Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-048 Melatonin

Stand: April 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Melatonin
[Schlafstörungen bei Kindern und Jugendlichen mit ADHS und/oder weiteren Vorerkrankungen]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Es sind keine Arzneimittel explizit für Schlafstörungen bei Kindern und Jugendlichen mit den genannten Vorerkrankungen zugelassen. Unter *II. Zugelassene Arzneimittel im Anwendungsgebiet* sind diejenigen Hypnotika und Sedativa aufgelistet, die gemäß der Zulassung grundsätzlich bei Kindern und Jugendlichen eingesetzt werden können.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Indikationen für die Anwendung der Psychotherapie gemäß § 26 Psychotherapie-Richtlinie: - Nichtorganische Schlafstörungen - Verhaltens- und emotionale Störungen mit Beginn in der Kindheit und Jugend
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung (Anlage III zur AM-RL): 32. Hypnotika/Hypnogene oder Sedativa (schlaferzwingende, schlafanstoßende, schlaffördernde oder beruhigende Mittel) zur Behandlung von Schlafstörungen, - ausgenommen zur Kurzzeittherapie bis zu 4 Wochen - ausgenommen für eine länger als 4 Wochen dauernde Behandlung in medizinisch begründeten Einzelfällen - ausgenommen zur Behandlung eines gestörten Schlaf-Wach-Rhythmus (Nicht-24-Stunden-Schlaf-Wach-Syndrom) bei vollständig blinden Personen. Eine längerfristige Anwendung von Hypnotika/Hypnogenen oder Sedativa ist besonders zu begründen. Diese nicht verschreibungspflichtigen Arzneimittel sind, von den genannten Ausnahmen abgesehen, auch für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr aufgrund des besonderen Gefährdungspotentials unzweckmäßig.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Melatonin – Slenyto®	Slenyto ist indiziert für die Behandlung von Schlafstörungen (Insomnie) bei Kindern und Jugendlichen im Alter von 2–18 Jahren mit Autismus-Spektrum-Störung (ASS) und/oder Smith-Magenis-Syndrom, wenn Schlafhygienemaßnahmen unzureichend waren.
Flurazepam N05CD01 Flurazepam real®	– Kurzzeitbehandlung von Schlafstörungen Hinweis: Die Behandlung mit Benzodiazepinen ist nur bei Schlafstörungen von klinisch bedeutsamem Schweregrad angezeigt.
Nitrazepam N05CD02 Eatan® N	Eatan® N wird angewendet zur kurzzeitigen Behandlung von Schlafstörungen Hinweis: Benzodiazepine sollten nur bei Schlafstörungen von klinisch bedeutsamem Schweregrad angewendet werden.
Midazolam N05CD08 Midazolam-ratiopharm®	Bei Kindern und Erwachsenen […] • zur Kurzzeitbehandlung von Schlafstörungen, insbesondere von Einschlafstörungen
Lorazepam N05BA06 Tavor®	— Symptomatische Kurzzeitbehandlung von Angst-, Spannungs- und Erregungszuständen sowie dadurch bedingten Schlafstörungen Hinweis: Nicht alle Angst-, Spannungs- und Erregungszustände oder Schlafstörungen bedürfen einer medikamentösen Therapie. Oftmals sind sie Ausdruck körperlicher oder seelischer Erkrankungen und können durch andere Maßnahmen oder eine Behandlung der Grunderkrankung behoben werden. Angst- und Spannungszustände infolge von gewöhnlichem Alltagsstress sollten normalerweise nicht mit einem Tranquilizer behandelt werden. Der Einsatz von Lorazepam als Schlafmittel erscheint nur dann gerechtfertigt, wenn gleichzeitig Benzodiazepin- Wirkungen am Tag erwünscht sind.
Oxazepam N05BA04 Oxazepam-ratiopharm®	Zur symptomatischen Behandlung von Durchschlafstörungen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Melperon N05AD03 Melperon-neuraxpharm®	Zur Behandlung von Schlafstörungen, Verwirrtheitszuständen und zur Dämpfung von psychomotorischer Unruhe und Erregungszuständen, insbesondere bei - Patienten der Geriatrie und Psychiatrie, - Psychosen, Oligophrenie, organisch bedingter Demenz, Psychoneurosen (wenn Tranquilizer wegen Unverträglichkeit oder Abhängigkeitsgefahr nicht angewendet werden können), - Alkohol-Krankheit. *Gegenanzeige: Kinder unter 12 Jahren*
Pipamperon N05AD05 Pipamperon-neuraxpharm®	Als schwach potentes Neuroleptikum bei - Schlafstörungen, insbesondere bei geriatrischen Patienten, - psychomotorischen Erregungszuständen
Diphenhydramin N05CM Vivinox® Sleep	Zur Kurzzeitbehandlung von Schlafstörungen. Sedativa/Hypnotika sollten nur bei Schlafstörungen von klinisch bedeutsamem Schweregrad angewendet werden.
Doxylamin R06AA09 Gittalun®	Zur Beruhigung vor dem Einschlafen und bei unruhigem Schlaf, soweit medikamentös behandlungsbedürftig.
Hydroxyzin N05BB01 Atarax®	Ein- und Durchschlafstörungen, sofern sie nicht Folgeerscheinung anderer, behandlungsbedürftiger Grunderkrankungen sind. *Gegenanzeigen: Atarax darf nicht eingenommen werden von:* - *Kindern unter 6 Jahren*
Tryptophan N06AX02 Ardeydorm®	– fördert die Schlafbereitschaft – erleichtert das Einschlafen bei Schlafstörungen
Baldrianwurzel N05CP01 Baldrian-ratiopharm®	Baldrian-ratiopharm® ist ein pflanzliches Arzneimittel zur Beruhigung. Baldrian-ratiopharm® wird angewendet bei leichter nervöser Anspannung und bei Schlafstörungen.
Baldrian-Kombination N05CP51 Kytta-Sedativum®	Unruhezustände und nervös bedingte Einschlafstörungen.

