the purposes of healing, alleviation, or prevention of said disorders, vitamin D preparations are classified as medicinal products by presentation within the meaning of Section 2 (1) line 1 AMG [115].

6.3.4 General legal bases for the reimbursement of costs within the public health system

Since phototherapy devices are not mentioned in HeilM-RL [76], they typically do not qualify for reimbursement. Medical devices are generally not eligible to be prescribed, but, where medically necessary in exceptional cases, they can be prescribed like drugs to be reimbursed by the SHI (positive list). The medical devices currently rated as such by the G-BA are listed in Annex V of its Pharmaceuticals Guideline. However, this list does not include any phototherapy devices for treating mild depression. After all, according to a frequently cited justification with reference to Section 12 SGB V, SHIs must not approve services unless they are adequate, appropriate, and efficient and do not exceed what is necessary [117]. Since sufficient outdoor exercise might lead to the same result, the costs of administering artificial light as in phototherapy are not covered.

As far as can be ascertained, even vitamin D preparations not deemed medicinal products are generally not reimbursable. According to the Pharmaceuticals Guideline, nonprescription drugs shall be prescribed if they are medically necessary, appropriate, and adequate for the treatment of a disorder. The cost of vitamin D treatment is covered only in specified exceptional cases (“Approved exceptions from the exclusion of nonprescription drugs from the SHI benefit package”) – which do not include SAD treatment with vitamin D.

6.4 Results on organizational aspects

The information processing on organizational aspects followed the grid template proposed by Perleth et al. 2014 [43] for the assessment of organizational consequences of treatment methods. The evaluation of organizational aspects was based on 7 publications (studies, guideline, stakeholder websites).

6.4.1 Influence on the prerequisites of service provision

Phototherapy: Phototherapy can be either self-administered by patients at their homes [16] or provided on an outpatient basis in medical offices or hospitals offering phototherapy. The application of phototherapy requires no formal qualifications, but physicians must be able to diagnose SAD, be aware of the option of using phototherapy devices, and purchase a phototherapy device. No additional staff is needed since phototherapy can be self-administered by patients. Where phototherapy is offered by physicians in hospitals and practices, a professional must provide brief initial instructions to the patient and make a room available.

Vitamin D therapy: Vitamin D is self-administered in the form of tablets, capsules, and droplets by patients at their homes [118]. Physicians do not require any additional qualifications for prescribing vitamin D, but laboratory tests are initially needed to establish vitamin D deficiency. However, it must be noted that SAD currently does not represent an indication for vitamin D therapy and this HTA report did not find any studies proving the efficiency and safety of vitamin D therapy in SAD.

6.4.2 Influence on processes

Phototherapy: Despite the fact that the National Disease Management Guideline lists both phototherapy and antidepressants as first-line therapies for SAD [13], SHIs cover the costs of antidepressants – but not of phototherapy. In Germany, antidepressant therapy is the most common treatment method for acute SAD [28]. An increased use of the nondrug alternative of phototherapy would not be expected to result in any service provider rearrangements since it involves the same healthcare professionals as antidepressant therapy. No additional forms of communication would be needed since its administration does not require coordination with other service providers.

Vitamin D therapy Vitamin D is not listed as a treatment option in SAD [13]. More widespread supplementation with vitamin D might put pressure on resources since it requires more laboratory testing for vitamin D deficiency. For this purpose, physicians who do not have their own laboratory must collaborate with an external laboratory.

7 Synthesis of results

The overarching question of whether nondrug interventions such as phototherapy and vitamin therapy might lead to better outcomes in SAD can be answered only in part because studies were found on phototherapy, but not on vitamin D therapy. Below, the domain-specific results are presented and synthesized.

For phototherapy with patient-facing light boxes, indications of benefit were derived. Patients using such light boxes responded more frequently to therapy, were more successful in achieving remission of depression, and reported less severe symptoms of depression at the end of the intervention than patients receiving sham treatment. However, it must be noted that the studies suffered from a high risk of bias as well as a risk of random errors due to small study sizes. In addition, slightly less than half of users neither showed any response nor achieved remission despite phototherapy. For phototherapy with HMUs, no hint of benefit was derived, and for dawn simulation, a hint of benefit was derived only for the outcome of response [45–47,49–51,53,56–58,60,67,68,70–73].

In direct comparison with other treatment options, no hint can be derived of light box therapy having any greater benefit than the antidepressant fluoxetine or cognitive behavioural therapy [54,55,59,60,62,66]. Response or remission rates for all 3 interventions were around 50%, but the confidence intervals were broad. Overall, AEs such as headache or eye pain were reported only in isolated cases. There is no hint of phototherapy being more likely to lead to AEs than placebo [46,47,57,67,71,73]. Since the studies surveyed AEs only until the end of the intervention, it is not possible to assess any long-term harm of phototherapy, e.g. permanent eye damage. However, there is a hint of certain AEs being more commonly caused by fluoxetine treatment than by phototherapy [54,55]. Light box therapy is therefore likely associated with a short-term benefit regarding depression-related outcomes and with few short-term AEs. However, the long-term effects of light box therapy are unknown.

No studies were found on the outcome of mortality. Since only 1 study each reported the outcomes of functioning and health-related quality of life, no meaningful conclusions about the benefit of the interventions can be drawn with regard to these outcomes.

The health economic systematic review found 2 health economic studies, but they failed to meet the central methodological standards. Due to the U.S. setting and a lack of relevant comparators, these studies were of very limited informative value and their conclusions are not transferable to the German healthcare system. However, it was possible to calculate intervention costs for the German healthcare context.

Phototherapy can be administered either at home or on an outpatient basis at a hospital or medical practice. When administered at a practice or hospital, a set of 28 sessions at

40 minutes each costs patients between EUR210 and 390.32. Phototherapy is typically an out-of-pocket service and is reimbursed by few SHIs. In case of therapy at home with the patient's own device, costs primarily include the device's purchase price, ranging from EUR59.99 to EUR430. The initial and final consultations cost about EUR102 extra. However, some SHIs offer a (partial) reimbursement in this case as well. Vitamin D therapy is not reimbursable for the indication of SAD [80]. The intervention costs for 8 weeks of vitamin D therapy include 50 vitamin D soft capsules at a dose of 20 000 IU each as well as an additional ligand-binding assay plus the costs of psychiatric care, for a total of approximately EUR182. In terms of the intervention costs of the comparator therapies, the focus was on SSRI treatment with fluoxetine as well as cognitive behavioural therapy since, in the benefit assessment, studies were found only on these two interventions. For fluoxetine therapy (acute treatment and follow-up), the reimbursable costs ranged from EUR184.91 to 185.10. The total cost of cognitive behavioural therapy is EUR1115.23 in a group of 4, EUR834.67 in a group of 8, and EUR1359.92 in individual therapy. This cost can be billed to the SHI.

