Sleep and Pain in Pediatric Illness: A Conceptual Review

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SUMMARY

Background: Sleep disruption is a common comorbidity of pediatric pain. Consequences of pain and disrupted sleep, evidence for the pain-sleep relation, and how aspects of illness, treatment, and pharmacological pain management may contribute to or exacerbate these issues are presented. **Aims:** This conceptual review explored the relation between pain and sleep in children diagnosed with chronic medical or developmental conditions. The goal of this review is to expand upon the literature by examining common themes in sleep disturbances associated with painful conditions across multiple pediatric illnesses. Populations reviewed include youth with intellectual and developmental disabilities (IDD), migraines, cystic fibrosis (CF), sickle cell disease (SCD), cancer, juvenile idiopathic arthritis (JIA), juvenile fibromyalgia (JFM), and functional gastrointestinal disorders (FGIDs). **Results:** Consistent evidence demonstrates that children with medical or developmental conditions are more vulnerable to experiencing pain and subjective sleep complaints than healthy peers. Objective sleep concerns are common but often under-studied. Evidence of the pain-sleep relationship exists, particularly in pediatric SCD, IDD, and JIA, with a dearth of studies directly examining this relation in pediatric cancer, JFM, CF, and FGIDs. Findings suggest that assessing and treating pain and sleep disruption is important when optimizing functional outcomes. **Conclusion:** It is essential that research further examine objective sleep, elucidate the pain-sleep relationship, consider physiological and psychosocial mechanisms of this relationship, and investigate nonpharmacological interventions aimed at improving pain and sleep in vulnerable pediatric populations.

Introduction

Pain is a relatively common experience among children and adolescents [1–3]; yet, due to methodological differences among studies, prevalence rates often vary [4,5]. Approximately 25–40% of youth report persistent or recurrent pain [3]. Most commonly, pain reported by pediatric patients is related to headaches, abdominal pain, and musculoskeletal pain [1,4,5]. Youth who report pain in multiple locations often endorse higher pain intensity scores than those who report pain in a single location [2,3], and females typically report higher rates of pain than males [1–8]. Pain prevalence rates reported for all youth also commonly increase with increased psychosocial stressors [3,5] and age [5].

Persistent/recurrent pain also commonly occurs in association with a number of pediatric chronic conditions (e.g., osteogenesis imperfecta, sickle cell disease, juvenile idiopathic arthritis, hemophilia, cancer) and may be a symptom of the underlying health conditions [9,10]. Relatedly, Kozlowski and colleagues reported that 86% of hospitalized pediatric patients reported pain, with moderate-to-severe pain indicated by 40% [11]. Regardless of the precipitating factors, etiology, or location of pain, pediatric chronic/recurrent pain can negatively impact quality of life and emotional functioning [7,12–14] and lead to deconditioning and

functional disability [15]. Chronic and recurrent pain in childhood and adolescence has been associated with psychiatric comorbidity in adulthood [16,17] and increased risk of chronic/recurrent pain across the lifespan [16–18]. As such, recurrent and/or persistent pediatric pain remains a serious developmental health concern [5,10].

A common comorbidity of pediatric pain is poor sleep [19] although the nature of this relationship remains somewhat unclear. Poor sleep may be characterized by difficulty falling or staying asleep, poor sleep quality, short sleep duration, and/or poor sleep hygiene [20]. In children without pain, poor or insufficient sleep impacts mood, behavior, cognitive functioning, and the propensity for obesity [21]. Sleep disturbance also plays a role in stress response, stress management, quality of life, and general physiological health. Indeed, across a number of populations, poorer physical functioning, reduced cognitive abilities, and increased social, emotional, and behavioral difficulties are associated with inadequate sleep [20,22–24].

Approximately half of pediatric patients with pain report disturbed sleep [24–26]. The 2015 Sleep in America Poll™ conducted by the National Sleep Foundation revealed that Americans with chronic pain obtain substantially less sleep than those with no pain or than those with acute pain. Youth with pain frequently

report sleep-onset and maintenance difficulties [24,27,28], increased cognitive and somatic arousal at bedtime [24], difficulty awakening in the morning, daytime sleepiness [27,28], and poorer sleep quality than healthy peers [24]. Sleep disruption often impacts daytime functioning and activity levels among youth with pain more than among those without pain [19,29]. In fact, studies with adults suggest poor sleep predicts poorer pain tolerance [30], and previous night sleep duration (<6 h or more than 9 h) is predictive of greater next-day pain [31]. Similarly, various disease-specific literature reviews (e.g., juvenile idiopathic arthritis [32], cancer [33], and cerebral palsy [34]) highlight that pain is associated with sleep disturbances among a number of specific pediatric populations.

Lewandowski and colleagues reviewed sleep disturbances associated with common pediatric medical conditions. Although this review was not focused *solely* upon the relationship between sleep and pain, a bidirectional relationship between sleep disturbances and health-related outcomes, in general, was postulated. More specifically, it was hypothesized that chronic medical conditions may contribute to sleep disruptions, which consequently adversely affect health-related outcomes [35]. Similarly, a recent review conducted by Walter *et al.* (2015) postulated that in pediatric oncology patients, sleep affects patients' perceived pain and pain affects sleep quality and disturbances in pediatric oncology patients [33].

