Therapeutic Options in the Management of Sleep Disorders in Visually Impaired Children: A Systematic Review

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ABSTRACT

Background: Treatment of sleep disorders in visually impaired children is complicated by a complex pathophysiology, a high incidence of sleep disorders in this population, and a dearth of management options. The significant impact on the health of these children and distress to their caregivers warrant a systematic assessment of the published literature on therapeutic approaches.

Objective: This systematic review aims to assess the current therapeutic options in the management of sleep disorders in visually impaired children to identify knowledge gaps and guide future research.

Methods: A search of primary literature was conducted using the bibliographic databases PubMed (1980–August 2010), EMBASE (1990–August 2010), Science Citation Index Expanded (1990–August 2010), and CINHAL (1992–August 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL). Additional studies were identified through snowballing search techniques (manually by searching retrieved references and electronically by using citation-tracking software). Search terms included *behavioral treatment, children, circadian rhythm, hypnosedatives, intellectual disability, light therapy, melatonin, phototherapy, random allocation, randomized controlled trial (RCT), sleep disorder,* and *visual impairment.* Randomized and quasi-randomized clinical trials of therapeutic options (behavioral treatment, light therapy, melatonin, or hypnosedatives) used in participants aged 3 months to 18 years who had both a visual impairment and a sleep disorder were included. Independent extraction of articles was performed by 2 authors using predefined data fields, including quality of the therapeutic options, based on the Strength of Recommendation Taxonomy evidence-rating system.

Results: Two RCTs were retrieved for melatonin, with improved effect on sleep latency ($P = 0.019$ and $P < 0.05$, respectively). However, separate analysis for visual impairment was not conducted. No RCTs were retrieved for behavioral intervention, light therapy, or hypnosedatives. Three studies using behavioral therapy (2 case reports and 1 case series) anecdotally showed improvement in sleep habit. No improvement in sleep rhythm was observed with a case series applying light therapy as an intervention.

Conclusions: Children with visual impairment and sleep disorders are a heterogeneous patient group, making diagnosis and treatment difficult. RCTs on treatment options remain in their infancy, with a lack

of evidence for appropriate therapeutic strategies. Trials across a range of selected diagnoses need to be conducted with adequate sample populations to differentiate the efficacy of 4 different treatment modalities (behavioral therapy, light therapy, melatonin, and hypnosedatives) as agents for improving sleep. (*Clin Ther*. 2011;33:168–181) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: children, chronobiology, sleep disorder, visual impairment.

INTRODUCTION

Sleep is integral to a child's development, and visual impairment adversely affects this fundamental biological function.[1] In the late 1970s, Kestenberg[2] highlighted the importance of altered sleep disorders in visually impaired children. Numerous aspects of human physiology and behavior are dominated by 24-hour rhythms that have a major impact on health and well-being.[3] Circadian rhythms in biological systems are fundamental to life, with sight, light exposure, and light-dark perception playing important roles in adjusting behavioral and physiologic processes.

Approximately 25% of all children experience some type of sleep disturbance during childhood.[4] This number is closer to 80% in those with intellectual disability and visual impairment.[5] Visually impaired children are especially vulnerable, as they often have additional disabilities, including hearing impairment, cerebral palsy, and intellectual disability—all of which can produce sleep disorders in their own right.[1] Non–24-hour sleep–wake syndrome (N24HSWS) is common in individuals who are totally blind, half of whom are adversely affected.[6-8] Sleep disorders such as N24HSWS are also common in adolescence[9] and can be compounded by poor sleep hygiene and age-related changes. The cyclic nature of sleep disorders results from a mismatch or poor coupling between the child's attempts to live in accordance with the behavioral zeitgeber (literally, "time-giver") of a 24-hour "social day" and the child's internal circadian system, which runs on a non–24-hour intrinsic period.[10]

The pathogenesis of circadian rhythm sleep disorders is complex, with numerous mechanisms working simultaneously. Signaling molecules that play a key role in circadian setting include serotonin (5-HT), pituitary adenylate cyclase-activating peptide (PACAP), neuropeptide Y (NYP), γ-aminobutyric acid (GABA),

and melatonin, with suprachiasmatic nucleus (SCN) and cholinergic inputs also involved (Figure 1).[11-14] Figure 2 illustrates the classic process C and process H for the sleep–wake rhythm.[15,16]

Melatonin is a neurohormone secreted from the pineal gland during the night that plays an important role in the regulation of sleep via the circadian sleep–wake rhythm.[17] Onset of secretion coincides with timing of the increase in nocturnal sleepiness. The SCN involved with melatonin production is sensitive to the presence of zeitgebers or environmental cues, the most powerful of which are light and darkness. Responses to these cues are impeded in children with visual impairment.[1] Disturbed sleep patterns have been associated with abnormal melatonin production in adults,[18] and delays in the secretory pattern of melatonin in children with severe visual impairment.[19]

The repercussions of pediatric sleep disorders extend beyond behavioral and growth difficulties to substantial socioeconomic and health burdens on caregivers. They can lead to inability to provide continuous care, impaired performance, and increased accidents at work, home, and during travel,[20] hence the critical need for evidence-based, effective therapies. The objective of this systematic review is, therefore, to evaluate the therapeutic options for the management of sleep disorders in visually impaired children, based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[21] and to identify knowledge gaps to guide future research. Therapeutic options were evaluated, based on the Strength of Recommendation Taxonomy evidence-rating system.[22]

METHODS
Types of Studies

Randomized and quasi-randomized clinical trials on therapeutic options (behavioral treatment, light therapy, melatonin, or hypnosedatives) were included. No language or publication status restrictions were imposed.