The focus on biological causes might lead to SAD being less stigmatized in society than nonseasonal depression. However, societal doubts as to whether SAD is actually a clinical picture or a "normal" part of winter represent ethical and social challenges [103]. Patients report perceiving physicians as lacking awareness of SAD, which might lead to delayed or missed diagnosis and late or no treatment of SAD [104]. Considering the greater vulnerability of many SAD patients, protecting them is particularly important.

Patient acceptance of phototherapy is likely high, particularly because it represents a nondrug alternative and many people have negative attitudes toward drug therapies [9,108]. Given the high sales of vitamin D preparations in Germany, the acceptance of vitamin D in the general population seems equally high [10]. In this context, the ethical and social challenge is the lack of SHI coverage of phototherapy and vitamin D therapy, while the cost of comparator therapies such as fluoxetine or cognitive behavioural therapy are covered. In acute SAD, drug therapy with antidepressants is recommended most frequently [28], despite the fact that the benefit assessment failed to show a hint of greater benefit of antidepressants in comparison with phototherapy in SAD patients.

A particularly relevant issue from a legal perspective is for physicians to inform patients about nondrug SAD treatment options, such as phototherapy. While specialists in the clinical setting often recommend phototherapy to SAD patients [28], patients report that this is not yet the case in the general practice setting. In addition, patients expect to receive more information as well as support and consultation in the selection of light devices [104].

From an organizational perspective, the implementation of phototherapy and vitamin D therapy does not require more personnel because both therapies can be independently implemented by the patient. An increased use of phototherapy in hospitals or practices is not

expected to lead to any shifts in services because the same healthcare professionals responsible for these therapies are also responsible for antidepressant therapy. No further forms of communication would be needed, because the treatment methods do not require any coordination with other service providers.

7.1 Cross-domain discussion

When compared to sham treatment, light box therapy is likely associated with a benefit in the treatment of SAD. Due to the limited available evidence for this comparison, it remains unclear whether phototherapy is more or less effective than alternative treatments (fluoxetine, cognitive behavioural therapy). Depending on the device cost, the intervention costs for phototherapy are similar to those of antidepressant therapy and lower than those for cognitive behavioural therapy. Unlike the costs of antidepressant therapy, the costs of phototherapy are incurred only once. Nevertheless, SHIs typically do not cover the costs of phototherapy, a fact which can not only influence the choice of treatment, but also promote social inequality. Phototherapy is generally well-accepted. Patients expect fewer AEs from phototherapy than from antidepressants, for instance. If phototherapy is to be effective, it must be integrated into patients' daily routines. Informed decision-making requires that physicians be more aware of SAD and provide more information about the disorder as well as its treatment options.

Vitamin D therapy is a relatively inexpensive intervention which is associated with few ethical, organizational, and social challenges. However, there is no evidence of vitamin D being an effective and safe treatment for SAD: The benefit assessment did not find any study on this topic. Even the National Disease Management Guideline for unipolar depression does not list vitamin D as a treatment option for SAD [13].

8 Discussion

8.1 HTA report compared with other publications

A 2017 systematic review showed that phototherapy has a favourable effect on symptoms of depression and the circadian rhythm. The review included RCTs as well as observational studies and nonrandomized interventional studies [119]. Another systematic review which included only RCTs likewise concluded that phototherapy is effective for SAD treatment and can reduce the severity of depression symptoms when compared with placebo [29]. The effect sizes of phototherapy were similar to those of antidepressant therapy. The review did not survey AEs [29]. Yet another systematic review based on RCTs on morning phototherapy with white light showed a minor favourable effect resulting from the reduction of symptoms of depression. The authors critically noted, however, that the included studies were of poor quality [120]. The results of the other systematic reviews are consistent with the findings of the present benefit assessment. Based on studies with largely high risk of bias, the benefit assessment also revealed a minor favourable effect of light box therapy on depression-related outcomes.

The studies included in this HTA report observed few AEs in patients receiving phototherapy. According to a systematic review which investigated explicitly eye-specific AEs of phototherapy, between 0% and 45% of patients, depending on the study, had eye complaints due to phototherapy. However, there was no evidence of phototherapy causing eye injury. The authors see a need for further research on patients with existing eye disorders and patients taking photosensitizing medications [121].

A Cochrane Review compared phototherapy versus antidepressants (fluoxetine) in SAD treatment. The review identified the same RCTs which were included in the present HTA report. The studies were inconclusive as to whether phototherapy or antidepressant therapy works better against SAD [23].

The present HTA report did not find any studies on vitamin D therapy of SAD. A 2017 systematic review [122] reported on an RCT in which 8 SAD patients received 100 000 IU of vitamin D and 7 SAD patients received phototherapy [21]. After 1 week, the reduction of depressive symptoms was greater on vitamin D therapy than on phototherapy, but since the intervention period was shorter than 2 weeks, the study was excluded from this HTA report.

8.2 HTA report compared with guidelines

The AMWF National Disease Management Guideline for unipolar depression recommends phototherapy and antidepressants (SSRI) as first-line therapies for SAD [13]. For phototherapy, it recommends using patient-facing light boxes. The present HTA report revealed an indication of their benefit. While the guideline recommends using devices

emitting fluorescent white light of at least 2500 lux in the mornings, the present HTA also included studies with phototherapy devices emitting lower lux levels (at least 300), different light colours, and therapy at different times of day. However, those studies were in the minority.

The National Disease Management Guideline [13] does not mention vitamin D as a treatment option and therefore does not take a stance in favour or against taking vitamin D – neither in the treatment of SAD nor in the treatment of nonseasonal depression. This is consistent with the evidence gap identified in this regard by this HTA report.

The British National Institute for Health and Care Excellence guideline recommends antidepressant and psychotherapy for the treatment of depression and recommends treating all types of depression in the same way. It explicitly states that SAD patients should be made aware of the uncertain evidence regarding the effectiveness of phototherapy due to the studies being mostly small and barely conclusive [123].

8.3 Critical reflection on the approach used

During the HTA process, necessary specifications were made regarding the intervention and comparator intervention; these specifications facilitate the HTA, but adversely impact its informative value. The term “vitamin therapies” was narrowed down to vitamin D therapy because vitamin D deficiency in the winter months is believed to be a potential cause of the development of SAD [12]. Other SAD-related vitamin therapies were disregarded. As comparator therapies, placebo, no therapy, and active interventions recommended for the treatment of SAD were included, namely second-generation antidepressants and psychotherapeutic measures recognized in Germany [13]. Other measures, such as a change in diet or outdoor exercise were not included as comparator interventions, and therefore, no conclusions can be drawn about them.