Although a relationship between sleep and pain is evident, the nature of this relationship warrants additional investigation. Lewin and Dahl initially proposed a bidirectional model in which daytime pain predicts nighttime sleep disturbances, and sleep disturbances predict next-day pain [36,37]. Valrie and colleagues add to this and suggest a model that emphasizes the biopsychosocial context is warranted. This model proposes a bidirectional relationship between sleep and pain and suggests that each is affected by physiology and other factors such as sex, ethnicity, mood, and social variables [20]. Previous studies also have demonstrated that higher pain is predictive of poorer sleep quality, which in turn is predictive of higher pain the following day [38,39]. Conversely, other studies indicate a unidirectional model rather than one indicative of a reciprocal relationship. In particular, among adolescents with chronic pain, daily pain did not predict nighttime sleep quality, although longer sleep duration, poorer subjective sleep quality, and more minutes of wake after sleep onset (WASO) predicted increased next-day pain [40,41]. Similar findings exist for chronic pain in adults; although pain was related to sleep complaints, it was not predictive of disturbances and difficulties with sleep [42]. Population-based longitudinal studies support this unidirectional model using both subjective and objective assessments of sleep and pain and indicate that sleep difficulties are more predictive of pain than pain is of sleep [43]. Growing research suggests that the relationship between sleep and pain is valid, but of more importance are processes that impact the relationship. Specifically, it is thought that sleep may be responsible for neural processes that influence development and maintenance of pain by aiding in pain modulation. Additionally, consistent with the model proposed by Valerie *et al.* (2015) [44], growing research also suggests that biopsychosocial factors such as positive or negative affect, opioid and dopamine systems, and social factors may play a role in the relationship between sleep and pain [43].

Given the high prevalence of pain and sleep disruption in pediatric populations and the relationship between pain and sleep, the primary aim of this article was to conceptually examine the evidence regarding this relationship in pediatric chronic health conditions and to identify conditions where additional research regarding this relationship is warranted. The current manuscript examines common themes in sleep disturbances associated with painful conditions across illnesses. Although previous reviews have examined sleep disturbances among youth with common medical conditions [35], sleep problems associated more generally with pediatric pain [20], and the relationship between sleep and pain in specific disease populations [32–34], this conceptual review further extends the literature by providing a more focused examination of common themes in sleep disturbances *associated with pain* among specific pediatric conditions. For a summary of studies reviewed, please refer Table 1. For additional details regarding the nature of the pain and sleep relationship, interventions, and targets for future research, please refer Table 2.

Intellectual and Developmental Disabilities

Pain may occur more frequently in children with IDD (35/52%) [45,46] compared with those without intellectual and developmental disabilities (IDD) [2]. Children with IDD of broad etiologies as well as those with more specific developmental disabilities (i.e., Autism, Cerebral Palsy, Down Syndrome, Fragile X Syndrome) suffer from sleep problems at a higher rate than typically developing children [45,47]. Neurological impairments that often accompany IDD may make this group more susceptible to sleep problems [48]. Sleep difficulties are also common among children with physical disabilities [49], which are frequent comorbidities in children with IDD [45]. Furthermore, medical conditions are often the cause of sleep problems in this population [50]. Studies reviewed often utilized objective sleep and/or pain measures in addition to parent reports regarding levels of pain [45–47].

Studies suggest that pain exacerbates sleep problems in children with physical disabilities. Those with physical disabilities who reported pain were 3.4 times more likely to report sleep problems; furthermore, pain was the strongest predictor of sleep problems in this group [49]. Those with IDD and pain have significantly shorter sleep duration, and pain appears to disrupt sleep in this population even if pain is pharmacologically managed [45]. However, the relation between pain and sleep problems in children with IDD has not been well studied. In fact, only one study has specifically investigated this relationship and found it to be correlational in nature [45]; no studies have looked at the directionality of the pain and sleep relation. A better understanding of pain and sleep among children with IDD is warranted to inform treatment efforts addressing pain and sleep disturbance in this population.

Chronic Headaches and Migraines

Up to 57.6% of youth experience monthly or weekly headaches, while 3.0–14.7% experience pain on more than 7 days per month or nearly daily headaches or migraines [51–53]. Subjective sleep disturbances, including shorter sleep duration, difficulties