Quellen: ATC-Code, AMIS-Datenbank, Fachinformationen, Stand: 04/2018

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-048 (Melatonin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. April 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	DAHTA Datenbank
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Schlafstörungen, gekennzeichnet durch Ein- und/oder Durchschlafstörungen, bei Kindern und Jugendlichen im Alter von 2–18 Jahren.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Schlafstörungen* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 756 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 9 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2016 [3].

Psychotherapie-Richtlinie des Gemeinsamen Bundesauschusses über die Durchführung der Psychotherapie (Psychotherapie-Richtlinie) in der Fassung vom 19. Februar 2009, veröffentlicht im Bundesanzeiger Nr. 58 (S. 1 399) vom 17. April 2009, in Kraft getreten am 18. April 2009; zuletzt geändert durch Beschluss vom 16. Juni 2016, in der Fassung vom 24. November 2016, veröffentlicht im Bundesanzeiger (BAnz AT 15.02.2017 B2), in Kraft getreten am 16.02.2017

§ 26 Indikationen zur Anwendung von Psychotherapie

Indikationen zur Anwendung von Psychotherapie gemäß Abschnitt B und Maßnahmen der psychosomatischen Grundversorgung gemäß Abschnitt C der Richtlinie bei der Behandlung von Krankheiten können nur sein:

[…]

6. Nichtorganische Schlafstörungen

[…]

9. Verhaltens- und emotionale Störungen mit Beginn in der Kindheit und Jugend.

G-BA, 2017 [2].

Anlage III: Übersicht über Verordnungseinschränkungen und –ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie Verordnungseinschränkungen und –ausschlüsse von sonstigen Produkten; Stand: 4. November 2017

Arzneimittel und sonstige Produkte

Hypnotika/Hypnogene oder Sedativa (schlaferzwingende, schlafanstoßende, schlaffördernde oder beruhigende Mittel) zur Behandlung von Schlafstörungen,

- ausgenommen zur Kurzzeittherapie bis zu 4 Wochen
- ausgenommen für eine länger als 4 Wochen dauernde Behandlung in medizinisch begründeten Einzelfällen

Rechtliche Grundlagen und Hinweise

Verordnungsausschluss aufgrund von Rechtsverordnung für Allobarbital, Amobarbital, Aprobarbital, Barbital, Cyclobarbital, Pentobarbital, Phenobarbital (außer zur Anwendung bei Epilepsie), Proxybarbal, Secobarbital, Vinylbital. [2]

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

Diese nicht verschreibungspflichtigen Arzneimittel sind, von den genannten Ausnahmen abgesehen, auch für Kinder bis zum vollendeten 12. Lebensjahr und Entwicklungsstörungen

bis zum 12 Anlage III Stand (letzte Änderung in Kraft getreten am): 4. November 2017
für Jugendliche mit vollendeten 18. Lebensjahr

3.2 Cochrane Reviews

Es konnten keine Cochrane Reviews im vorliegenden AWG identifiziert werden.

3.3 Systematische Reviews

Es konnten keine systematischen Reviews im vorliegenden AWG identifiziert werden.

3.4 Leitlinien

Howes OD et al, 2018 [4].

British Association for Psychopharmacology

Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology

Fragestellung

In view of the uncertainties, the British Association for Psychopharmacology coordinated the development of this consensus guideline to review and make recommendations for the assessment and management of ASD with a focus on drug treatments.

Methodik

Grundlage der Leitlinie

A consensus meeting was held with the support of the British Association of Psychopharmacology (BAP) involving a group of experts on ASD in children, adolescents and adults. The group consisted of psychiatrists, psychologists, researchers in the field, and service user representatives. Members of the group gave presentations summarising each topic discussed in this paper, followed by discussion on the nature and quality of the evidence and its implications. Following the consensus meeting, a further literature review was conducted to support the consensus points. Drafts of the review and the recommendations were circulated to the expert group for comments, which were then revised by the expert group to derive the final version of the guidelines.

Recherche/Suchzeitraum:

k.A.