For phototherapy, an inclusive approach was taken. Since the HTA report focused on phototherapy in general, different forms and applications of phototherapy (lux level, device type, light colour, time and duration of phototherapy) were included. Nevertheless, a post-hoc subgroup analysis by type of phototherapy was conducted to permit more specific conclusions on its effectiveness. In general, thresholds had to be defined as to the conditions under which phototherapy was deemed an active intervention versus placebo. This report used the threshold of 400 lux, loosely following the definition in the systematic review by Golden 2005 [29]. Even if studies classified the use of a light box emitting less than 300 lux as an active intervention, it was considered a placebo for the purposes of this HTA since the lux level was below the defined threshold. On the other hand, any placebos defined as such by study authors were deemed placebos in this HTA, even if thresholds deviated; for instance, the placebo lamp emitted 500 lux in one study [72] and 400 lux in another [68]. Consequently,

the lux levels in these interventions, which were classified as placebo, were higher or equal to the “active phototherapy” of another study, at 400 lux [51]. These types of interventions with 400 and 500 lux lamps can also be viewed as low-dose phototherapy. Using low-dose active therapy as the placebo leads to the effect of phototherapy being underestimated. Comparing low-dose active therapy with placebo likewise underestimates the effect of phototherapy. The fact that an indication of greater benefit of phototherapy was nevertheless found under these conditions underscores its effectiveness.

The patient interviews revealed that depression-related outcomes such as response or remission were relevant from the patient perspective. In the literature, response is often defined as a 50% reduction of the baseline depression score, while remission requires a 50% reduction as well as achievement of a score not to exceed a defined threshold. Studies have shown that this operationalization is valid for various scales [124,125].

As one of the inclusion criteria, an intervention period of at least 2 weeks was specified. This decision was made in consultation with the clinical expert Dr Maximilian Huhn and with the intention to ensure that any observed effects were actually due to the intervention – which would be unlikely in case of a shorter intervention period. This specification is the reason why studies of a shorter intervention period were disregarded in this HTA.

9 Conclusion

Twenty-one studies on SAD treatment with data on a total of 1441 adults were found. Sixteen studies compared phototherapy versus placebo, 3 versus cognitive behavioural therapy, and 2 versus the antidepressant fluoxetine. No studies were found which compared phototherapy versus other types of psychotherapy or different antidepressants. For phototherapy, 4 studies used an HMU, while the others used light boxes. Two studies investigated the effect of dawn simulation as well as light box therapy. No studies were found on SAD treatment with vitamin D. Therefore, no conclusions can be drawn on the effectiveness and safety of vitamin D therapy against SAD.

A joint analysis of all types of phototherapy versus placebo resulted in no hint of benefit for the outcomes of response, remission of depression, severity of depressive symptoms, functioning, or AEs. No data are available on the outcomes of mortality or health-related quality of life. Subgroup analyses evaluating light box therapy separately from phototherapy with HMUs differ in results. There are hints of a short-term benefit of light box therapy in comparison with placebo with regard to depression-related outcomes (response, remission, severity of depressive symptoms). There is no hint of any difference in the number of AEs or changes in cognitive functioning. For phototherapy with HMUs, in contrast, no hint of any benefit can be derived with regard to response, remission, severity of depressive symptoms, or AEs. Regarding the outcome of functioning, no data are available for this comparison.

For dawn simulation versus placebo, there is a hint of benefit with regard to response, but none for remission, severity of depressive symptoms, or AEs. No data are available for this comparison regarding the outcomes of mortality, functioning, and health-related quality of life.

In general, long-term effects of phototherapy in comparison with placebo remain unknown since the outcomes were surveyed at the end of the intervention period of 2 to 8 weeks.

A direct comparison with other treatment options provides no hint of light box therapy being of greater benefit in SAD treatment than the antidepressant fluoxetine or cognitive behavioural therapy. After 5 to 8 weeks, all 3 interventions were associated with response or remission rates of about 50%, and the severity of depressive symptoms was comparable. Two studies additionally investigated the long-term effect of light box therapy versus cognitive behavioural therapy, showing similar remission rates after 1 year. There is a hint of fluoxetine causing more AEs during treatment than light box therapy. No such hint was found for cognitive behavioural therapy. Regarding mortality and functioning, no data were available for either the comparison of phototherapy versus fluoxetine nor for phototherapy versus cognitive behavioural therapy. Data on health-related quality of life are available only for the comparison of phototherapy versus fluoxetine, and these data do not provide any hint of

greater benefit of phototherapy. No conclusions can be drawn on the benefit and harm of phototherapy in comparison with other antidepressants or other types of psychotherapy because no studies were found on these topics.

At a light box price of EUR100, the intervention costs for 4 weeks of light box therapy, including consultations, amounts to approximately EUR202. Hence, the costs are similar to those of 6 weeks of antidepressant therapy with fluoxetine (approx. EUR184.91 to EUR190.10), but lower than those of cognitive behavioural therapy. The total costs of 4 weeks of cognitive behavioural therapy, administered twice weekly, equal EUR834.67 in a group of 8 and EUR1359.92 for individual therapy. At about EUR182, vitamin D therapy is associated with the lowest intervention costs. In this context, it is worth noting that the cost of a phototherapy device is incurred only once, which is relevant in case of a recurrence of depressive episodes in subsequent winters.

The 2 identified health economic studies compared phototherapy versus cognitive behavioural therapy or no treatment. They were conducted in the United States and the informative value was considerably lower due to methodological limitations. Therefore, their results are not transferable to the German healthcare system.

Currently, German SHIs typically do not cover the costs of phototherapy or vitamin D therapy, while they do cover the costs of treatment with antidepressants and psychotherapy. Drug therapy with antidepressants is currently the most common treatment method for acute SAD. Lack of coverage of therapies can not only influence the choice of treatment, but also promote social inequalities.

Ethical and social challenges related to SAD particularly include societal doubts as to whether SAD is actually a clinical picture or represents a “normal” part of the dark season. In this context, physician awareness of SAD should be promoted in order to prevent its diagnosis or treatment from being delayed or missed. Physicians are also required by law to inform patients about all available treatment options for SAD and to obtain informed consent to treatment. From an organizational perspective, the implementation of phototherapy and vitamin D therapy does not require more personnel, because both therapies can be self-administered by the patient.

References

Please see full HTA report for the full reference list.

1. Rosenthal NE, Sack DA, Gillin J, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984; 41(1): 72-80.

2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva, Switzerland: World Health Organization; 1993.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013.

4. Tam EM, Lam RW, Robertson HA, Stewart JN, Yatham LN, Zis AP. Atypical depressive symptoms in seasonal and non-seasonal mood disorders. J Affect Disord 1997; 44(1): 39-44.

5. Partonen T, Rosenthal N. Diagnostic assessment. In: Partonen T, Pandi-Perumal SR (Ed). Seasonal affective disorder practice and research. New York: Oxford University Press; 2010. p. 247-254.

6. Rastad C, Wetterberg L, Martin C. Patients' experience of winter depression and light room treatment. Psychiatry J 2017; 2017: 6867957.