Table 1 Summary of studies reviewed

Chronic health condition	Overview of pain	Overview of sleep	Overall summary of pain & sleep	Articles
Intellectual & developmental disabilities (IDD)	<ul style="list-style-type: none"> 35–52% of those with IDD report pain at least once per week 	<ul style="list-style-type: none"> Neurological impairments increase likelihood of sleep problems Experience more sleep problems than typically developing children 	<ul style="list-style-type: none"> Those with physical disabilities who reported pain were 3.4 times more likely to report sleep problems, and pain was found to be strongest predictor of sleep problems Those with IDD and pain have significantly shorter sleep duration 	[2,45–50]
Chronic headaches & migraines	<ul style="list-style-type: none"> 57.6% report monthly or weekly pain 3.0–14.7% report pain nearly every day or on at least 7 days per month 	<ul style="list-style-type: none"> Associated with problematic sleep initiation, maintenance, sleep-disordered breathing, shorter sleep duration, and greater PLM and arousal indices 	<ul style="list-style-type: none"> Subjective sleep disturbance is more common in youth with headaches or migraines compared with healthy peers 	[51–61, 67–69]
Cystic fibrosis (CF)	<ul style="list-style-type: none"> 42–84% experienced pain in past month 45.6% report pain within past week Headache, abdominal pain most common Pain significantly related to decreased levels of daily activity and impacts quality of life Pain remains underassessed and undertreated 	<ul style="list-style-type: none"> Lower sleep efficiency and more frequent nocturnal awakenings Cough, upper airway obstruction, hypoxia, and increased work of breathing may contribute to sleep disruptions 	<ul style="list-style-type: none"> Unclear which specific factors impact sleep in patients with CF or the extent to which pain may influence sleep and vice versa 	[71–75,78]
Sickle cell disease (SCD)	<ul style="list-style-type: none"> Report experiencing pain on 22% of days 	<ul style="list-style-type: none"> Parents identify their children to have poor sleep on 43% of days Sleep-disordered breathing is the most common finding on PSG Higher hemoglobin associated with problematic sleep onset 	<ul style="list-style-type: none"> Avascular necrosis (AVN) contributes to more subjective sleep-related difficulties than those without AVN 49% of parents identify pain to interfere with child's sleep Bidirectional relationship between sleep quality and pain is <i>moderated</i> by pain medication use and stress and <i>mediated</i> by negative mood 	[41,80,83,84,86–89,92]

(continued)

Table 1 (Continued)

Chronic health condition	Overview of pain	Overview of sleep	Overall summary of pain & sleep	Articles
Pediatric oncology	<ul style="list-style-type: none"> 49% report experiencing pain at diagnosis and during early phases of treatment Pain is more distressing and pronounced near end of life 	<ul style="list-style-type: none"> Fatigue (46.2%) and sleep disturbance (29.0%) cited as most common psychological symptoms Excessive daytime sleepiness most common sleep symptom reported Sleep can be impacted directly or indirectly by cancer 	<ul style="list-style-type: none"> One study found no significant relationship between pain, subjective sleep experiences and activity patterns 	[98–102, 104, 106, 107, 110]
Juvenile idiopathic arthritis (JIA)	<ul style="list-style-type: none"> 39% report daily pain Arthritis-related pain common on more than 60% of days 	<ul style="list-style-type: none"> 44–70% have disturbed sleep Associated with greater subjective sleep disturbance and objective sleep fragmentation 	<ul style="list-style-type: none"> Higher pain is associated with more sleep disturbances. Daily functional limitations due to sleep quality and difficulty initiating sleep partially mediated by pain intensity Unidirectional relationship between sleep quality and pain 	[38, 39, 112, 116–121]
Juvenile fibromyalgia (JFM)	<ul style="list-style-type: none"> 97% report diffuse pain 76% report headaches More severe muscle pain than CFS Greater pain than JRA 	<ul style="list-style-type: none"> 69% report sleep disturbance 20–52% endorse fatigue 40–70% exhibit persistent sleep problems More sleep disturbance than CFS Greater fatigue and sleep problems than JRA 	<ul style="list-style-type: none"> Conflicting evidence regarding whether alpha/delta sleep in JFM is related to pain and sleep disruption 	[129–134]
Functional GI disorders (FGIDs)	<ul style="list-style-type: none"> 29% report being awakened by pain 	<ul style="list-style-type: none"> 75% report poor sleep quality Associated with prolonged sleep-onset latency, snoring, difficulties waking, and daytime sleepiness 12–30% above clinical cutoffs on Sleep Disorders Scale for Children 	<ul style="list-style-type: none"> Although pain and sleep are common experiences in patients with FGIDs, studies rarely examine the pain–sleep relationship 	[27, 137–139]

CFS, chronic fatigue syndrome; JRA, juvenile rheumatoid arthritis; PLM, periodic limb movement; PSG, polysomnography.

Table 2 Summary of specifics related to pain and sleep in pediatric illness

Population	Pain-sleep relation	Assessment (no. of studies) ^a	Pharmacological interventions ^b	Nonpharmacological interventions ^b	Future research
Intellectual and developmental disabilities (IDD)	<ul style="list-style-type: none"> Correlational 	<ul style="list-style-type: none"> CSHQ (2) Sleep Diary (1) NCCPC-R (1) Actigraphy (1) 	<ul style="list-style-type: none"> Pain disrupts sleep, even if pharmacologically managed Sleep medication significantly related to increased parent-reported bedtime resistance and sleep duration^e 	—	<ul style="list-style-type: none"> Better understanding of how medical comorbidities common in IDD impact pain and sleep Investigate the pain-sleep relation to inform interventions Include validated pain, subjective sleep, and objective sleep measures Develop or validate measures specific to this population
Chronic headaches & migraines	<ul style="list-style-type: none"> Correlational 	<ul style="list-style-type: none"> PSG (3) Actigraphy (1) SHS (1) SDSC (3) PDSS (1) CSHQ (2) PSQ (1) Headache Intake Questionnaire (3) 	—	<ul style="list-style-type: none"> CBT is associated with improved headaches but not objective sleep 	<ul style="list-style-type: none"> Include prospective or longitudinal designs Examine both directions of the pain-sleep relation Utilize objective measures of sleep patterns Target interventions for headaches and sleep
Cystic fibrosis (CF)	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Actigraphy (1) BPI (3)^c MPI (1)^c DPA-CF (1)^c Faces Pain Scale (1) VAS for pain (2) 	—	—	<ul style="list-style-type: none"> Examine the connection between pain and sleep Explore effective pain and sleep interventions Improve understanding of factors that impact sleep in CF