Types of Participants

Participants between 3 months and 18 years of age with visual impairment and a sleep disorder were considered. *Sleep disorder* was defined as a disorder of sleep initiation, maintenance, or scheduling. *Visual impairment* was defined as loss of vision due to ocular conditions or damage to the posterior visual pathways and visual cortex of cortical, retinal, or mixed origin.
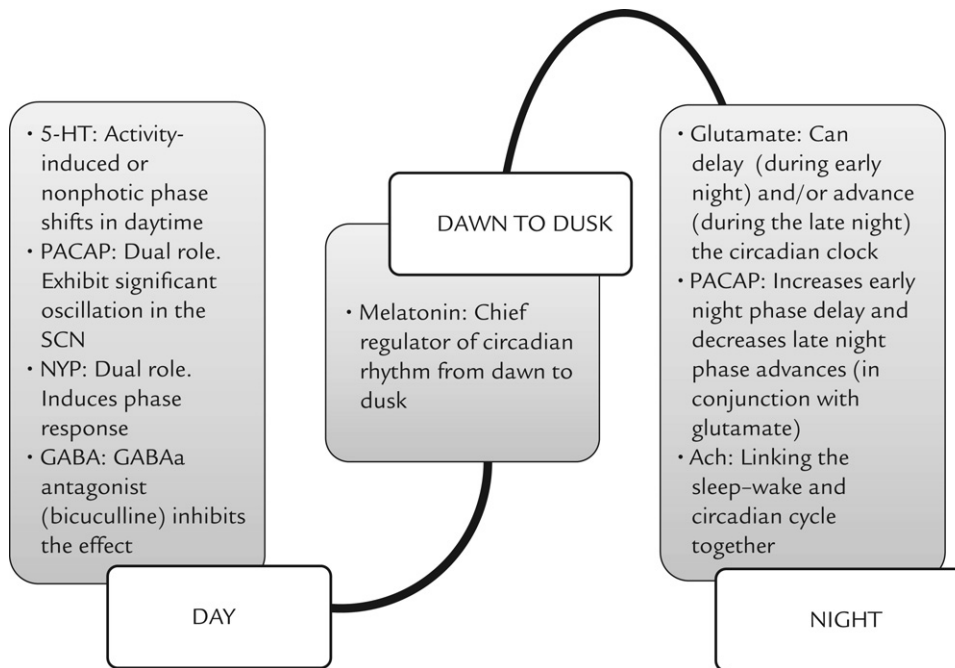
Figure 1. Circadian clock regulation through signaling molecules. Several signaling molecules play a key role in circadian setting. The circadian clock is regulated and sensitive during daylight to serotonin (5-HT), pituitary adenylate cyclase-activating peptide (PACAP), neuropeptide Y (NYP), and γ-aminobutyric acid (GABA). The pineal hormone melatonin is a chief regulator of circadian rhythm during dawn and dusk. In totally blind individuals, the photic input to the pineal gland is absent, and the circadian clock free runs with a rhythm, slightly different from that of a 24-hour period. At night, the suprachiasmatic nucleus (SCN) is responsive to phase adjustment by glutamate and PACAP and by cholinergic inputs (acetylcholine [Ach]) that regulate sleep and wakefulness.

Types of Intervention and Outcome Measures

Trials evaluating the therapeutic effect of behavioral treatment, light therapy, melatonin, or hypnosedatives were included. Primary outcome measures were sleep timing and sleep scheduling. Secondary outcome measures were adverse events of any therapeutic option and quality of life.

Information Sources

A search of primary literature was conducted using the bibliographic databases: PubMed (1980–present), EMBASE (1990–present), Science Citation Index Expanded (1990–present), CINHAL (1992–present) databases and Cochrane Central Register of Controlled Trials (CENTRAL). Additional studies were identified through snowballing search techniques (manual searching of retrieved references and electronic searching by using citation-tracking software). Search terms included *behavioral treatment, children, circadian rhythm, hypnosedatives,* *intellectual disability, light therapy, melatonin, phototherapy, random allocation, randomized controlled trial (RCT), sleep disorder,* and *visual impairment.* Additional search terms used were *benzodiazepine, chloral hydrate, nitrazepam,* and *nonbenzodiazepines.*

Search Strategy

The following search strategy was used in PubMed to evaluate the trials involving melatonin in visually impaired children:

1. Melatonin/
2. adolescent/ or child/ or child, preschool/ or infant/
3. (baby or babies or infant$ or child$ or boy$ or girl$ or toddler$ or preschool$ or pre-school$ or teen$ or schoolchild$ or adolescen$ or juvenil$).tw.
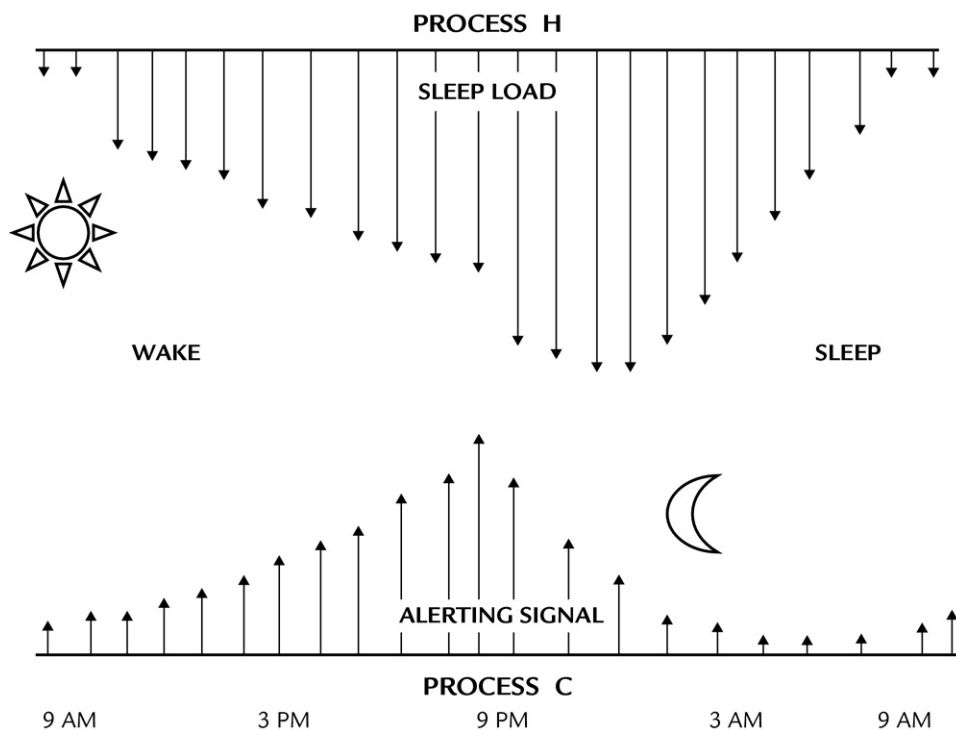4. 2 or 3