7. Wirz-Justice A, Graw P, Krauchi K, Wacker HR. Seasonality in affective disorders in Switzerland. Acta Psychiatr Scand Suppl 2003; (418): 92-95.

8. Pjrek E, Baldinger-Melich P, Spies M, Papageorgiou K, Kasper S, Winkler D. Epidemiology and socioeconomic impact of seasonal affective disorder in Austria. Eur Psychiatry 2016; 32: 28-33.

9. Schwartz PJ, Brown C, Wehr TA, Rosenthal NE. Winter seasonal affective disorder: a follow-up study of the first 59 patients of the National Institute of Mental Health Seasonal Studies Program. Am J Psychiatry 1996; 153(8): 1028-1036.

10. Magnusson A, Partonen T. The diagnosis, symptomatology, and epidemiology of seasonal affective disorder. CNS Spectr 2005; 10(8): 625-634.

11. Levitan RD. The chronobiology and neurobiology of winter seasonal affective disorder. Dialogues Clin Neurosci 2007; 9(3): 315-324.

12. Rimaldi S, Partonen T. Self-care options. In: Partonen T, Pandi-Perumal SR (Ed). Seasonal affective disorder practice and research. New York: Oxford University Press; 2010. p. 321-329.

13. DGPPN, BÄK, KBV, AWMF, AKDÄ, BPTK et al. S3-Leitlinie/Nationale VersorgungsLeitlinie: Unipolare Depression; Langfassung. Deutschland: DGPPN BÄK KBV AWMF AdkÄ BPtK BApK DAGSHG DEGAM DGPM DGPs DGRW für die Leitliniengruppe Unipolare Depression; 2015.

14. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectr 2005; 10(8): 647-663; quiz 672.

15. Levitan RD. What is the optimal implementation of bright light therapy for seasonal affective disorder (SAD)? J Psychiatry Neurosci 2005; 30(1): 72-72.

16. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N et al. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology 2011; 64(3): 152-162.

17. Danilenko KV, Ivanova IA. Dawn simulation vs. bright light in seasonal affective disorder: treatment effects and subjective preference. J Affect Disord 2015; 180: 87-89.

18. Terman M, Schlager D, Fairhurst S, Perlman B. Dawn and dusk simulation as a therapeutic intervention. Biol Psychiatry 1989; 25(7): 966-970.

19. Avery D, Bolte MA, Millet M. Bright dawn simulation compared with bright morning light in the treatment of winter depression. Acta Psychiatr Scand 1992; 85(6): 430-434.

20. Lingjaerde O, Foreland AR, Dankertsen J. Dawn simulation vs. lightbox treatment in winter depression: a comparative study. Acta Psychiatr Scand 1998; 98(1): 73-80.

21. Gloth FM 3rd, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nutr Health Aging 1999; 3(1): 5-7.

22. Neumeister A, Konstantinidis A, Praschak-Rieder N, Willeit M, Hilger E, Stastny J et al. Monoaminergic function in the pathogenesis of seasonal affective disorder. Int J Neuropsychopharmacol 2001; 4(4): 409-420.

23. Thaler K, Delivuk M, Chapman A, Gaynes BN, Kaminski A, Gartlehner G. Second-generation antidepressants for seasonal affective disorder. Cochrane Database Syst Rev 2011; (12): CD008591.

24. Young M, Yap B. Psychological and biological traits in seasonal affective disorder and seasonality. In: Partonen T, Pandi-Perumal SR (Ed). Seasonal affective disorder practice and research. New York: Oxford University Press; 2010. p. 189-208..

25. Rohan KJ, Meyerhoff J, Ho SY, Evans M, Postolache TT, Vacek PM. Outcomes one and two winters following cognitive-behavioral therapy or light therapy for seasonal affective disorder. Am J Psychiatry 2016; 173(3): 244-251.

26. Gemeinsamer Bundesausschuss (G-BA). Richtlinie des Gemeinsamen Bundesausschusses über die Durchführung der Psychotherapie [online]. 16.02.2017 [Accessed: 12.11.2018]. URL: https://www.g-ba.de/downloads/62-492-1266/PT-RL_2016-11-24_iK-2017-02-16.pdf.

27. Gemeinsamer Bundesausschuss (G-BA). Systemische Therapie: Anerkennung des Nutzens und der medizinischen Notwendigkeit als Psychotherapieverfahren [online]. 22.11.2018 [Accessed: 04.12.2018]. URL: https://www.g-ba.de/informationen/beschluesse/3588/.

28. Nussbaumer-Streit B, Winkler D, Spies M, Kasper S, Pjrek E. Prevention of seasonal affective disorder in daily clinical practice: results of a survey in German-speaking countries. BMC Psychiatry 2017; 17(1): 247.

29. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry 2005; 162(4): 656-662.

30. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. [GA17-01] Steigerung der Effizienz der Studienselektion [online]. [Accessed: 12.09.2018]. URL: https://www.iqwig.de/de/projekte-ergebnisse/projekte/institutsleitung/ga17-01-steigerung-der-effizienz-der-studienselektion.7847.html.

31. Schwarzer G. Meta: an R package for meta-analysis. R News 2007; 7(3): 40-45.

32. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. Netmeta: network meta-analysis using frequentist methods. 2019.

33. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.

34. Statistisches Bundesamt. Harmonisierter Verbraucherpreisindex (inkl. Veränderungsraten) [online]. [Accessed: 17.05.2019]. URL: https://www-genesis.destatis.de/genesis/online.

35. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.

36. The World Bank. World Bank country and lending groups [online]. [Accessed: 22.01.2018]. URL: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

37. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Int J Technol Assess Health Care 2013; 29(2): 117-122.

38. International Society for Pharmacoeconomics and Outcomes Research. Assessing the evidence for health care decision makers [online]. [Accessed: 05.11.2018]. URL: https://www.healthstudyassessment.org/.

39. European Network for Health Technology Assessment. EUnetHTA HTA adaptation toolkit: work package 5; version 5 [online]. 10.2011 [Accessed: 06.08.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2011/01/EUnetHTA_adptation_toolkit_2011_version_5.pdf.

40. Hofmann B, Droste S, Oortwijn W, Cleemput I, Sacchini D. Harmonization of ethics in health technology assessment: a revision of the Socratic approach. Int J Technol Assess Health Care 2014; 30(1): 3-9.

41. Lysdahl KB, Mozygemba K, Chilcott JB, Brönneke JB, Hofmann Be. Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in compley technologies [online]. URL: https://www.integrate-hta.eu/downloads/.