(continued)

Table 2 (Continued)

Population	Pain-sleep relation	Assessment (no. of studies) ^a	Pharmacological interventions ^b	Nonpharmacological interventions ^b	Future research
Sickle cell disease (SCD)	<ul style="list-style-type: none"> • Bidirectional 	<ul style="list-style-type: none"> • PSG (5) • VAS for pain and sleep quality (6) • CSHQ (1) • PSQ (1) • PSQ (1) • PROMIS Fatigue Short Form (1) 	<ul style="list-style-type: none"> • Pain medication use moderates pain-sleep relationship and results in better functioning 	—	<ul style="list-style-type: none"> • Include healthy controls and child report • Determine aspects of sleep that are disrupted outside of sleep-disordered breathing • Identify interventions to improve pain and sleep
Oncology	<ul style="list-style-type: none"> • Unknown 	<ul style="list-style-type: none"> • Actigraphy (2) • VAS for fatigue⁴ • Sleep diary⁴ • MSAS (1) • Preschool & Adolescent Body Outline (1) • ESS^d • SSS^d • PDSS^d • MSLT^d 	<ul style="list-style-type: none"> • Opioids may impact arousal and awakening 	—	<ul style="list-style-type: none"> • Include validated pain measures • Investigate the prevention and intervention of sleep disorders and fatigue • Establish nature of sleep disorders for specific cancers • Identify interventions to improve pain and sleep
Juvenile idiopathic arthritis (JIA)	<ul style="list-style-type: none"> • Correlational • Unidirectional (1 study) 	<ul style="list-style-type: none"> • PSG (3) • MSLT (1) • Actigraphy (2) • CSHQ (5) • PedsQL MFS (2) 	—	—	<ul style="list-style-type: none"> • Include self-report, objective and subjective measures of excessive daytime sleepiness • Investigate interventions to improve sleep and pain
Juvenile Fibromyalgia (JFM)	<ul style="list-style-type: none"> • Unknown 	<ul style="list-style-type: none"> • PSG with MSLT and Actigraphy (1) • PSQ (2) • SHS (1) 	—	<ul style="list-style-type: none"> • Inconsistent findings on benefit of CBT for sleep and pain • Physical and occupational therapy improve subjective sleep quality and energy levels 	<ul style="list-style-type: none"> • Directly examine the pain-sleep relationship • Investigate interventions to improve sleep and pain

(continued)

Table 2 (Continued)

Population	Pain-sleep relation	Assessment (no. of studies) ^a	Pharmacological interventions ^b	Nonpharmacological interventions ^b	Future research
FGIDs	<ul style="list-style-type: none"> Correlational 	<ul style="list-style-type: none"> Actigraphy (1) SDSC (1) CSQ with Modified ESS (1) 	—	<ul style="list-style-type: none"> Yoga associated with improved sleep quality, fatigue, and abdominal pain in young adults 	<ul style="list-style-type: none"> Increase research in this population Directly examine the pain-sleep relationship Develop interventions that target both pain and sleep disruption

BPI, Brief Pain Inventory; CSHQ, Children's Sleep Habits Questionnaire; DPA-CF, Daily Pain Assessment-CF; ESS, Epworth Sleepiness Scale; MSAS, Memorial Symptom Assessment Scale; MPI, Multidimensional Pain Inventory; NCCPC-R, Non-Communicating Children's Pain Checklist-Revised; PDSS, Pediatric Daytime Sleepiness Scale; PSQ, Pediatric Sleep Questionnaire; PedsQL MFS, Pediatric Quality of Life Multidimensional Fatigue Scale; PSG, polysomnography; SDSC, Sleep Disturbance Scale for Children; SHS, sleep habits survey; SSS, Stanford Sleepiness Scale; VAS, Visual Analog Scale; CBT, cognitive-behavioral therapy; FGIDs, functional GI disorders; MSLT, multiple sleep latency testing.

^aSleep and pain measures that are well-established or approaching well-established.

^bOnly interventions that targeted sleep and pain were examined and included in the table.

^cBased on findings from a systematic review of pain in adults with CF [73].

^dBased on findings from a review of sleep and pain in Pediatric Oncology [33].

^eBased on findings from Breau and Camfield (2011) [45].

initiating and maintaining sleep, bruxism, and poor sleep quality [54–61], are more likely in youth with headaches or migraines than healthy peers. Predictors of sleep disturbance include evening or nighttime headaches, migraines versus other headaches, greater pain and headache frequency, and a longer time since onset of chronic headaches [54,60,62–65].

Findings are mixed regarding objective sleep evaluated by polysomnography (PSG) and actigraphy. Although there are no significant PSG differences between those with and without episodic migraines [66], chronic migraines are associated with problematic sleep initiation and maintenance, sleep-disordered breathing, shorter sleep duration, and greater periodic limb movement (PLM) and arousal indices [56,67]. Increased frequency, intensity, and duration of migraines are associated with higher PLMs [56], but little is known about other sleep outcomes. When examining sleep-wake patterns using actigraphy, earlier rise times and restless sleep were found in those with headaches versus those without [68] and shorter sleep duration at age 7 is associated with a greater likelihood of migraines at age 11 than those obtaining more sleep [69].