LoE und GoR; Categories of evidence and strength of recommendations

Categories of evidence for causal relationships and treatment

- Ia: Evidence from meta-analysis of randomised controlled trials
- Ib: Evidence from at least one randomised controlled trial
- IIa: Evidence from at least one controlled study without randomisation
- IIb: Evidence from at least one other type of quasi-experimental study
- III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
- IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Categories of evidence for observational relationships

- I: Evidence from large, representative population samples
- II: Evidence from small, well-designed, but not necessarily representative samples
- III: Evidence from non-representative surveys, case reports

- IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated from category I evidence
- C Directly based on category III evidence or extrapolated from category II evidence
- D Directly based on category IV evidence or extrapolated from category III evidence
- S Standard of good clinical care

Sonstige methodische Hinweise

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Empfehlungen: Treatment of sleep problems in children with ASD

Consensus recommendations of pharmacological treatment of co-occurring conditions and symptoms in children and adults with ASD

Sleep disorders in children

- Melatonin, if possible, in combination with a behavioural intervention. (strength of recommendation: A) Prolonged use of benzodiazepines and related GABA agonists is not recommended. (strength of recommendation: S)

Evidence Melatonin: A meta-analysis of five small studies supports the use of melatonin for sleep disorder in ASD (Rossignol and Frye, 2011) (evidence level Ia). Sleep duration was increased (the mean increase was 73min versus baseline and 44min versus placebo) and sleep onset latency decreased (mean decrease of 66min compared with baseline, and in comparison with a 39min decrease with placebo.) However, there were no changes in night-time awakenings in children with ASD (Rossignol and Frye, 2011). The length of melatonin usage in these studies ranged from 14 days to over four years. Melatonin use was associated with minimal to no side effects. A further large study reported a small increase in total sleep time (by a mean of 22 minutes) and an improvement in sleep onset (with a mean improvement of 38 minutes), though waking times became earlier too (Gringras et al., 2012). There is also evidence that melatonin combined with CBT is superior to melatonin only, CBT only and placebo in reducing symptoms of insomnia (Cortesi et al., 2012). The combination group also had a greater proportion of treatment responders reaching clinically significant improvements and fewer dropouts after 12 weeks (Cortesi et al., 2012) (evidence level Ib). Thus, overall, melatonin has proven to be an effective and well-tolerated drug in treating sleeping problems in children with ASD. Adding a behavioural intervention may be of additional value, at least in the short term.

[1)] Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011; 53:783–792. [PubMed: 21518346]
[2)] Cortesi F, Giannotti F, Sebastiani T, et al. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. Journal of Sleep Research. 2012; 21:700–709. [PubMed: 22616853]
[3)] Gringras P, Gamble C, Jones A, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. BMJ. 2012; 345:e6664. [PubMed: 23129488]

NICE, 2018 [5].

National Institute for Health and Care Excellence (NICE); NICE guideline [NG87]

Attention deficit hyperactivity disorder: diagnosis and management

Fragestellung

This guideline covers recognising, diagnosing and managing attention deficit hyperactivity disorder (ADHD) in children, young people and adults. It aims to improve recognition and diagnosis, as well as the quality of care and support for people with ADHD.

Methodik

Grundlage der Leitlinie

This guideline updates and replaces the NICE guideline on attention deficit hyperactivity disorder. This update covers the areas of identification of risk factors, post-diagnostic advice, non-pharmacological and pharmacological management and intervention adherence for children, young people and adults with a diagnosis of ADHD (with or without any co-existing conditions). For further details please refer to the scope for this guideline (published on the NICE website) and the review questions in section 2.1.This guideline is the basis of QS39.

Recherche/Suchzeitraum:

- All searches were updated 04/2018

LoE und GoR

- The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Overall quality of outcome evidence in GRADE

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

Sonstige methodische Hinweise

New recommendations have been added on recognition, information and support, managing attention deficit hyperactivity disorder (ADHD; including non-pharmacological treatment), medication, follow-up and monitoring, adherence, and review of medication and discontinuation.

These are marked as [2018].

Empfehlungen: Sleep

1.8.17 Monitor changes in sleep pattern (for example, with a sleep diary) and adjust medication accordingly. [2018]

Why the committee made the recommendations

Evidence showed clinically important differences in sleep disturbance, decreased appetite and weight changes in people taking ADHD medication. In the committee's experience, these are some of the most troublesome adverse effects. Because of concerns about decreased appetite and weight change, the committee advised that weight should be checked every 3 months in children aged 10 years and under, and at least every 6 months in older children and young people; BMI should be monitored in adults. The committee recommended that changes in sleep pattern should be recorded and medication adjusted accordingly.

There was some evidence that people on atomoxetine may experience sexual dysfunction, in particular erectile dysfunction, and the committee agreed that this should be monitored.

SIGN, 2016 [8].

Scottish Intercollegiate Guidelines Network

Assessment, diagnosis and interventions for autism spectrum disorders A national clinical guideline

Fragestellung

This guideline provides recommendations based on current evidence for best practice in the assessment, diagnosis and interventions for children, young people, adults and older adults with ASD. It includes screening and surveillance, diagnosis and assessment, clinical interventions and service provision, as well as recommendations for research and audit.