42. Mozygemba K, Hofmann B, Bakke Lysdal K, Pfadenhauer L, Van der Wilt G, Gerhardus A. Guidance to assess socio-cultural aspects [online]. In: Lysdahl KB, Mozygemba K, Burns L, Chilcott JB, Brönneke JB, Hofmann B (Ed). Guidance for assessing effectiveness, economic aspects, ehtical aspects, socio-cultural aspects and legal aspects in complex technologies. 01.02.2016 [Accessed: 06.08.2018]. URL: http://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

43. Perleth M, Gibis B, Velasco Garrido M, Zentner A. Organisationsstrukturen und Qualität. In: Perleth M, Busse R, Gerhardus A, Gibis B, Zentner A (Ed). Health Technology Assessment: Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014. p. 265-279.

44. Brönneke JB, Hofmann B, Bakke Lysdal K, Van der Wilt G, Buchner B. Guidance to assess legal aspects [online]. In: Lysdahl KB, Mozygemba K, Burns L, Chilcott JB, Brönneke JB, Hofmann B (Ed). Guidance for assessing effectiveness, economic aspects, ehtical aspects, socio-cultural aspects and legal aspects in complex technologies. 01.02.2016 [Accessed: 06.08.2018]. URL: http://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

45. Anderson JL, Glod CA, Dai J, Cao Y, Lockley SW. Lux vs. wavelength in light treatment of seasonal affective disorder. Acta Psychiatr Scand 2009; 120(3): 203-212.

46. Avery DH, Eder DN, Bolte MA, Hellekson CJ, Dunner DL, Vitiello MV et al. Dawn simulation and bright light in the treatment of SAD: a controlled study. Biol Psychiatry 2001; 50(3): 205-216.

47. Desan PH, Weinstein AJ, Michalak EE, Tam EM, Meesters Y, Ruiter MJ et al. A controlled trial of the Litebook light-emitting diode (LED) light therapy device for treatment of seasonal affective disorder (SAD). BMC Psychiatry 2007; 7: 38.

48. Yale University. Environmental treatment for seasonal affective disorder (SAD): study results [online]. In: ClinicalTrials.gov. 06.03.2013 [Accessed: 07.03.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00139997.

49. Eastman CI, Lahmeyer HW, Watell LG, Good GD, Young MA. A placebo-controlled trial of light treatment for winter depression. J Affect Disord 1992; 26(4): 211-221.

50. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: a placebo-controlled trial. Arch Gen Psychiatry 1998; 55(10): 883-889.

51. Glickman G, Byrne B, Pineda C, Hauck WW, Brainard GC. Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). Biol Psychiatry 2006; 59(6): 502-507.

52. Joffe RT, Moul DE, Lam RW, Levitt AJ, Teicher MH, Lebegue B et al. Light visor treatment for seasonal affective disorder: a multicenter study. Psychiatry Res 1993; 46(1): 29-39.

53. Levitt AJ, Joffe RT, Moul DE, Lam RW, Teicher MH, Lebegue B et al. Side effects of light therapy in seasonal affective disorder. Am J Psychiatry 1993; 150(4): 650-652.

54. Lam RW, Levitt AJ, Levitan RD, Enns MW, Morehouse R, Michalak EE et al. The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry 2006; 163(5): 805-812.

55. Michalak EE, Murray G, Levitt AJ, Levitan RD, Enns MW, Morehouse R et al. Quality of life as an outcome indicator in patients with seasonal affective disorder: results from the Can-SAD study. Psychol Med 2007; 37(5): 727-736.

56. Levitt AJ, Joffe RT, King E. Dim versus bright red (light-emitting diode) light in the treatment of seasonal affective disorder. Acta Psychiatr Scand 1994; 89(5): 341-345.

57. Levitt AJ, Wesson VA, Joffe RT, Maunder RG, King EF. A controlled comparison of light box and head-mounted units in the treatment of seasonal depression. J Clin Psychiatry 1996; 57(3): 105-110.

58. Michalon M, Eskes GA, Mate-Kole CC. Effects of light therapy on neuropsychological function and mood in seasonal affective disorder. J Psychiatry Neurosci 1997; 22(1): 19-28.

59. Rohan KJ, Lindsey KT, Roecklein KA, Lacy TJ. Cognitive-behavioral therapy, light therapy, and their combination in treating seasonal affective disorder. J Affect Disord 2004; 80(2-3): 273-283.

60. Rohan KJ, Roecklein KA, Tierney Lindsey K, Johnson LG, Lippy RD, Lacy TJ et al. A randomized controlled trial of cognitive-behavioral therapy, light therapy, and their combination for seasonal affective disorder. J Consult Clin Psychol 2007; 75(3): 489-500.

61. Henry M. Jackson Foundation for the Advancement of Military Medicine. cognitive behavioral therapy for the treatment of seasonal affective disorder (SAD): study details [online]. In: ClinicalTrials.gov. 25.06.2014 [Accessed: 07.03.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT00076245.

62. Rohan KJ, Mahon JN, Evans M, Ho SY, Meyerhoff J, Postolache TT et al. Randomized trial of cognitive-behavioral therapy versus light therapy for seasonal affective disorder: acute outcomes. Am J Psychiatry 2015; 172(9): 862-869.

63. Rohan KJ, Evans M, Mahon JN, Sitnikov L, Ho SY, Nillni YI et al. Cognitive-behavioral therapy vs. light therapy for preventing winter depression recurrence: study protocol for a randomized controlled trial. Trials 2013; 14: 82.

64. Rohan KJ, Meyerhoff J, Ho SY, Evans M, Postolache TT, Vacek PM. Outcomes one and two winters following cognitive-behavioral therapy or light therapy for seasonal affective disorder. Am J Psychiatry 2016; 173(3): 244-251.

65. University of Vermont. Cognitive-behavioral therapy vs. light therapy for preventing SAD recurrence: study details [online]. In: ClinicalTrials.gov. 26.02.2014 [Accessed: 07.03.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT01714050.

66. Ruhrmann S, Kasper S, Hawellek B, Martinez B, Hoflich G, Nickelsen T et al. Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. Psychol Med 1998; 28(4): 923-933.

67. Spezzano Mark A. The efficacy of bright light treatment on the symptoms of seasonal affective disorder on a college-aged population. Diss Abstr Int 2007; 67(9-b): 5423.

68. Spies M, James GM, Vraka C, Philippe C, Hienert M, Gryglewski G et al. Brain monoamine oxidase A in seasonal affective disorder and treatment with bright light therapy. Transl Psychiatry 2018; 8(1): 198.

69. Medical University of Vienna. Influence of light exposure on cerebral MAO-A in seasonal affective disorder and healthy controls measured by PET: study details [online]. In: ClinicalTrials.gov. 05.05.2018 [Accessed: 07.03.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02582398.

70. Teicher MH, Glod CA, Oren DA, Schwartz PJ, Luetke C, Brown C et al. The phototherapy light visor: more to it than meets the eye. Am J Psychiatry 1995; 152(8): 1197-1202.

71. Terman M, Terman JS. Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder.[Erratum appears in Am J Psychiatry. 2007 Mar;164(3):529]. Am J Psychiatry 2006; 163(12): 2126-2133.