Cognitive-behavioral therapy (CBT; including coping strategies, relaxation training, and sleep hygiene education) is associated with improvements in headaches but not in objective sleep [70]. Overall, findings indicate a variety of sleep problems in those with migraines or headaches compared to healthy peers, with greater disturbances associated with more pain. The majority of the studies were of case-control and correlational design despite the significant increase in the number of studies conducted since the Valrie and colleagues (2013) [20] review, with recent studies utilizing a prospective or longitudinal design [62,69]. Additional research is needed regarding objective sleep-wake patterns and sleep hygiene, the direction of the pain-sleep relation, and appropriate interventions to target symptoms of headaches and sleep disturbance.

Cystic Fibrosis

Pain is common among patients with cystic fibrosis (CF), particularly given the involvement of several organ systems [71,72]. Some studies have utilized well-established assessment measures to evaluate pain in patients with CF [71–74]. Approximately 42–84% of patients with CF experience pain [75], with headache, abdominal, back, chest, and limb pain being the most commonly identified [71,73,75]. Pain is significantly related to decreased daily activity, altered quality of life, and interference with treatments [71–73,75]. Chest pain, headaches, back, joint, and limb pain also occur in patients with CF [72,76,77]. Chronic pain was described beginning at the age of 3 years in those with CF, with a significant increase in prevalence rates after the age of 8 years [71]. Nearly half (45.6%) of CF patients reported experiencing pain at least once a week, and a majority (67.4%) indicated that their pain caused some emotional disturbance [72]. Even patients with mild levels of CF reported experiencing regular painful symptoms [71] that can persist into adulthood [77,78] and be present at end-stage disease [76]. However, pain in CF remains underassessed and subsequently undertreated; routine assessment and monitoring of pain in patients with CF should be an integral component of treatment [71].

Sleep disturbance is not a direct symptom of CF, but coughing has been found to interfere with sleep [75]. It is important to note, however, that a causal relationship between cough and sleep disturbance has not been substantiated [78]. Findings from PSG studies indicate that in addition to nocturnal cough, upper airway obstruction, hypoxia and increased work of breathing related to lower airway obstruction may also contribute to disruptions in sleep [74]. Actigraphy results suggest that children with CF have lower sleep efficiency and more frequent nocturnal awakenings compared with matched healthy controls [78].

Despite the general literature suggesting a pain–sleep connection and the presence of pain in patients with CF, no studies have investigated the possible relationship between pain and sleep in children with CF; therefore, the nature of this relationship remains unknown. Future research is warranted to not only identify the various factors that impact sleep in these patients but also the extent to which pain may influence sleep disturbances and vice versa.

Sickle Cell Disease

Sickle cell disease (SCD) is an inherited blood disorder that affects millions of individuals around the world, including those of sub-Saharan African descent and individuals from Cuba, South America, India, Saudi Arabia, and countries in the Mediterranean [79]. On average, individuals with SCD report pain on 22% of days [41] and those with a diagnosis of avascular necrosis (AVN) experience more subjective sleep difficulties than those with SCD but no radiological evidence of AVN [80]. Studies of sleep disturbance in pediatric SCD have included both subjective [41,80–89] and objective [85,90–93] sleep measures; however, studies frequently lack a healthy control group and child self-report.

Sickle cell disease is associated with subjective difficulties with sleep initiation and maintenance, daytime sleepiness, sleep-disordered breathing, fatigue, restless legs symptoms, and poor sleep quality [80–83,89]. Although a number of studies note parent-reported subjective sleep problems, one study found no significant sleep concerns on most domains [82]. Sleep-disordered breathing is the most common finding on PSG in children with SCD, including snoring, episodic hypoxemia [92], and upper airway obstruction or obstructive sleep apnea (OSA) [85,90–93]. More frequent oxygen desaturations and lower minimal oxygen saturations are seen in children with SCD than in those without SCD presenting with sleep-disordered breathing concerns [90,91]. Nearly one-quarter of youth with SCD also exhibit a PLM Index ≥ 5 , which is associated with a greater arousal index and lower sleep efficiency [85].

Hemoglobin is inconsistently associated with fatigue measures [81], while higher hemoglobin is associated with problematic sleep onset [83]. A large portion of parents (49%) rate pain as interfering with child sleep [88] and identify poor sleep to occur on 43% of pain days versus 3% of pain-free days with shorter sleep duration during pain episodes [84,86]. A bidirectional relationship between sleep quality and pain is evident in children with SCD [41,89]. This relation is moderated by pain medication use and stress (i.e., better functioning with medication use and lower stress) and mediated by negative mood [41,87,89]. One

study reported that pain frequency and severity were significant predictors of fatigue [81].

In sum, pediatric SCD is commonly associated with sleep-disordered breathing; however, additional research is needed to determine whether other aspects of sleep (including self-report) are disrupted. Further, sleep disturbance and pain appear to have a bidirectional relationship in this population, and this relationship is impacted by medication use, mood, and stress.