Figure 2. A schematic representation of the "opponent process" model. Alternation of wakefulness and sleep results from the interaction of homeostatic (H) and circadian (C) process. Process H represent sleep load, which is determined by the temporal sequence of behavioral states. Process H increases during waking and declines as sleep ensues. In contrast, Process C is regulated by the suprachiasmatic nucleus, the circadian pacemaker, without regard to behavioral state. The solid line represents the resulting course of sleepiness as a function of time during the day. This figure was created based on data from previously published studies.[15,16]

5. Visually Impaired Persons/
6. exp Vision Disorders/
7. ((vision$ or visual$) adj3 (handicap$ or disabili$ or disabl$ or impair$ or disorder$)).tw.
8. blind$.tw.
9. 5 or 6 or 7 or 8
10. exp Sleep Disorders/
11. insomni$.tw.
12. (sleep adj3 (disorder$ or problem$ or pattern$)).tw.
13. (wakefulness or waking).tw.
14. 10 or 11 or 12 or 13
15. 1 and 4 and 9 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. drug therapy.fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. humans.sh.
26. 24 and 25
27. 15 and 26

Study Selection

Eligibility assessment was performed independently in an unblended standardized manner by 2 reviewers. Disagreement (if any) between reviewers was resolved by consensus.

Data Collection Process

A data extraction sheet was developed, and the pilot was tested on randomly selected studies and refined accordingly. One author extracted data from included

studies, and 2 authors checked the extracted data. Disagreement was resolved by discussion between the 2 authors. If no agreement could be reached, it was planned for a third author to adjudicate. Information was extracted from each included trial on (1) characteristics of trial participants (age, type of sleep disorder, visual impairment), (2) type of intervention (type, dose, duration, and frequency), and (3) type of outcome measure. To explore variability in study results (heterogeneity), it was hypothesized that effect size may differ according to the methodological quality of the studies.

RESULTS
The study selection process and justification are provided in a flow diagram (Figure 3) and Table I, respectively. Two RCTs on melatonin met the review inclusion criteria, but none of the behavioral interventions, hypnosedative, or light therapy studies retrieved met the inclusion criteria.

The 2 melatonin studies were randomized, controlled, and published in English. Neither study was designed specifically to evaluate response in children with visual impairment. The study by Coppola et al[23] involved 25 children with intellectual disability, only 4 (16%) of whom were visually impaired, and the study by Dodge and Wilson[24] also included only 4 (20%) children with visual impairment in the 20 with intellectual disability recruited for the study. Patients were recruited from multiple centers. The intervention received was placebo, 5 mg melatonin,[23] or 3, 6 or 9 mg melatonin.[24] Age ranges were from 3.6 to 26 years[23] and from 1 to 12 years,[24] with the intervention lasting 8 weeks. Primary outcomes assessed were sleep latency and night waking, with secondary measures of daytime mood and side effects. The assessments were measured by caregivers, who maintained a sleep diary throughout the study. Quality of life was not an outcome in either study, although anecdotal comments are described. Table II highlights potential bias in the 2 melatonin studies.