72. Wileman SM, Eagles JM, Andrew JE, Howie FL, Cameron IM, McCormack K et al. Light therapy for seasonal affective disorder in primary care: randomised controlled trial. Br J Psychiatry 2001; 178: 311-316.

73. Yale University. A trial of negative ion generation versus light-emitting diode phototherapy for seasonal affective disorder (SAD): study results [online]. In: ClinicalTrials.gov. March 6, 2013 [Accessed: 07.03.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00809523.

74. Universitätsmedizin der Johannes-Gutenberg-Universität Mainz. Lichttherapie [online]. [Accessed: 17.05.2019]. URL: http://www.unimedizin-mainz.de/psychiatrie/patienten/weitere-behandlungsangebote/lichttherapie.html.

75. Bundesministerium der Justiz und für Verbraucherschutz - Gesetze im Internet. Sozialgesetzbuch (SGB) Fünftes Buch (V) - Gesetzliche Krankenversicherung - (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477) § 61 Zuzahlungen [online]. [Accessed: 18.05.2019]. URL: https://www.gesetze-im-internet.de/sgb_5/__61.html.

76. Gemeinsamer Bundesausschuss (G-BA). Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung - Heilmittel-Richtlinie/HeilM-RL [online]. Letzte Änderung: 21.09.2017 BAnz AT 23.11.2017 B1, In Kraft getreten am: 01.01.2018 [Accessed: 16.05.2019]. URL: https://www.g-ba.de/downloads/62-492-1484/HeilM-RL_2017-09-21_iK-2018-01-01.pdf.

77. MediSana GmbH. Lichttherapie-Lampen [online]. [Accessed: 13.05.2019]. URL: https://www.medisana.de/Therapieprodukte/Lichttherapie-Lampen/Tageslichtlampen-Lichtduschen/.

78. Beurer GmbH. Tageslichtlampen [online]. [Accessed: 13.05.2019]. URL: https://www.beurer.com/web/de/produkte/wellbeing/lichttherapie/tageslichtlampen/.

79. mhplus Krankenkasse. Lichttherapie: Anwendungsgebiete und Wirkungsweisen. [online]. [Accessed: 13.05.2019]. URL: https://www.mhplus-krankenkasse.de/privatkunden/gesundheits_leistungen/versorgung_plus/psychische_erkrankungen/lichttherapie/.

80. Gemeinsamer Bundesausschuss (G-BA). Arzneimittelrichtlinie des G-BA, Anlage I: OTC-Übersicht [online]. [Accessed: 12.06.2019]. URL: https://www.g-ba.de/richtlinien/anlage/17/.

81. Dr. Maximilian Huhn. Korrespondenz zu Interventionskosten bzw. klinischem Behandlungsablauf am 23.05., 22.06., 24.06., 28.06.2019. 2019.

82. Praschak-Rieder N, Willeit M. Treatment of seasonal affective disorders. Dialogues Clin Neurosci 2003; 5(4): 389-398.

83. Avery D. Seasonal affective disorder: treatment [online]. In: UpToDate. 09.11.2017 [Accessed: 20.05.2019]. URL: https://www.uptodate.com/contents/seasonal-affective-disorder-treatment.

84. Ross LM. Cost-benefit and cost-utility analyses of cognitive-behavioral therapy versus light therapy for seasonal affective disorder [Dissertation]. Washington, D.C.: American University; 2017 URL: http://hdl.handle.net/1961/auislandora:68591.

85. Freed MC. Costs and cost-effectiveness of seasonal affective disorder treatment: comparing light therapy, group cognitive-behavioral therapy, and their combination [Dissertation]. Washington, D.C.: American University; 2005. URL: http://hdl.handle.net/1961/thesesdissertations:3193.

86. Walbert H. With IGeL (individual health allowance) against winter blues. MMW Fortschr Med 2009; 151(45): 11.

87. Cheung A, Dewa C, Michalak EE, Browne G, Levitt A, Levitan RD et al. Direct health care costs of treating seasonal affective disorder: a comparison of light therapy and fluoxetine. Depression Research and Treatment 2012; 2012: 628434.

88. Freed MC, Rohan KJ, Yates BT. Estimating health utilities and quality adjusted life years in seasonal affective disorder research. J Affect Disord 2007; 100(1-3): 83-89.

89. Rohan KJ, Mahon JN, Evans M, Ho SY, Meyerhoff J, Postolache TT et al. Randomized trial of cognitive-behavioral therapy versus light therapy for seasonal affective disorder: acute outcomes. Am J Psychiatry 2015; 172(9): 862-869.

90. Drummond M, Sculpher M. Common methodological flaws in economic evaluations. Med Care 2005; 43(7): II5-II14.

91. Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. J Affect Disord 1998; 48(1): 25-36.

92. Kolovos S, Bosmans JE, van Dongen JM, van Esveld B, Magai D, Van Straten A et al. Utility scores for different health states related to depression: individual participant data analysis. Qual Life Res 2017; 26(7): 1649-1658.

93. nstitute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 06.08.2020]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

94. Antonuccio DO, Thomas M, Danton WG. A cost-effectiveness analysis of cognitive behavior therapy and fluoxetine (prozac) in the treatment of depression. Behav Ther 1997; 28(2): 187-210.

95. Sturm R. Economic grand rounds: the myth of medical cost offset. Psychiatr Serv 2001; 52(6): 738-740.

96. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992; 146(4): 473-481.

97. Winkler D, Praschak-Rieder N, Willeit M, Lucht MJ, Hilger E, Konstantinidis A et al. Seasonal affective depression in 2 German speaking university centers: Bonn, Vienna; clinical and demographic characteristics. Nervenarzt 2002; 73(7): 637-643.

98. Wallin MS, Rissanen AM. Food and mood: relationship between food, serotonin and affective disorders. Acta Psychiatr Scand Suppl 1994; 377: 36-40.

99. European Depression Association. Depression manifesto [online]. [Accessed: 09.04.2019]. URL: http://eddas.eu/wp-content/uploads/2016/04/DepressionManifesto_01_04.pdf.

100. Preston J. Pharmacologie treatment of depression. J Fam Psychother 2007; 17(3-4): 35-52.

101. Kemp DE, Malhotra S, Franco KN, Tesar G, Bronson DL. Heart disease and depression: don't ignore the relationship. Cleve Clin J Med 2003; 70(9): 745-761.

102. Martin MW. Depression and Identity. In: Martin MW (Ed). From morality to mental health: virtue and vice in a therapeutic culture. New York: Oxford University Press; 2006. URL: https://oxford.universitypressscholarship.com/view/10.1093/0195304713.001.0001/acprof-9780195304718-chapter-12.

103. Winkler D, Pjrek E, Spies M, Willeit M, Dorffner G, Lanzenberger R et al. Has the existence of seasonal affective disorder been disproven? J Affect Disord 2017; 208(C): 54-55.