Methodik

Grundlage der Leitlinie:

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by an Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006–2014. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

Recherche/Suchzeitraum:

- evidence published between 2006 and 2014

LoE und GoR

- **1++:**
  High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

- **1+:**
  Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- **1-:**
  Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- **2++:**
  High-quality systematic reviews of case-control or cohort studies

  High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- **2+:**
  Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- **2-:**
  Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- **3:**
  Non-analytic studies, eg case reports, case series
- **4:**
  Expert opinion

Recommendations

- Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).
- The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.
- Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.
- R: For 'strong' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.
- R: For 'conditional' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-Practice Points

- ✓ Recommended best practice based on the clinical experience of the guideline development group.

Sonstige methodische Hinweise

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BEHAVIOURAL/PSYCHOLOGICAL INTERVENTIONS

SLEEP MANAGEMENT

By the age of one year most children are able to sleep through the night. If after this time a child is regularly unable to sleep, or has a period of good sleep which is disrupted, then this constitutes a sleep problem. Sleep disturbance is reported to be a common problem for children and young people with ASD.

One moderate-quality RCT compared cognitive behavioural therapy, melatonin, combined melatonin and CBT to a placebo pill in children aged 4–10 years with ASD and sleep problems (40 in each arm of the trial). Participants in the CBT arm received four weeks of family therapy. All three active arms showed improvements in sleep onset latency (SOL), total sleep time, waking after sleep onset and sleep efficiency compared to placebo at 12 weeks, based on actigraph data.[172] The best results were reported for the combination of CBT and melatonin with a 22% increase in total sleep time from baseline (0.07% placebo), increase in naptime 67.85% (3.3% placebo) and sleep efficiency 20% (1.12% placebo) and a reduction in SOL of 60.75% (-0.02% placebo). Cognitive behavioural therapy alone saw improvements in: total sleep time 9.31%; SOL 60.75%; naptime 37.14% and sleep efficiency 11.26%. **[1+]**

Due to paucity of evidence NICE used expert opinion to recommend the development of a sleep plan to address sleep problems and establish a regular night-time sleep pattern. Behavioural interventions should be tried before a pharmacological intervention.[151] **[4]**

An RCT of the use of weighted blankets compared to placebo to improve sleep in children with ASD did not find any significant difference in SOL (mean difference 2.1), sleep efficiency (mean difference -0.3) or night-time waking (mean difference -0.2).[173]

The intervention was well received by children and parents, however, with 48% of children using the weighted blanket choosing the 'really liked' category in the assessment questionnaire, compared to 31% placebo. Fifty-one per cent of parents felt that their child's sleep had very much improved/much improved compared to 16% placebo, and that their child was calmer (35 v 14%). Limitations of the study were that the participants' diagnosis of ASD was not assessed directly by the research team.

Melatonin for sleep management is covered in section 8.8.

Behavioural therapy should be considered for children and young people with ASD who experience sleep problems. **[✓]**

Children with ASD who present with signs of possible obstructive sleep apnoea, or sleep disordered breathing (loud snoring, choking or periodic stopping of breathing during sleep) should be referred to sleep medicine services for assessment. **[✓]**

Referenzen aus Leitlinien

[172] Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21(6):700-9. National Institute for Health and Care Excellence (NICE). Autism:

[151] The management and support of children and young people on the autism spectrum (NICE guideline CG170). London: National Collaborating Centre for Women's and Children's Health; 2013. (CG170). [cited 24/05/2016]. Available from url: http://www.nice. org.uk/guidance/CG170
[173] Gringras P, Green D, Wright B, Rush C, Masako S, Pratt K, et al. Weighted Blankets and Sleep in Autistic Children—A Randomized Controlled Trial. Pediatrics 2014;134(2):298-306.

Auger RR et al, 2015 [1].

American Academy of Sleep Medicine

Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline

Fragestellung

The purpose of the present publication is to provide an evidence-based update of existing recommendations for the treatment of the intrinsic CRSWDs: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). The extrinsic or predominantly environ-mentally influenced CRSWDs, namely shift work and jet lag disorder, are not addressed in this paper.

Methodik

Grundlage der Leitlinie

The present document replaces/updates the previous American Academy of Sleep Medicine (AASM) Practice Parameters pertaining to the intrinsic CRSWDs (i.e., ASWPD, DSWPD, N24SWD, and ISWRD).

Recherche/Suchzeitraum:

k.A.

LoE und GoR

- High: corresponds to a high level of certainty that the true effect lies close to that of the estimate of the effect.
- Moderate: corresponds to a moderate level of certainty in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: corresponds to a low level of certainty in the effect estimate; the true effect may be substantially different from the estimate of the effect.
- Very low: corresponds to very little certainty in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of GRADE approach to rating quality of evidence

Study Design	Initial Quality of a Body of Evidence	Downgrade if	Upgrade if	Quality of a Body of Evidence
Randomized trials	High →	Risk of bias −1 Serious −2 Very serious	Large effect +1 Large +2 Very large	High (four plus: ⊕⊕⊕⊕)
		Inconsistency −1 Serious −2 Very serious	Dose response +1 Evidence of a gradient	Moderate (three plus: ⊕⊕⊕⊖)
Observational studies	Low →	Indirectness −1 Serious −2 Very serious	All plausible residual confounding +1 Would reduce a demonstrated effect	Low (two plus: ⊕⊕⊖⊖)
		Imprecision −1 Serious −2 Very serious	+1 Would suggest a spurious effect if no effect was observed	Very Low (one plus: ⊕⊖⊖⊖)
		Publication bias −1 Serious −2 Very serious		

Definitions of AASM strengths of recommendations

AASM Strength of Recommendation		Example Characteristics Guiding Recommendation
FOR	STRONG	• There is a high degree of clinical certainty in the net benefits of this patient-care strategy. • The vast majority of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
	WEAK	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (e.g., net benefits) of this patient-care strategy. • The majority of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
AGAINST	WEAK	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (e.g., net harms) of this patient-care strategy. • The majority of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
	STRONG	• There is a high degree of clinical certainty in the net harms of this patient-care strategy. • The vast majority of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.