Meta-analysis was not feasible because of the marked variability in study designs, participants, interventions, and reported outcome measures. Neither of the 2 RCTs on melatonin examined responses to interventions of the visually impaired population separately from those of the recruitment population of children with intellectual disability. We therefore focused on descriptive analysis of study results and limitations.
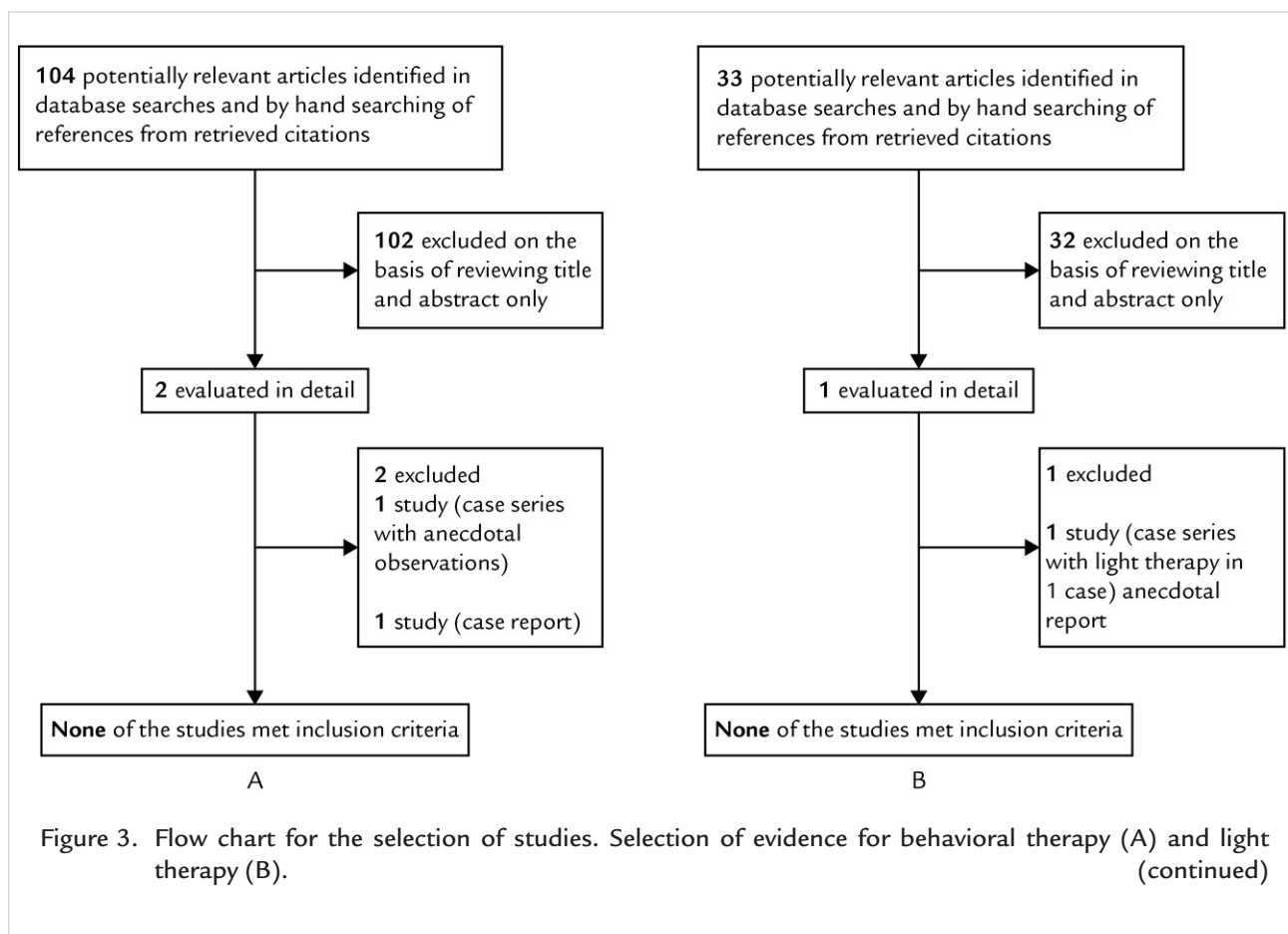
Owing to a lack of RCTs, there is only limited discussion of other interventions. Table III provides evidence-based ratings of different treatment modalities using the SORT evidence-rating system.[22]

DISCUSSION
Despite the lack of RCTs, behavioral treatments such as bedtime parenting practices are widely used in visually impaired children.[25] Various behavioral techniques such as sleep scheduling, chronotherapy, extinction, graduated extinction, scheduled waking, positive bedtime routine, bedtime fading, response cost, positive reinforcement, parent education, advice, and support have been tried in children with sleep disorders of multiple origins.[26]

Chronotherapy, in the context of behavioral intervention, has been tried in children with visual impairment in 3 studies, 1 case series, and 2 case reports. In 1 case report[27] a 2-year-old boy with visual impairment displayed sustained improvement, based on a sleep diary, for the 6 months following the institution of treatment (a schedule of 9:30 PM bedtime with a set bedtime routine; a 6:30 AM wakeup time; naptime at 1 PM; and meals at 8 AM, noon, and 6 PM). On dechallenge, there was a drift in sleep pattern that improved gradually after reimplementation of the strict daily schedule. In contrast, Okawa et al[28] evaluated the impact of forced awakening in a case series of 4 visually impaired children. Therapy was ineffective in 1 case and questionable in 2 cases. Although the treatment was effective in 1 child with a free-running sleep–wake rhythm, she was forced to stay awake by being kept in a sitting position, and her wake pattern conformed to the 24-hour rhythm only after she began taking nitrazepam. In the remaining case report,[29] sleep maintenance was improved in a 4.5-year-old girl with visual impairment and a gradual extinction procedure, from being awake 25 minutes (range 0–150 minutes) during the baseline period to sleeping "on time" (range 0–63 minutes) postintervention.

These studies provide weakly positive and anecdotal support for the use of behavioral interventions to improve sleep, but objective data remain insufficient to recommend widespread application. However, the importance of preventive measures in the form of parental training with children at special risk is an important area for research. When administered by trained caregivers, techniques such as the setting of consistent time cues that include meals and

Figure 3. Flow chart for the selection of studies. Selection of evidence for behavioral therapy (A) and light therapy (B).   (continued)