104. Nussbaumer-Streit B, Pjrek E, Kien C, Gartlehner G, Bartova L, Friedrich M-E et al. Implementing prevention of seasonal affective disorder from patients' and physicians' perspectives: a qualitative study. BMC Psychiatry 2018; 18(1): 372-372.

105. Kramer P. Listening to Prozac. New York: Penguin; 1997.

106. Hodge DR, Bonifas RP. Using spiritually modified cognitive behavioral therapy to help clients wrestling with depression: a promising intervention for some older adults. J Relig Spiritual Soc Work 2010; 29(3): 185-206.

107. Yokoya S, Maeno T, Sakamoto N, Goto R, Maeno T. A brief survey of public knowledge and stigma towards depression. J Clin Med Res 2018; 10(3): 202-209.

108. Cassell EJ. Recognizing suffering. Hastings Cent Rep 1991; 21(3): 24-24.

109. Bund für Lebensmittelrecht und Lebensmittelkunde. Markt für Nahrungsergänzungsmittel in Deutschland 2018 [online]. URL: https://www.bll.de/de/der-bll/organisation/arbeitskreise/arbeitskreis-nahrungsergaenzungsmittel-ak-nem/20181029-zahlen-nahrungsergaenzungsmittel-markt-2018.

110. Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10(1): 101-129.

111. Meesters Y, Gordijn MC. Seasonal affective disorder, winter type: current insights and treatment options. Psychol Res Behav Manag 2016; 9: 317-327.

112. Bürgerliches Gesetzbuch (BGB) [online]. 20.11.2019 [Accessed: 02.12.2019]. URL: https://www.gesetze-im-internet.de/bgb/BJNR001950896.html.

113. Strafgesetzbuch (StGB) [online]. [Accessed: 02.12.2019]. URL: https://www.gesetze-im-internet.de/stgb/index.html.

114. Europäisches Parlament, Europäischer Rat. Richtlinie 93/42/EWG des Rates [online]. 11.10.2007 [Accessed: 02.12.2019]. URL: https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:01993L0042-20071011&from=DE.

115. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Bundesinstitut für Arzneimittel und Medizinprodukte. Gemeinsame Expertenkommission zur Einstufung von Stoffen Stellungnahme zu Vitamin-D-haltigen Produkten (01/2016): Revision 1.1 (2017) [online]. 16.02.2017 [Accessed: 01.07.2019]. URL: https://www.bvl.bund.de/SharedDocs/Downloads/01_Lebensmittel/expertenkommission/Zweite_Stellungnahme_VitaminD_Revision1.1.pdf;jsessionid=6ED031A6CDEF9AD1F83883275912EF15.2_cid340?__blob=publicationFile&v=2.

116. Verordnung über diätetische Lebensmittel (Diätverordnung DiätV) in der Fassung der Bekanntmachung vom 28.04.2005 (BGBl. I S 1161), die zuletzt durch Artikel 60 der Verordnung vom 31.08.2015 (BGBl. I S 1474) geändert worden ist, [online]. [Accessed: 02.12.2019]. URL: http://extwprlegs1.fao.org/docs/pdf/ger89197.pdf.

117. Spickhoff A (Ed). Medizinrecht³. München: C.H.Beck; 2018.

118. BVL / BfArM. Gemeinsame Expertenkommission zur Einstufung von Stoffen. 2017. (Stellungnahme zu Vitamin-D-haltigen Produkten).

119. Menculini G, Verdolini N, Murru A, Pacchiarotti I, Volpe U, Cervino A et al. Depressive mood and circadian rhythms disturbances as outcomes of seasonal affective disorder treatment: a systematic review. J Affect Disord 2018; 241: 608-626.

120. Martensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: a critical review of the evidence. J Affect Disord 2015; 182: 1-7.

121. Brouwer A, Nguyen H, Snoek F, van Raalte D, Beekman A, Moll A et al. Light therapy: is it safe for the eyes? Acta Psychiatr Scand 2017; 136(6): 534-548.

122. Parker GB, Brotchie H, Graham RK. Vitamin D and depression. J Affect Disord 2017; 208: 56-61.

123. National Institute for Health and Care Excellence. Depression in adults: recognition and management [online]. 28.10.2009 [Accessed: 20.08.2019]. (Clinical guidelines; Volume 90). URL: https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742636741.

124. Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. J Affect Disord 2017; 210: 287-293.

125. Leucht S, Fennema H, Engel R, Kaspers-Janssen M, Lepping P, Szegedi A. What does the HAMD mean? J Affect Disord 2013; 148(2-3): 243-248.

126. European Network for Health Technology Assessment. EUnetHTA Joint Action 2: work package 8; HTA core model; version 3.0 [online]. 25.01.2016 [Accessed: 06.08.2018]. URL: https://meka.thl.fi/htacore/model/HTACoreModel3.0.pdf.

127. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

128. Lefebvre C, Manheimer E, Glanville J. Searching for studies [online]. In: Higgings JPT, Green S (Ed). Cochrane handbook for systematic reviews of interventions: version 5.1.0. 03.2011 [Accessed: 05.09.2018]. URL: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm.

129. Glanville J, Fleetwood K, Yellowlees A, Kaunelis D, Mensinkai S. Development and testing of search filters to identify economic evaluations in MEDLINE and EMBASE. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. URL: http://www.cadth.ca/media/pdf/H0490_Search_Filters_for_Economic_Evaluations_mg_e.pdf.

130. Eady AM, Wilczynski NL, Haynes RB. PsycINFO search strategies identified methodologically sound therapy studies and review articles for use by clinicians and researchers. J Clin Epidemiol 2008; 61(1): 34-40.

The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin-thema-vorschlagen/hta-berichte/ht18-04.html

Appendix A – Topics of the EUnetHTA Core Model

EUnetHTA is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [126] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 5 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 5: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Method: Section 3.1 Results: Chapter 4
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Method: Section 3.2 Results: Chapter 5
Ethical analysis (ETH)	**Ethical aspects** Method: Section 3.3 Results: Section 6.1
Patients and social aspects (SOC)	**Social aspects** Method: Section 3.4 Results: Section 6.2
Legal aspects (LEG)	**Legal aspects** Method: Section 3.5 Results: Section 6.3
Organizational aspects (ORG)	**Organizational aspects** Method: Section 3.4 Results: Section 6.4

Appendix B – Search strategies

B.1 – Search strategies for benefit assessment and economic evaluation

B.1.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to January Week 1 2019
- Ovid MEDLINE(R) Daily Update January 09, 2019

The following filters were adopted:

- Systematic review: Wong [127] – High specificity strategy
- RCT: Lefebvre [128] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)
- Economic evaluation: Glanville [129] – Emory University (Grady) filter