Pediatric Oncology

Cancer remains one of the leading causes of nonaccidental death in children, although mortality rates have significantly declined over the past several decades [94]. Children with cancer experience numerous distressing symptoms due to disease process and treatment. One of the most concerning and common symptoms is pain [95–97], although few studies have utilized well-established measures to assess pain [95,98]. More specifically, 49% of children reported pain at diagnosis; throughout treatment, pain related to surgery, procedures (e.g., bone marrow aspiration, lumbar puncture), side effects of chemotherapy (e.g., mucositis), and disease progression were most often identified and typically were most prevalent during the early phases of treatment [99–101]. However, these symptoms are even more pronounced and distressing to patients and their families near end of life. In advanced cancer patients, pain remained the most common physical symptom (47.7–56%) followed by fatigue (46.2%); sleep disturbance was cited as a common psychological symptom (29.0%) [98,102].

In addition to pain, fatigue, and sleep loss [97,103], excessive daytime sleepiness is the most common sleep symptom reported by pediatric oncology patients, particularly those with tumors of the central nervous system [104]. Often, well-established subjective measures are utilized to assess sleep disturbance and fatigue in pediatric oncology [33], and objective measures appear to be applied less frequently [105]. Sleep can be directly affected by cancer (i.e., physical presence of a tumor) or indirectly impacted by cancer due to treatments, medications (i.e., steroids), surgery, and subsequent side effects or medical complications [106,107]. Of note, following outpatient chemotherapy, participants were found to have increased numbers of nighttime awakenings on actigraphy [105]. Additionally, the normal circadian rhythm may be impacted by cancer and pain management medications [33,108,109]. A review by Walter and colleagues (2015) [33] highlights the impact of insufficient sleep quantity and poor sleep quality among children with cancer and also emphasizes the lack of research available regarding the prevention and intervention of sleep disorders and fatigue in pediatric oncology.

Given the connection between pain and sleep, it is prudent that both are routinely monitored and treated to ensure good quality of life for patients during their treatment and in subsequent years. Much attention has been paid to sleep and pain as independent constructs within pediatric oncology, although little is known about how these domains interact with each other and the subsequent indications for prevention and intervention [33]. Although one study found no significant relationship between ratings of pain, subjective sleep experiences, and activity patterns among a small sample of hospitalized patients

[110], additional research investigating the pain–sleep relationship in children with cancer is warranted, as the nature of this relationship remains unclear and therefore makes it difficult to establish effective interventions.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a common rheumatic disease affecting 1 to 4 per 1000 children [111]. Most children experience arthritis-related pain on more than 60% of days, while 39% experience daily pain [112]. Studies included validated subjective sleep measures (typically parent reports) [38,39,113–117], daily assessments of pain and sleep [118,119], PSG, multiple sleep latency testing (MSLT), and/or actigraphy [114,117,120–123].

Between 44 and 70% of those with JIA score above the cutoff for disturbed sleep on the Children's Sleep Habits Questionnaire (CSHQ) [39,116,117], with higher pain associated with more sleep disturbances [38,39]. JIA is associated with more difficulties in sleep initiation and maintenance, presleep anxiety, parasomnias, sleep-disordered breathing, daytime sleepiness, and less time in slow-wave sleep than healthy peers [38,113,115,123]; however, two studies found no significant differences [121,123]. Predictors of fatigue in JIA include more pain and tender or swollen joints [39,124]. Findings are inconsistent or nonsignificant regarding disease activity as a predictor of fatigue, subjective sleep disturbance, and PSG sleep variables [38,39,114,122,124].

Juvenile idiopathic arthritis has also been associated with more sleep fragmentation [120,123] and higher proportion of alpha/delta non-REM sleep than healthy peers [120,121,123]. Predictors of alpha activity include increased pain and greater joint involvement [121]. MSLT indicates a shorter mean sleep-onset latency (indicating increased sleepiness) in JIA with active disease compared with controls and those with inactive disease, but the findings are mixed regarding whether daytime sleepiness is clinically significant [122,123]. Actigraphy demonstrated short sleep duration and poor sleep efficiency; however, there was no relation to disease activity, and healthy controls were not utilized [117]. Prospective assessments support a unidirectional relationship between sleep quality and pain, as poor sleep quality predicted next-day pain rather than daily pain predicting nighttime sleep, and mood served as a moderator [119]. Similarly, daily mood and stress were predictors of pain and fatigue [125]. Furthermore, the relation of daily functional limitations to sleep quality and difficulty initiating sleep were partially mediated by pain intensity [118]. Findings overall indicate that JIA is associated with greater subjective sleep disturbance and objective sleep fragmentation. Most studies included correlational, case–control designs, and studies examining directionality typically focused only on sleep predicting next-day pain. Additional research is needed regarding child-reported sleep, objective and subjective measures of excessive daytime sleepiness, directionality of the pain–sleep relation, and appropriate interventions to improve sleep and pain in this population.

Juvenile Fibromyalgia

Juvenile fibromyalgia (FM) is a condition affecting 1.2–6.2% of youth and is characterized by chronic widespread pain and fatigue

of a largely unexplained etiology [126]. Although nine studies were reviewed, only one included validated sleep measures [127] and three used objective sleep measures [127–129].