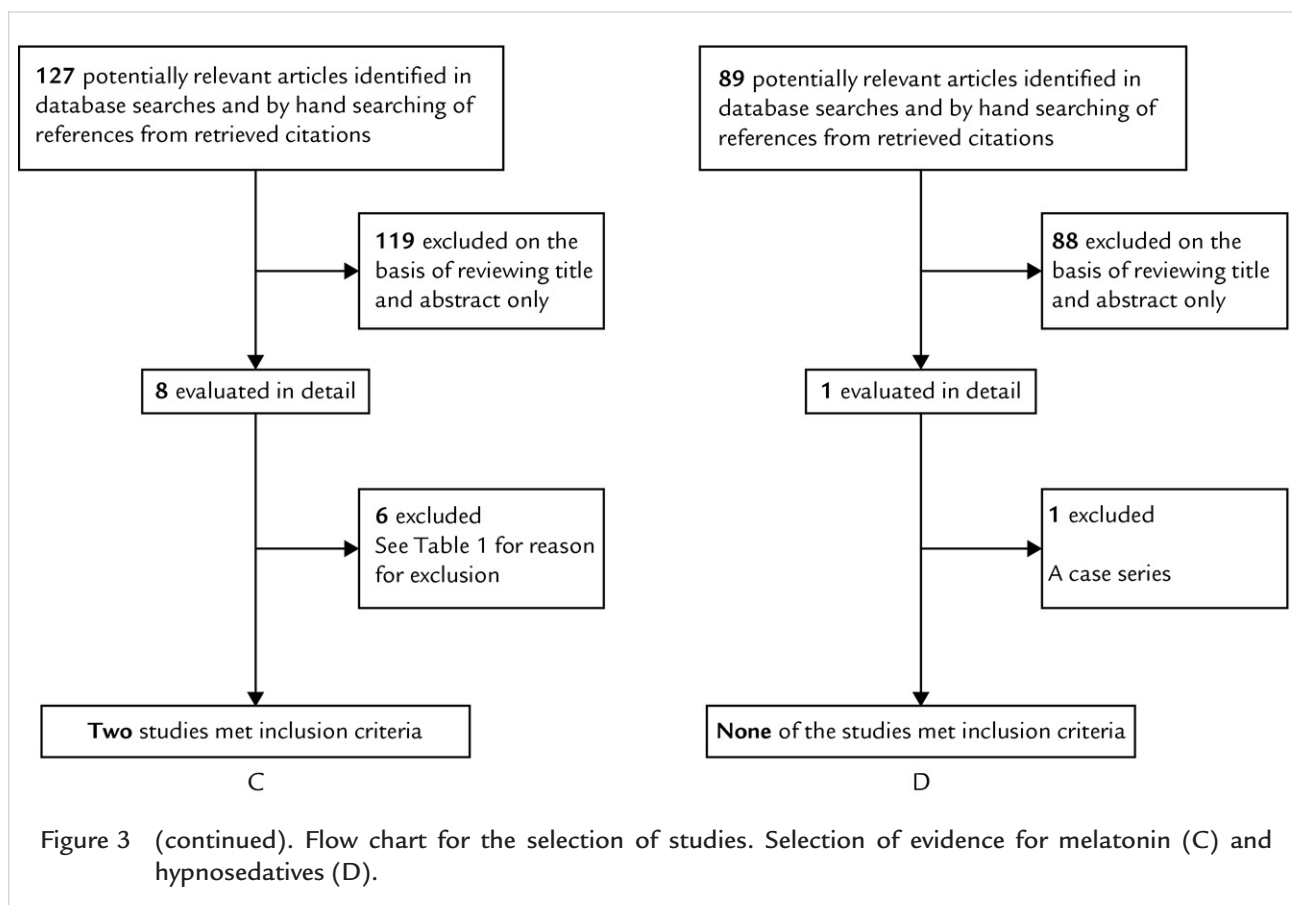bedtime routines may be helpful in the case of visually impaired children.

Light therapy is a widely cited intervention to manage N24HSWS.[9,30,31] However, only one case of a congenitally blind child with circadian sleep–wake rhythm disorder who received light therapy (2000 lux administered at 6:00 AM for 1 hour to entrain the usual 24-hour rhythm of sleep–wake) was found. This intervention was unsuccessful.[28] It is therefore not surprising that light therapy alone has failed to find a place as a major treatment option in this cohort. It is difficult to create a placebo/comparative dummy when evaluating the effect of light therapy, and even more difficult to use blinded study designs when bright light therapy is the active intervention. Thus, studies of interventions with rigorous design are difficult. Early studies also failed to reach consensus on a standardized approach to lux parameters for the active treatment, duration of the trial, and characteristics of the placebo control conditions.[32]

Lack of funds and sponsorship to support the development and testing of this intervention is a major contributing factor to the paucity of effective studies.[32] Although adverse effects such as headache, eye strain, nausea, and agitation have been reported in the results of adult studies,[33,34] pediatric pharmacovigilance data are lacking.

Behavioral intervention and light therapy have not yet provided good evidence as synchronizers for circadian rhythms in children with visual impairment. This may be secondary to difficulties with study design or with lack of effectiveness; therefore, research into pharmacotherapeutic interventions has become more prevalent. One promising therapeutic agent for the treatment of N24HSWS is melatonin. This compound has been used commonly in children with visual impairment.[23,24,35–40]

One large case series[36] of 100 patients treated a specific cohort of children with visual impairment. Initially, a small number of the children (data not provided) were treated with melatonin or placebos in a double-blind, crossover, randomized design. However, after the initial study was completed, the placebo phase

Figure 3 (continued). Flow chart for the selection of studies. Selection of evidence for melatonin (C) and hypnosedatives (D).

was discontinued. Outcomes were measured with subjective sleep diaries only. The authors reported, at variable doses, that children were generally asleep after 30 minutes, with sustained improvement for 2 to 4 weeks after 3 to 4 days. However, treatment failure was reported in 17% of the children, and objective data are lacking.