Sonstige methodische Hinweise

/

Empfehlungen: Delayed Sleep-Wake Phase Disorder (DSWPD)

5.2.6.1a The TF suggests that clinicians treat DSWPD in adults with and without depression with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.6.2.1a The TF suggests that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.6.2.2a The TF suggests that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.9.2a The TF suggests that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR]

Empfehlungen: Irregular sleep-wake rhythm disorder (ISWRD)

5.4.6.2a The TF suggests that clinicians use strategically timed melatonin as a treatment for ISWRD in children/ adolescents with neurologic disorders (versus no treatment). [WEAK FOR]

Veeremann G et al, 2014 [9].

Belgian Health Care Knowledge Centre (KCE)

Management of autism in children and young people: a good clinical practice guideline. Good Clinical Practice (GCP)

Fragestellung

<u>The scope of the guideline focuses on two main questions:</u>

1. What is the current scientific evidence for psychosocial interventions, educational, pharmacological and biomedical treatments for children and young people with ASD, with or without a double diagnosis ASD, intellectual disability or other associated features?

2. What is good clinical practice (GCP) management for children and young people with ASD and their families?

Methodik

<u>Grundlage der Leitlinie</u>

- The KCE guideline is drawn up according to codified principles, based on scientific information from the international literature. This guideline was developed based on the ADAPTE methodology.

<u>Recherche/Suchzeitraum:</u>

- The initial search was performed without restrictions on date and language. Subsequently, based on the initial screening of titles and abstract, it was decided to select only references from the last five years (2008-current). All searches for guidelines were performed on June 24th, 2013.

<u>LoE</u>

- For every clinical question, the evidence base and recommendations were extracted from each selected guideline and summarized in text form. Data extraction was performed by one researcher and checked by a second researcher. It is noteworthy that the NICE guideline included only SR and RCTs published in English. The HAS provided an additional analysis of the French literature and of non-randomized studies. The structure of the NICE guideline provides the backbone of the current report. The HAS report is summarized under the appropriate headings but mention is made of different subheadings in order to respect slightly different definitions. HAS worked in agreement with l'Agence Nationale de l'Evaluation et de la Qualité des Etablissements et Services Sociaux et Médico-sociaux (ANESM). The NICE guideline used the critical outcomes defined by their guideline development group to structure the guideline chapters and the results of the literature, and this structure has been taken over in the current report. The guideline is based on the

diagnostic criteria available at the time of development (DSM-IV-TR). At the time of the production of the NICE guideline, DSM-5 had not yet been published.

GoR

- NICE used GRADE in formulating recommendations.20, 21 HAS used a score A for level 1 evidence (RCTs or meta-analyses), a score B for level 2 evidence (low level RCT, non-randomised studies and cohort studies) and a score C for level 3 and 4 evidence (comparative studies with bias, retrospective or case studies).
- However in both guidelines evidence was scarce and evidence levels could mostly not be attributed. Since the ADAPTE method was applied on two existing guidelines and the great majority of recommendations were expert based, it was not possible to use GRADE for allocating levels of evidence or strengths of recommendation. The final KCE recommendations for management and treatment of ASD are consensus based and therefore their level of evidence is low.

Sonstige methodische Hinweise

- Leitlinienadaption
- The AGREE II instrument was used to evaluate the methodological quality of the identified CPGs (http://www.agreetrust.org/).

Summary of recommendations by NICE and HAS guidelines on associated features of autism and coexisting conditions: common medical and functional problems.

Intervention domain: Common medical and functional problems

NICE guideline:

Psychosocial and pharmacological interventions:

- CBT vs. placebo
- Melatonin vs. placebo
- Melatonin vs. placebo
- COMB vs. placebo
- COMB vs. CBT
- COMB vs. Melatonin
- Atomoxetine vs. Placebo

NICE Recommendation: For sleep problems offer an assessment that identifies:

- what the sleep problem is (for example, delay in falling asleep, frequent waking, unusual behaviours, breathing problems or sleepiness during the day)
- day and night sleep patterns, and any change to those patterns
- whether bedtime is regular
- what the sleep environment is like, for example:
  - the level of background noise
  - use of a blackout blind
  - a television or computer in the bedroom

- whether the child shares the room with someone
- presence of co morbidities especially those that feature hyperactivity or other behavioural problems
- levels of activity and exercise during the day
- possible physical illness or discomfort (for example, reflux, ear or toothache, constipation or eczema)
- effects of any medication
- any other individual factors thought to enhance or disturb sleep, such as emotional relationships or problems at school
- The impact of sleep and behavioural problems on parents or carers and other family members.