#	Searches
1	seasonal affective disorder/
2	seasons/
3	depressive disorder/
4	depression/
5	mood disorders/
6	or/3-5
7	and/2,6
8	((seasonal* or winter*) adj5 (disorder* or mood* or depress*)).ti,ab.
9	(winter* and (wellbeing* or (well* adj1 being*))).ti,ab.
10	or/1,7-9
11	phototherapy/
12	light/
13	light*.ti,ab.
14	phototherap*.ti,ab.
15	exp vitamin d/
16	(vitamin* adj1 (d or d3)).ti,ab.
17	or/11-16
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.
20	(randomized or placebo or randomly or trial or groups).ab.
21	drug therapy.fs.
22	or/18-21

#	Searches
23	22 not (exp animals/ not humans.sh.)
24	cochrane database of systematic reviews.jn.
25	(search or medline or systematic review).tw.
26	meta analysis.pt.
27	or/24-26
28	(economic$ or cost$).ti.
29	cost benefit analysis/
30	treatment outcome/ and ec.fs.
31	or/28-30
32	31 not ((animals/ not humans/) or letter.pt.)
33	or/23,27,32
34	and/10,17,33
35	34 not (comment or editorial).pt.

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 08, 2019
- Ovid MEDLINE(R) Epub Ahead of Print January 09, 2019

#	Searches
1	((seasonal* or winter*) and (disorder* or mood* or depress*)).ti,ab.
2	(winter* and (wellbeing* or (well* and being*))).ti,ab.
3	or/1-2
4	light*.ti,ab.
5	phototherap*.ti,ab.
6	(vitamin* and (d or d3)).ti,ab.
7	or/4-6
8	(clinical trial* or random* or placebo).ti,ab.
9	trial.ti.
10	(search or meta analysis or medline or systematic review).ti,ab.
11	(economic$ or cost$).ti,ab.
12	or/8-11
13	and/3,7,12

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 January 09

The following filters were adopted:

- Systematic review: Wong [127] – High specificity strategy
- RCT: Wong [127] – Strategy minimizing difference between sensitivity and specificity
- Economic evaluation: Glanville [129] – Embase G

#	Searches
1	seasonal affective disorder/
2	exp season/
3	circannual rhythm/
4	or/2-3
5	affective neurosis/
6	depression/
7	or/5-6
8	and/4,7
9	((seasonal* or winter*) adj5 (disorder* or mood* or depress*)).ti,ab.
10	(winter* and (wellbeing* or (well* adj1 being*))).ti,ab.
11	or/1,8-10
12	phototherapy/
13	exp light/
14	simulation*.hw.
15	light*.ti,ab.
16	phototherap*.ti,ab.
17	exp vitamin d/
18	(vitamin* adj1 (d or d3)).ti,ab.
19	or/12-18
20	(random* or double-blind*).tw.
21	placebo*.mp.
22	(meta analysis or systematic review or medline).tw.
23	(cost adj effectiveness).ab.
24	(cost adj effectiveness).ti.
25	(life adj years).ab.
26	(life adj year).ab.
27	qaly.ab.
28	(cost or costs).ab. and controlled study/

#	Searches
29	(cost and costs).ab.
30	or/20-29
31	and/11,19,30
32	31 not medline.cr.
33	32 not (exp animal/ not exp human/)
34	33 not (conference abstract or conference review or editorial).pt.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews Issue 1 of 12, January 2019
- Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2019

ID	Search
#1	[mh ^"seasonal affective disorder"]
#2	[mh ^"seasons"]
#3	[mh ^"depressive disorder"]
#4	[mh ^"depression"]
#5	[mh ^"mood disorders"]
#6	#3 or #4 or #5
#7	#2 and #6
#8	((seasonal* or winter*) near/5 (disorder* or mood* or depress*)):ti,ab
#9	(winter* and (wellbeing* or (well* near/1 being*))):ti,ab
#10	#1 or #7 or #8 or #9
#11	[mh ^"phototherapy"]
#12	[mh ^"light"]
#13	light*:ti,ab
#14	phototherap*:ti,ab
#15	[mh "vitamin d"]
#16	(vitamin* near/1 (d or d3)):ti,ab
#17	#11 or #12 or #13 or #14 or #15 or #16
#18	#10 and #17 in Cochrane Reviews, Cochrane Protocols
#19	#10 and #17 in Trials

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Seasonal Affective Disorder
2	MeSH DESCRIPTOR Seasons
3	((seasonal* OR winter*) AND (disorder* OR mood* OR depress*))
4	(winter* AND (wellbeing* OR (well* NEXT being*)))
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Phototherapy
7	MeSH DESCRIPTOR Light
8	(light*)
9	(phototherap*)
10	MeSH DESCRIPTOR Vitamin D EXPLODE ALL TREES
11	((vitamin* NEXT (d OR d3)))
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11
13	(#5 AND #12) IN HTA

5. PsycINFO

Search interface: Ovid

- PsycINFO 1806 to December Week 5 2018

The following filters were adopted:

- Systematic review: Eady [130] – Combination of terms for detecting systematic reviews: best specificity
- RCT: Eady [130] – Combination of terms for detecting studies of treatment: small drop in specificity with a substantive gain in sensitivity

#	Searches
1	seasonal affective disorder/
2	exp season/
3	circannual rhythm/
4	or/2-3
5	affective neurosis/
6	depression/
7	or/5-6
8	and/4,7
9	((seasonal* or winter*) adj5 (disorder* or mood* or depress*)).ti,ab.
10	(winter* and (wellbeing* or (well* adj1 being*))).ti,ab.

#	Searches
11	or/1,8-10
12	phototherapy/
13	exp light/
14	simulation*.hw.
15	light*.ti,ab.
16	phototherap*.ti,ab.
17	exp vitamin d/
18	(vitamin* adj1 (d or d3)).ti,ab.
19	or/12-18
20	(random* or double-blind*).tw.
21	placebo*.mp.
22	(meta analysis or systematic review or medline).tw.
23	(cost adj effectiveness).ab.
24	(cost adj effectiveness).ti.
25	(life adj years).ab.
26	(life adj year).ab.
27	qaly.ab.
28	(cost or costs).ab. and controlled study/
29	(cost and costs).ab.
30	or/20-29
31	and/11,19,30
32	31 not medline.cr.
33	32 not (exp animal/ not exp human/)
34	33 not (conference abstract or conference review or editorial).pt.

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(seasonal affective disorder OR seasonal mood OR seasonal depression OR winter depression) OR (winter AND (wellbeing OR well being OR well-being)) [DISEASE]

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
(seasonal affective disorder) OR (seasonal mood) OR (seasonal depression) OR (winter depression) OR (winter AND (wellbeing OR (well being) OR well-being))

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
seasonal affective disorder OR seasonal mood OR seasonal depression OR winter depression OR winter AND wellbeing OR winter AND well being OR winter AND well-being