Two studies[23,24] that incidentally recruited children with visual impairment in a population of children with intellectual disability did not separately analyze the visually impaired group. A study by Copolla et al,[23] verified the clinical efficacy of melatonin in children with intellectual disability, with or without epilepsy. Out of the total study population (N = 25), 4 were visually impaired. A significant effect on sleep latency was reported as measured by sleep logs (P = 0.019). The resulting mean sleep latency appeared to decrease with melatonin (0.3 hour) compared with those of the baseline (1.6 hours) and placebo (0.7 hour) phases, and no effect on nocturnal waking was observed. However, it is unclear whether the P value refers to melatonin versus baseline or melatonin versus placebo, thus making interpretation of this report difficult. Responses (sleep latency, total sleep time during the night in hours, diurnal sleep time in hours, night awakenings, and early arousal [number of patients in which this condition was present]) were seen at doses of 3 mg (29.2% of patients), 6 mg (45.8% of patients), 9 mg (20.8% of patients), and 12 mg (4.2% of patients). These doses are higher than what has been recommended anecdotally in other populations.[41]

It should be noted that information from Copolla et al[23] was lacking on what threshold was considered a "response." The authors suggest an increase in total sleep time, both on melatonin and on placebo versus baseline (7.9, 7.0, and 4.4 hours, respectively). However, the P values were above the range to be considered statistically significant. The number of early arousals (number of patients) were not statistically significant (P = 0.123, Fisher exact test) as observed in patients on melatonin, placebo, and baseline (2, 6, and 13, respectively). Importantly, no significant adverse

Table I. Excluded studies on melatonin.

First Author, Title, Reference	Reason(s) for Exclusion
Jan J. The treatment of sleep disorders with melatonin. *Dev Med Child Neurol*. 1994;36:97–107.	Inadequate randomization; case series
Palm L. Long-term treatment in blind children and young adults with circadian sleep–wake disturbances. *Dev Med Child Neurol*. 1997;39: 319–325.	Inadequate randomization and blinding
Espezel J. The use of melatonin to treat sleep–wake rhythm disorders in children who are visually impaired. *J Vis Impair Blind*. 1996;90:43–50.	Inadequate randomization
Schmitt-Mechelke TH. Melatonin in the treatment of sleep problems in neuropaediatric patients. *Schweiz Medizinische Wochenschrift*. 1997;127(Suppl 87):9.	Case series; not blinded
Hung JC. The use of melatonin in the treatment of sleep disturbances in children with neurological or behavioural disorders. *J Pediatr Pharm Pract*. 1998;3:250–256.	Inadequate randomization
Jan JE. Clinical trials of controlled-release melatonin in children with sleep–wake cycle disorders. *J Pineal Res*. 2000;29:34–39.	Comparison of melatonin formulation

effects were noted, even at higher doses. Variable effects, both positive and negative, were seen in patients with a concurrent seizure disorder. All returned to baseline after melatonin was ceased. Approximately half of families reported better daytime functioning, but statistical data were not provided.

The other study, by Dodge and Wilson,[24] explored the safety and efficacy of synthetic melatonin in the treatment of sleep problems in 20 children with developmental disabilities, 4 of whom were visually impaired. In comparing the mean sleep latency between different treatment conditions, all but 2 children showed a decrease in sleep latency when receiving melatonin as opposed to placebo or baseline. The decrease in mean sleep latency with melatonin as suggested by the authors was significant at $P < 0.05$ by analysis of variance. Mean sleep latency was 0.7 hour, 1.2 hours, and 1.2 hours with melatonin, placebo, and baseline, respectively. As in the aforementioned study, it is not clear whether a direct comparison was made between melatonin versus placebo from the provided results, making interpretation difficult. Interestingly,

Table II. Risk of bias—studies on melatonin.

Trials	Concealment of Randomization	RCT Stopped Early	Patients Blinded	Health Care Providers Blinded	Data Collectors Blinded	Outcome Assessors Blinded
Copolla et al[23]	Yes	No	Yes	No	Information not available	No
Dodge and Wilson[24]	Yes	No	Yes	No	Information not available	No

RCT = randomized controlled trial.
Note: These studies recruited children with intellectual disability. Recruitment of children with intellectual disability *and* visual impairment was incidental. No separate analysis was performed; thus, results may be biased for reasons of heterogeneity of the study population.

Table III. SORT evidence-based rating for therapeutic options in sleep disorders in visually impaired children.

Clinical Status	Evidence Rating	References
Behavioral approach is promising based on anecdotal reports but lacks randomized controlled studies, and these strategies are difficult to implement in visually impaired children and caregivers.	C	27, 28, 29
Light therapy: There are no randomized controlled trials in visually impaired children. Apart from lack of information on efficacy, the ideal duration of phototherapy has not been determined in visually impaired children, and a duration response curve is nonexistent.	C	28
Melatonin is a potential option in the short-term management of N24HSWS in visually impaired children. Data on efficacy and safety is, however, inconclusive.	B	23, 24
Hypnosedatives are prescribed in some cases and as an adjunct to behavioral approaches, but there have been no randomized controlled studies in visually impaired children.	C	28

Evidence rating based on Strength of Recommendation Taxonomy (SORT), wherein the strength of recommendation is rated as A, B, and C. A = consistent and good-quality patient-oriented outcome; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening; N24HSWS = non–24-hour sleep–wake syndrome.

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total sleep time improved ($P < 0.007$) with melatonin (8.1 hours) as compared with baseline (7.1 hours), but not when compared with placebo (7.8 hours). No difference in the mean number of night awakenings was noted with the melatonin (0.9), placebo (0.7), and baseline (0.9) groups. However, both of these studies failed to analyze children with visual impairment as a separate cohort.

Populations with intellectual disability may have other attributes that confound these results when examining effects in children with visual impairment.