Youth with JFM frequently endorse diffuse pain (97%), report headaches (76%), describe sleep disturbance (69%), and endorse fatigue (20–52%), with 40–70% exhibiting persistent problems [129–132]. Other studies note that nearly all with JFM report poor subjective sleep compared with 14% of healthy peers [129,131]. JFM is associated with more severe muscle pain and sleep disturbance than chronic fatigue syndrome [133] and with greater pain, fatigue, and sleep problems than juvenile rheumatoid arthritis and healthy comparison groups [134]. When examining objective sleep–wake patterns, JFM is associated with greater sleep-onset latency, decreased total sleep time and sleep efficiency, more fragmented sleep, more periodic limb movements, and greater alpha/delta slow-wave sleep than healthy peers [127–129]. There is conflicting evidence regarding whether alpha/delta sleep in JFM is related to pain and sleep disruption [127,128].

Several studies have examined interventions in JFM. Findings are inconsistent in reporting outcomes of CBT in JFM and changes in sleep and pain; however, one study citing nonsignificant improvements in pain and sleep quality compared with a control group did not include a sleep component to treatment [131,135]. Pain, subjective sleep quality, and energy levels improved following physical and occupational therapy interventions in JFM despite limited changes in objective sleep [127]. Overall, findings indicate subjective and objective sleep concerns in JFM. Limited research remains in this population, and few studies directly examine the relation between pain and sleep, indicating that continued research is needed to further clarify this in JFM.

Functional GI Disorders

Functional GI disorders (FGIDs) are a group of conditions (e.g., recurrent abdominal pain, irritable bowel syndrome, functional abdominal pain) that include symptoms of abdominal pain or discomfort, other somatic complaints (e.g., changes in bowel movements), and a combination of genetic, physiological, and psychological contributors [136]. Of the five studies included, only two included validated subjective sleep measures [27,137] and one used objective sleep measures [138].

In FGIDs, 29% report being awakened by pain, and 75% report poor sleep quality [138]. There are no significant differences in subjective sleep–wake patterns between youth with FGIDs and healthy peers; however, FGIDs are associated with prolonged sleep-onset latency, snoring, difficulties sleeping and waking, and daytime sleepiness [27,139]. Approximately 12–30% of those with FGIDs were above clinical cutoffs on the Sleep Disorders Scale for Children for difficulties initiating/maintaining sleep, sleep–wake transition disorder symptoms, and excessive sleepiness [137], although no significant differences in objective sleep–wake patterns have been found between children with FGIDs and healthy peers [138]. Yoga has been associated with improved sleep quality, fatigue, and abdominal pain in young adults, although significant improvements were not found in adolescents [140]. Overall, findings indicate subjective sleep complaints in FGIDs. There continues to be a dearth of research in this patient

population, and studies are typically correlational in nature and seldom directly examine the relation between pain and sleep; therefore, continued research is needed to elucidate the relation of sleep and pain.

The Effect of Medications on Sleep and Pain

Although the majority of research investigating the connection between pain medication and sleep has primarily been conducted in adults, it is important to consider this relationship when working with pediatric populations. Pain medications such as aspirin and ibuprofen impact sleep in adults by increasing the number of awakenings and time spent awake, in addition to decreasing sleep efficiency. Importantly, however, aspirin and ibuprofen were not significantly different from placebo, although sleep was most disturbed in the ibuprofen group [141].

Opioids (e.g. morphine, oxycodone, fentanyl) are often prescribed for youth with painful conditions or when youth experience significant illness- and/or treatment-related pain [142,143]. Although opioids often diminish nociceptive pain, use of these medications may also negatively impact sleep. For example, Valrie and colleagues found that use of pain medications among children with SCD eliminated the negative impact of pain on sleep; however, analgesic/opioid medications did contribute to poor sleep quality regardless of pain severity while remaining unrelated to sleep duration [41]. Indeed, opioids are believed to play a role in arousal and awakening, although the nature of the opioid-sleep relationship remains unclear [108,109] and current evidence is conflicting. Nonetheless, long-term opioid therapy has been linked to respiratory disturbances and more severe oxygen desaturation during non-REM sleep [144,145]. Furthermore, acute administration of morphine reduces the duration of slow-wave and REM sleep and increases non-REM stage 2 sleep [146]. Conversely, some findings indicate that use of long-acting opioids results in improved sleep quality, increased sleep duration, decreased sleep-onset latency, reduced need for sleep medication, and decreased pain interference [147–149].

A number of other medications may also impact pain and/or sleep and are important to consider for youth with developmental disabilities and chronic illness as they are frequently prescribed multiple medications. For example, benzodiazepines (e.g., diazepam, clonazepam, lorazepam, alprazolam, triazolam) [150–152] are among classes of medications indicated for pre-operative anesthesia, myoclonic epilepsy, status epilepticus, and muscle tension [152]. Some of these medications are used for the treatment of insomnia due to their sedating effect; however, benzodiazepines may worsen sleep-disordered breathing and are associated with increased daytime sleepiness [150,151]. Antihistamines (e.g., diphenhydramine, dimenhydrinate), anticholinergics (e.g., scopolamine), dopamine antagonists (e.g., chlorpromazine, metoclopramide), and/or serotonin antagonists (granisetron, ondansetron) are commonly used to treat nausea and emesis associated with various conditions and/or sequelae of disease-related therapies [153]; yet, these medications also may induce sedation and are associated with increased daytime drowsiness and lethargy [152,153]. Similarly, classes of medication commonly used to treat neuropathic pain, including anticonvulsants (e.g.,