If the child or young person with autism snores loudly, chokes or appears to stop breathing while sleeping, refer to a specialist to check for obstructive sleep apnoea.

Develop a sleep plan (this will often be a specific sleep behavioural intervention) with the parents or carers to help address the identified sleep problems and to establish a regular night-time sleep pattern. Ask the parents or carers to record the child or young person's sleep and wakefulness throughout the day and night over a 2-week period. Use this information to modify the sleep plan if necessary and review the plan regularly until a regular sleep pattern is established.

Do not use a pharmacological intervention to aid sleep unless:

- sleep problems persist despite following the sleep plan
- Sleep problems are having a negative impact on the child or young person and their family or carers.

If a pharmacological intervention is used to aid sleep it should:

- only be used following consultation with a specialist pediatrician or psychiatrist with expertise in the management of autism or paediatric sleep medicine
- be used in conjunction with non-pharmacological interventions
- Be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.

If the sleep problems continue to impact on the child or young person or their parents or carers, consider:

- referral to a paediatric sleep specialist, and

  Short breaks and other respite care for one night or more. Short breaks may need to be repeated regularly to ensure that parents or carers are adequately supported. Agree the frequency of breaks with them and record this in the care plan.

HAS guideline

Melatonin

HAS Recommendation

Recommended for severe sleep disorders resistant to a non-pharmacological approach

Behavioural interventions on eating disorders

Insufficient evidence, no recommendation provided

[4] Santé HAd. Autisme et autres troubles envahissants du developpement: interventions éducatives et thérapeutiques coordonnées chez l'enfant et l'adolescent. France: HAS; 2012. Mars 2012 Available from: http://www.anesm.sante.gouv.fr/spip.php?article398

[5] NICE. Autism - management of autism in children and young people: NICE guideline. London: National Institute for Health and Care Excellence,; 2013. CG170 Available from: http://guidance.nice.org.uk/CG170/NICEGuidance/pdf/English

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NICE, 2013 [6].

National Institute for Health and Care Excellence; Clinical guideline [CG170]

Autism spectrum disorder in under 19s: support and management

Fragestellung

This guideline covers children and young people with autism spectrum disorder (across the full range of intellectual ability) from birth until their 19th birthday. It covers the different ways that health and social care professionals can provide support, treatment and help for children and young people with autism, and their families and carers, from the early years through to their transition into young adult life.

Methodik

Grundlage der Leitlinie

We now use a single, unified process to develop guidelines.

Recherche/Suchzeitraum:

- We reviewed the evidence in September 2016. We found nothing new that affects the recommendations in this guideline.
- Next review: 2018

LoE und GoR

- NICE clinical guidelines are recommendations, based on the best available evidence, for the care of people by healthcare and other professionals.
- Developing NICE guidelines: the manual appendix H

Sonstige methodische Hinweise

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Empfehlungen: Interventions for sleep problems

1.7.4 If a child or young person with autism develops a sleep problem offer an assessment that identifies:

- what the sleep problem is (for example, delay in falling asleep, frequent waking, unusual behaviours, breathing problems or sleepiness during the day)
- day and night sleep patterns, and any change to those patterns
- whether bedtime is regular
- what the sleep environment is like, for example:
  - the level of background noise
  - use of a blackout blind
  - a television or computer in the bedroom
  - wether the child shares the room with someone
- presence of comorbidities especially those that feature hyperactivity or other behavioural problems
- levels of activity and exercise during the day
- possible physical illness or discomfort (for example, reflux, ear or toothache, constipation or eczema)
- effects of any medication
- any other individual factors thought to enhance or disturb sleep, such as emotional relationships or problems at school
- the impact of sleep and behavioural problems on parents or carers and other family members.

1.7.5 If the child or young person with autism snores loudly, chokes or appears to stop breathing while sleeping, refer to a specialist to check for obstructive sleep apnoea.

1.7.6 Develop a sleep plan (this will often be a specific sleep behavioural intervention) with the parents or carers to help address the identified sleep problems and to establish a regular night-time sleep pattern. Ask the parents or carers to record the child or young person's sleep and wakefulness throughout the day and night over a 2‑week period. Use this information to modify the sleep plan if necessary and review the plan regularly until a regular sleep pattern is established.

1.7.7 Do not use a pharmacological intervention to aid sleep unless:

- sleep problems persist despite following the sleep plan
- sleep problems are having a negative impact on the child or young person and their family or carers.

If a pharmacological intervention is used to aid sleep it should:

- only be used following consultation with a specialist paediatrician or psychiatrist with expertise in the management of autism or paediatric sleep medicine
- be used in conjunction with non-pharmacological interventions
- be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.

1.7.8 If the sleep problems continue to impact on the child or young person or their parents or carers, consider:

- referral to a paediatric sleep specialist and
- short breaks and other respite care for one night or more. Short breaks may need to be repeated regularly to ensure that parents or carers are adequately supported. Agree the frequency of breaks with them and record this in the care plan

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE et al, 2013 [7].

Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin

Key points from the evidence

- Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep.
- Only 1 form of melatonin (prolonged-release tablets) is currently licensed in the UK for the short-term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over. Additional melatonin products are available from special-order manufacturers or specialist importing companies, or can be purchased directly online.
- No high-quality studies were identified that provided evidence for the efficacy of prolonged-release melatonin tablets (licensed in the UK) used off-label in children with sleep disorders and attention deficit hyperactivity disorder (ADHD).
- Limited evidence for unlicensed melatonin products was identified from 2 small (n=105 and 19) short-term randomised controlled trials (RCTs) and 1 small, long-term follow-up study (n=94). The evidence suggests that unlicensed melatonin products, taken for 10 days to 4 weeks, may reduce sleep onset latency (the time taken for a child to go to sleep) in children with sleep onset insomnia and ADHD by approximately 20 minutes. In addition melatonin may improve average sleep duration by 15 to 20 minutes. However, there are limitations to these small studies, and longer term efficacy is unclear.
- These RCTs included stimulant and non-stimulant treated children aged 6 to 14 years with ADHD and suffering from sleep onset insomnia. The studies used daily doses of between 3 and 6 mg of unlicensed melatonin described as 'fast-release' or 'short-acting', administered shortly before bedtime.

- Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.
- Unlicensed melatonin used in the RCTs appeared well tolerated in the short to medium term with only transient mild to moderate adverse effects reported.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 03.04.2018

#	Suchfrage
1	MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees
2	(sleep*):ti,ab,kw and (initiat* or maintenance* or maintain*):ti,ab,kw and (disorder*):ti,ab,kw (Word variations have been searched)
3	(insomnia* or DIMS or sleepness* or "early awakening"):ti (Word variations have been searched)
4	(sleep*):ti and (disorder* or problem* or difficult* or dysfunction* or disturb*):ti (Word variations have been searched)
5	#1 or #2 or #3 or #4
6	#5 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 06.04.2018

#	Suchfrage
1	(Sleep Initiation and Maintenance Disorders[MeSH Major Topic])
2	((sleep*[Title/Abstract]) AND (initiat*[Title/Abstract] OR maintenance*[Title/Abstract] OR maintain*[Title/Abstract])) AND disorder*[Title/Abstract]
3	(insomnia*[Title] OR DIMS[Title] OR sleepness*[Title] OR "early awakening"[Title])
4	(sleep*[Title]) AND (disorder*[Title] OR problem*[Title] OR difficult*[Title] OR dysfunction*[Title] OR disturb*[Title])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6 OR #7)
9	(#8) AND ("2013/04/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 06.04.2018

#	Suchfrage
1	Sleep Initiation and Maintenance Disorders[mh]
2	((sleep*[Title/Abstract]) AND (initiat*[Title/Abstract] OR maintenance*[Title/Abstract] OR maintain*[Title/Abstract])) AND disorder*[Title/Abstract]
3	(insomnia*[Title/Abstract] OR DIMS[Title/Abstract] OR sleepness*[Title/Abstract] OR "early awakening"[Title/Abstract])
4	(sleep*[Title/Abstract]) AND (disorder*[Title/Abstract] OR problem*[Title/Abstract] OR difficult*[Title/Abstract] OR dysfunction*[Title/Abstract] OR disturb*[Title/Abstract])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
7	(#6) AND ("2013/04/01"[PDAT] : "3000"[PDAT])

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5. **National Institute for Health and Care Excellence (NICE).** Attention deficit hyperactivity disorder: diagnosis and management [online]. London (GBR): NICE; 2018. [Zugriff: 28.09.2015]. (NICE guideline; Band 87). URL: https://www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933.

6. **National Institute for Health and Care Excellence (NICE).** Autism spectrum disorder in under 19s: support and management [online]. London (GBR): NICE; 2013. [Zugriff: 28.09.2015]. (Clinical guideline; Band 170). URL: https://www.nice.org.uk/guidance/cg170/resources/autism-spectrum-disorder-in-under-19s-support-and-management-pdf-35109745515205.

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Anhang

Veeremann G et al, 2014 [9].

Belgian Health Care Knowledge Centre (KCE)

Management of autism in children and young people: a good clinical practice guideline. Good Clinical Practice (GCP)

Common medical and functional problems

The common medical and functional problems for which evidence was reported in the NICE and HAS guideline are sleep problems and gastrointestinal problems.

Empfehlung 1: Psychosocial and pharmacological interventions aimed at common medical and functional problems

Evidence

- NICE[13] extracted relevant clinical evidence from three RCTs on this topic. Two of these studies examined the efficacy of psychosocial and/or pharmacological interventions on coexisting sleep problems as a direct outcome (target of the intervention), and one study examined effects on sleep problems as an indirect outcome. One four-armed trial compared CBT, melatonin, and combined CBT and melatonin to placebo and examined direct effects on sleep problems. Another trial also compared melatonin to placebo and examined effects on sleep problems as a direct outcome. Finally, one SNRI trial examined effects on sleep problems as an indirect outcome. More detailed information on the studies can be found in the table presented below, in the full NICE guideline from section 7.8.2 page 661 – 679 and in NICE Appendix 17 (evidence profiles) and 13 (forest plots).
- HAS[12] extracted one non-systematic review dealing with eating and sleep disorders and two RCTs studying the impact of behavioural interventions on feeding behaviour in very small group of children (from 1 to 3). More detailed information on these studies can be found in the full HAS guideline from section 5.4.5 page 239-240. HAS also extracted studies on melatonin (international recommendations n=2, SR n=1, HAS recommendation 2010, 3 RCTs and one retrospective study). More detailed information on these studies can be found in the full HAS guideline from section 5.4.5 page 291-293 and 303.