Melatonin appears to entrain free-running rhythms and causes phase-advance shifts when administered in the early evening and a phase delay when given in the early morning.[42] Soporific in pharmacologic doses, it needs to be administered at the same time each day (close to the desired bedtime) to reinforce the association between the circadian and social day.[42] Prior information on circadian phase is important for scheduling melatonin therapy. As sleep–wake cycle disturbances are often associated with disturbed timing of melatonin secretion, the measurement of endogenous melatonin may be helpful.[43] It is not clear how these effects relate to those observed in the 2 aforementioned RCTs,[23,24] as no time of administration for

melatonin was reported. It is also difficult to ascertain whether the effect of melatonin on sleep latency related to a change in sleep phase or to a soporific effect, or indeed to both. Thus, regardless of co-morbidities, future research should aim to ascertain sleep phase responses by additional measures such as wake times, body temperature, and the like. This would help determine whether children with visual impairment are preferentially affected by melatonin toward either sedation or an adjustment in sleep phase.

Measurement of dim-light melatonin onset is conducted in research settings that include measuring plasma or salivary melatonin concentrations. Endogenous melatonin exhibits a significant interindividual and age-related variability in its pharmacokinetics.[44] There is a need for simple, reliable, and sensitive methods for circadian testing. Besides, there is an inconsistent ratio between serum and salivary concentrations.[45] None of the clinical trials evaluated in Table I measured melatonin profiles as part of any diagnostic and therapeutic screening. The current methods to identify circadian abnormalities rely on subjective measures obtained from interviewing the patient and family members. Light therapy requires clear information on the circadian profile of the patient.[46] Without

valid circadian testing, the amount of light required for these patients remains unknown and is relegated to guesswork. Information on the circadian period would help in screening and evaluating the cause of circadian abnormalities, with possible implications for sleep disorder therapy. However, determination of the circadian period is a long, laborious process not directly associated with clinical application.[47]

Melatonin access varies markedly by country, ranging from nonprescription to orphan drug status.[48] As it is an endogenous substance, it cannot be patented; hence, the lack of financial incentives for its commercial development. The European Medicines Agency and Australian Drug Evaluation Committee (ADEC) have recently approved Circadin,[49] a sustained-release formulation of melatonin for primary insomnia in elderly patients, on the basis of subjective sleep measure data. It was appropriate that these agencies did not accept extrapolation of adult data to the elderly population. This approach should be emulated in the pediatric setting. The quality control of melatonin as a therapeutic substance is not universally standardized, and impurities in the product are a potential concern.[50] Chemical analogues of melatonin have been developed recently, such as agomelatine, but the trials of this drug are being done on adults and not for the purposes of managing sleep disorders.[51-53] Some analogues are undergoing clinical trials but not yet in visually impaired children with sleep disorders.

For the past decades the hypnosedatives— benzodiazepines and nonbenzodiazepines, such as barbiturates, tricyclic antidepressants, antihistamines, buspirone, zolpidem, and zopiclone— have been used widely for sleep induction and maintenance. Most studies have been conducted in adults presenting with insomnia with no psychiatric comorbidities.[54] Benzodiazepines act as allosteric modulators of the $GABA_A$ receptor complex, improving the binding efficiency of the main inhibitory neurotransmitter of the CNS, namely, GABA. In the context of parasomnias, the prime use for benzodiazepines in children is for sleep disorders,[55,56] but they have also been used to manage night terrors and partial arousals. In addition, they have been prescribed for blind children with circadian rhythm disturbances and for intellectually handicapped children with sleep disturbances.[57,58] However, no RCTs in these settings were retrieved. In 1 case series,[28] nitrazepam was administered to 4 congenitally blind children. Based on subjective measures, the

sleep–wake rhythm was improved; however, these children were also receiving behavioral intervention and anticonvulsant therapy (sodium valproate and phenobarbital). It should be noted that nitrazepam has a long half-life and presents with a risk of accumulation.[59]

Although not specifically labeled for sleep disorders, the shorter-acting midazolam is available in the United States in a child-friendly liquid formulation, with dosing recommendations based on pediatric data.[57] Although no longer favored, chloral hydrate has been prescribed for children with sleep-onset delay, but there remains some concern regarding safety.[56] Intellectually handicapped children with sleep disorders and blind children with circadian rhythm disturbances also have been prescribed chloral hydrate for management of sleep disorders; however, no data are provided on its efficacy or safety.[56,58]

Prescription hypnosedatives have neither an ADEC nor a US Food and Drug Administration approval for insomnia in adolescents <18 years. International guidelines no longer advocate over-the-counter hypnosedatives, such as antihistamines, for children <2 years of age.[60,61] A recent national survey[62] on the use of pharmacotherapy for insomnia in child psychiatry practice revealed a number of prescription medications such as α-agonists, trazodone, sedating antidepressants, benzodiazepines, short-acting hypnotics, and antihistamines specifically prescribed for insomnia. However, concerns about adverse effects and lack of empirical support regarding efficacy were cited as significant barriers to their use.

Over-the-counter medications such as melatonin were recommended by one third of the respondents in this survey. Although off-label use of the hypnosedatives, as an adjunct to behavioral modification, is often considered in the setting of insomnia, these drugs may further exacerbate an already complex situation by causing confusional states at night and rebound or hangover effects during the day in children, regardless of any underlying visual impairment or intellectual disability.[63,64] The risks associated with long-term use of hypnosedatives (particularly benzodiazepines similar to nitrazepam), such as tolerance, dependence, increased abuse potential, and withdrawal symptoms, cannot be overlooked.