gabapentin, carbamazepine, lamotrigine) and tricyclic antidepressants (e.g., imipramine, amitriptyline), often have a sedating effect [152,154]. Although there are a number of medications that induce sedation, other medications may cause insomnia. Corticosteroids (e.g., dexamethasone, prednisone), certain broad-spectrum antibiotics (e.g., quinolones), psychostimulants (e.g., methylphenidate), alpha-adrenergic agonists (e.g., epinephrine, midodrine), beta blockers (e.g., bisoprolol, propranolol), ephedrine, and pseudoephedrine are classes of medications which may induce insomnia [154]. Moreover, some individuals experience a paradoxical response to benzodiazepines and/or antihistamines, resulting in induction of insomnia rather than sedation [152,154]. Furthermore, antihistamines, dopamine antagonists, selective serotonin reuptake inhibitors (e.g., citalopram, paroxetine), selective norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine), and tricyclic antidepressants have been associated with increased disruptive behaviors during sleep among adults (e.g., restless leg syndrome) [155]; however, additional research is needed to examine this relationship in children with medical disorders [154,155]. Further research is needed to evaluate the effect of pharmacological pain management on sleep quality and efficiency, particularly in youth.

Clinical Implications

Although additional research is needed to further clarify the exact nature of the relationship between sleep and pain in youth with various developmental disabilities and/or chronic conditions, evidence suggests that, generally speaking, both pain and sleep disturbances are relatively common among these children and adolescents. As such, thorough assessment and regular monitoring of pain and sleep-related difficulties should be incorporated into the routine care of these youth; and information gleaned from assessments should, in turn, be used to inform and periodically update individualized intervention efforts.

A number of methods are available to assist in the assessment of pain and sleep-related difficulties. For example, clinical interviews could glean information about sleep habits, quality, disorders, and daytime impairments as well as current and lifetime pain symptoms and interventions attempted [156,157]. Use of a daily diary could aid in the comprehensive assessment and ongoing monitoring of sleep and pain [158], and added use of actigraphy, if available and when feasible, may provide objective multnight data including total time in bed, total sleep time, sleep-onset latency, WASO, and sleep efficiency [156,159]. Moreover, if information gathered during the clinical interview suggests the possibility of sleep disruptors such as periodic limb movement disorder or OSA, polysomnography should be incorporated as part of the diagnostic process [156].

Once collected, assessment data should be used to inform individualized intervention planning. Which intervention should be implemented at what point in time will be guided not only by initial information obtained but also by ongoing monitoring of progress. Behavioral interventions should be utilized if improvements related to sleep-onset latency and frequency/duration of night waking would aid in improving the child's functioning [160,161]. Similarly, cognitive-behavioral interventions including sleep restriction and stimulus control might be incorporated into

treatment of insomnia [156] and have been shown to be beneficial for sleep, fatigue, and pain [162]. Even in the context of pain, cognitive-behavioral therapy for insomnia, which incorporates use of sleep restriction and stimulus control, has demonstrated decreased sleep latency, decreased time awake after sleep onset, and increased sleep efficiency in adults, with outcomes maintained up to 12 months after conclusion of therapy [163–166]. A clinician's guide for behavioral interventions for common pediatric sleep problems [156] and a comprehensive review of pediatric pain assessment and treatment [167] are excellent resources for clinicians.

Discussion

Pain is clearly a component of many chronic conditions in children and adolescents. Although the exact relation between pain and sleep disturbance has not been fully elucidated, it is clear that sleep is disrupted in children and adolescents with chronic pain. Previously, a bidirectional relationship had been proposed; however, recent work has demonstrated that disrupted sleep may increase reports of pain as well as pain interference on daily activities. This is a very underdeveloped field of study, and much more research is certainly necessary to more fully understand the directional relation between pain and sleep, the pathophysiology of the relationship, and the most important elements of assessment and intervention to improve quality of life. In some cases, intervention for those with insomnia and pain should focus on ameliorating insomnia symptoms, which may in turn serve to improve pain and daytime function. Further, it is unclear whether the relation between pain and sleep varies based upon the chronic illness population of interest.

Children with developmental disorders and intellectual disabilities are at particular risk of both painful conditions and

sleep disturbance, and those with more neurological impairment and physical disabilities show even greater risk of sleep disruption. Children with painful conditions have been shown to have higher rates of sleep-disordered breathing, periodic limb movements, more difficulty with sleep initiation and maintenance, shorter sleep duration, fatigue, and daytime sleepiness. Importantly, mood has been demonstrated to impact the relation between pain and sleep in youth with SCD and in youth with JIA. Thus, a thorough assessment of mood in youth with chronic medical conditions is essential. It also points to the importance of inclusion of mood assessments in future studies investigating the pain/sleep relationship in youth with chronic conditions. Clearly, pharmacological management of pain should be optimized in children with medical conditions, but further research is essential to determine the role of adjunctive nonpharmacological interventions in managing both pain and sleep disturbance in these vulnerable populations. Additionally, determining the potential impact of prescribed medications on children's sleep is important, as consideration of other agents and/or adding pharmacological agents to improve sleep may be warranted. Certainly intervention studies in adults have shown promise with respect to use of cognitive-behavioral therapy for insomnia and its role in improving both pain and sleep in those with chronic pain, and this work could easily be modified and extended for application to children and adolescents. Furthermore, additional research in this area can highlight the appropriate off-label prescribing of sleep-promoting agents in youth with chronic pain.

Conflict of Interest

The authors declare no conflict of interest.

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