Effect of psychosocial and pharmacological interventions on common medical and functional problems

- NICE[13] found single study moderate quality evidence for large and statistically significant effects of CBT (relative to placebo pill) on nap time, bedtime, and sleep efficiency, and moderate and statistically significant effects on sleep onset latency and total sleep time as measured by actigraph. The only non-significant subscale for continuous actigraph data was for wake after sleep onset. However, dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency were also non-significant. There was also single study evidence for large and statistically effects of

CBT (relative to placebo pill) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, and night-waking), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, sleep duration, parasomnias, and sleep-disordered breathing subscales of the CSHQ.

- There was single study moderate quality evidence for large and statistically significant effects of melatonin (relative to placebo) on sleep onset latency, wake after sleep onset, bedtime, total sleep time, and sleep efficiency, and a moderate and statistically significant effect on nap time, as measured by actigraph. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over 25 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving melatonin were over 31 times more likely to show at least 85% for sleep efficiency than participants who received placebo.
- There was also moderate quality evidence for a large and statistically effects of melatonin (relative to placebo) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, night-waking, and sleep duration), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. Non-significant effects were observed for the sleep anxiety, parasomnias, and sleep-disordered breathing subscales of the CSHQ. Finally, there was moderate quality data from one trial for a large and statistically significant effect of melatonin (relative to placebo) on sleep onset latency as measured by sleep diary. However, effects on total sleep time were non-significant.
- There was single study moderate quality evidence for a large and statistically significant effect of melatonin (relative to CBT), in favour of melatonin, on sleep efficiency, and moderate and statistically significant effects on sleep onset latency, wake after sleep onset, and total sleep time. The only non-significant subscales for continuous actigraph data were for nap time and bedtime. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over four times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT, and participants receiving melatonin were over five times more likely to show at least 85% for sleep efficiency than participants who received CBT.
- There was also single study evidence for large and statistically effects of melatonin (relative to CBT), in favour of melatonin, on the total score for the CSHQ and on CSHQ subscales (night-waking, sleep duration), and for a moderate and statistically significant effects on the bed resistance and sleep onset delay subscales of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, parasomnias, sleep-disordered breathing, and daytime sleepiness subscales of the CSHQ.

- One paper narratively reports that no adverse events were reported or observed and none of the participants dropped out because of side effects and in another paper where treatment emergent signs and symptoms were reported and analysed and there was no evidence for statistically significant harms associated with melatonin (see section 4.6 Adverse events).
- There was moderate quality evidence for large and statistically significant effects of combined CBT and melatonin (COMB), relative to placebo and in favour of COMB, on all continuous actigraph outcome measures for sleep.
- There was also evidence for large and statistically significant effects of COMB on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received COMB being nearly 56 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving COMB were over 41 times more likely to show at least 85% for sleep efficiency than participants who received placebo. There was also evidence for large and statistically effects of COMB (relative to placebo), in favour of COMB, on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, sleep anxiety, night-waking, sleep duration, and daytime sleepiness). The only non-significant effects observed were for the parasomnias and sleep-disordered breathing subscales of the CSHQ. However, it is important to note that for the CSHQ data, unlike the actigraph data, the confidence in effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size.
- There was also evidence for benefits of COMB over CBT-only on sleep onset latency, wake after sleep onset, total sleep time, and sleep efficiency as measured by continuous actigraph data and evidence for large and statistically significant effects of COMB relative to CBT-only on dichotomous measures based on the actigraph data. Participants who received COMB were over nine times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT-only, and participants receiving COMB were nearly seven times more likely to show at least 85% for sleep efficiency than participants who received CBT-only. In addition, there was evidence for benefits of COMB relative to CBT-only on all but one subscale (sleep-disordered breathing) of the parent-completed CSHQ.
- Finally, there was also evidence for benefits of COMB over melatonin-only on sleep onset latency, wake after sleep onset, and total sleep time as measured by continuous actigraph data and evidence for a large and statistically significant effect of COMB relative to melatonin-only on a dichotomous measure based on the actigraph data, with participants who received COMB being more than twice as likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving melatonin-only. There was also evidence for benefits of COMB relative to melatonin-only on the total sleep problems score as measured by the CSHQ and on CSHQ subscales of bed resistance, sleep onset delay, sleep anxiety, and night-waking.
- There was no evidence for statistically significant effects of atomoxetine on sleep problems as an indirect outcome, as measured by a study-specific Sleep Measure Scale. This study did, however, find evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see chapter on adverse events) Due to the

lack of evidence and the low number of cases, HAS GDG12 did not consider that any specific interventions could be recommended for eating disorders. HAS concluded that melatonin has a positive effect on sleep disturbances.