Nonbenzodiazepines like zaleplon and zolpidem have a relatively short half-life and no demonstrable morning hangover and may be preferable to benzodiazepines with longer half-lives, especially in the pedi-

atric population.[41] However, there are no studies of safety or efficacy in children with visual impairment. A recent systematic review[65] on insomnia management in adults concluded that the clinical benefits of benzodiazepines were almost certainly inflated by reporting bias and needed to be offset by the evidence that these drugs pose a significant risk. Current pharmacotherapeutic research on insomnia management is moving away from the major inhibitory $GABA_A$ receptor system toward modulating more subtle endogenous pathways that control the sleep–wake cycle.[54] Such approaches may be more appropriate for helping particular subpopulations suffering from sleep disorders with a mismatched or poorly coupled sleep–wake cycle.

One main objective of this systematic review is to identify significant research and knowledge gaps in this vulnerable pediatric population. Across the interventions, studies have failed to measure changes in functional health status, and health-related quality of life measures have been neglected despite being one of the parameters used for defining insomnia per the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV) criteria.[63] Studies failed to analyze the baseline circadian rhythm before initiating therapy in such populations. Over the past 3 decades there has been little progress in sleep and circadian testing,[66] especially in children. Such data are lacking in children, healthy or sick. Studies failed to provide long-term evidence of efficacy (hypnosedatives/melatonin/light therapy) through longitudinal measures of sleep maintenance. It would be useful to look at whether any of these interventions can provide a long-term solution (12 months or more) and duration of effect.

Most studies conducted using melatonin and hypnosedatives have been of relatively short duration (the maximum being 8 weeks). This means that long-term safety data are lacking. A recent consensus statement on the pharmacologic management of insomnia in children and adolescents concluded that studies on the safety and efficacy of the pharmacologic treatment of insomnia are urgently needed.[25] Current options do not provide optimal balance between the tolerability and the efficacy profile, especially in the areas of sleep maintenance and long-term use.[67]

Editorial comment[68] has focused attention on the need to improve undergraduate and postgraduate medical training in the area of sleep medicine. Without detailed knowledge of sleep physiology and patho-

physiology, the development of rational management strategies for sleep disorders in children is difficult. When medications are used they typically do not have regulatory approval for pediatric use or for a specific sleep disorder. Most pharmacologic guidelines were developed for sleep disorders in adults and have been extrapolated empirically to children. At times, a decision to use medication in a child may be made not only to assist the patient, but also to help the parents or other family members cope. There is a lack of specialized training in sleep disorders for allied health professionals.

Noncompliance with medication is often an important issue in children with behavioral problems and must influence the development of therapies in this group. Drug interactions and adverse effects from polypharmacy must also be taken into consideration. The development of easy-to-swallow chewable or liquid forms of sleep medication is important in these young patients. The integration of behavioral and pharmacologic treatments may yield better patient outcomes. Improved training programs can play a lead role in enhancing pediatrician and health care team knowledge of the pharmacologic treatment of sleep disorders in children.[68]

This systematic review combines data across studies to estimate treatment effects with more precision than is possible in a single study. Although the process of conducting this review was robust, the major limitation was lack of consistent measures across the patient population, interventions, and outcome definitions across studies, leaving us with a lack of evidence upon which practice recommendations can be based.

CONCLUSIONS

Children with visual impairment and sleep disorders are a heterogeneous clinical group, which makes diagnosis and treatment difficult. The number of controlled studies that qualify for systematic review are limited. Across the 4 domains of treatment modalities that include behavioral therapy, light therapy, melatonin, and hypnosedatives, there are limited numbers of controlled studies that qualify for a systematic review or meta-analysis. A number of anecdotal reports suggest behavioral therapy as effective; however, evidence is weak owing to a lack of well-designed studies. Because of the difficulty in developing a rigorous study design, there is limited evidence for light therapy as an intervention. Case series and anecdotal reports suggest a

favorable effect on sleep initiation with the use of melatonin, but the evidence is not strong. Studies on melatonin are poorly designed without clear comparisons between the therapeutic effect of melatonin and a placebo. Some authors suggested an improvement on sleep latency, but the results were unclear. No significant effect was observed when comparing sleep latency with placebo on total sleep time and nocturnal arousal. Concerns about adverse effects and lack of empirical support regarding efficacy are significant barriers to the use of hypnosedatives. The safety profile of hypnosedatives urges caution in extrapolating adult data to children.

This review has identified the potential gap in research and practice over decades of limited studies in this specialized and vulnerable patient population of children with visual impairment. It is necessary to coordinate basic research, clinical research, health care practice, and public education, in addition to addressing policy and organizational issues, to improve therapeutic rationalization and outcomes in the management of sleep disorders for this highly vulnerable pediatric population.

Implications for Practice

Consistency in outcome measures of sleep and circadian pattern across different treatment modalities will be helpful for systematically evaluating and comparing end points in clinical trials in visually impaired children with sleep disorders. There is a need to validate subjective outcome measures used in RCTs in this population using standard quality-of-life and behavioral parameters as a component of the clinical study alongside objective measures, such as actigraphy.

Managing sleep disorders in children with visual impairment is a specialized area with limited indication for treatment modalities. Collaborative guidelines for management should be established. Multicenter collaboration through defined teams of developmental pediatricians, sleep physicians, and other health care professionals and researchers is essential, as many centers may not be employ specialized experts. Participation of collaborators with experience in evidence-based practice research is desirable owing to the lack of protocol on therapeutic modalities.

Implications for Research

Further diagnostic information on a child's circadian phase, period, amplitude, and susceptibility to phase-shifting, utilizing sleep and circadian measurement parameters, will greatly help in developing rational therapies. Further research should also concentrate on using and comparing the effects of standardized subjective and objective measurements (eg, sleep diary, polysomnography, actigraphy) within and between the studies for consistent primary and secondary outcome evaluation. In a specialized subpopulation, such as children with visual impairment, multicenter collaboration may be crucial in achieving a level of evidence to support or disprove the use of pharmacologic modalities.

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