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Review

Traumatic Brain Injury, Sleep Disorders, and Psychiatric Disorders: An Underrecognized Relationship

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Abstract: Traumatic brain injury (TBI) is commonplace among pediatric patients and has a complex, but intimate relationship with psychiatric disease and disordered sleep. Understanding the factors that influence the risk for the development of TBI in pediatrics is a critical component of beginning to address the consequences of TBI. Features that may increase risk for experiencing TBI sometimes overlap with factors that influence the development of post-concussive syndrome (PCS) and recovery course. Post-concussive syndrome includes physical, psychological, cognitive and sleep–wake dysfunction. The comorbid presence of sleep–wake dysfunction and psychiatric symptoms can lead to a more protracted recovery and deleterious outcomes. Therefore, a multidisciplinary evaluation following TBI is necessary. Treatment is generally symptom specific and mainly based on adult studies. Further research is necessary to enhance diagnostic and therapeutic approaches, as well as improve the understanding of contributing pathophysiology for the shared development of psychiatric disease and sleep–wake dysfunction following TBI.

Keywords: traumatic brain injury; anxiety; depression; post-traumatic stress; attention deficit disorder; sleep–wake disorders

1. Introduction

Traumatic brain injuries (TBI) are common in the pediatric population and can have neurocognitive consequences. Understanding the factors that influence risk for a child or adolescent to experience a TBI is an important first step in exploring the consequences of TBI. Several studies have reported specific risk factors, including pre-existing psychiatric and behavioral problems to increase the likelihood to sustain a traumatic brain injury in the pediatric population (Table 1). For instance, recent studies have shown that attention deficit hyperactivity disorder (ADHD), aggression, psychiatric prescription medication use, and use of mental health services increase the risk of TBI [1,2]. These factors have been ascertained by both prospective and retrospective analysis. The results of these findings highlight some overlap, but also identify some discrepancy in risk factors, leading one to question the influence of recall bias, influence of etiology of TBI or other contributing factors to these differences (Table 2) [1–7].

Table 1. Factors associated with increased risk for youth to experience traumatic brain injuries (TBI) [8,9].

TBI Risk Factors
Low Socioeconomic Status
Overcrowded households
Disadvantaged neighborhoods
High incidence of adverse life events
Young maternal age
Older siblings with few younger siblings
Previous TBI

Table 2. Comparison of risk factors for TBI and the development of post-concussive syndrome (PCS) based on retrospective and prospective studies [1–7].

Retrospective	Prospective	Overlap	Discrepancy
Male gender	Male gender		
Lower socioeconomic status (SES)	Behavioral problems		
Behavioral problems	Adverse family events		SES status
Attention deficit hyperactivity	during childhood	Male Gender	Maternal features
disorder (ADHD)	Punitive parenting practices	Behavioral Problems	Cognitive baseline
Cognitive problems	Maternal depression		Sports Participation
Contact Sports Participation	Maternal age		
Competitive Sports Participation	Maternal education		

Post-concussive syndrome (PCS) is defined by symptoms occurring after a head injury including, but not limited to, somatic, sleep, cognitive and/or emotional/behavioral difficulties (Table 3) [10–14]. It was previously thought that approximately 15% of those who suffer a single mild TBI (mTBI) will develop chronic PCS; however, McInnes found that this number is likely significantly higher [15]. In fact, a large proportion will continue to have a measurable impairment more than a year out from the injury [15]. In 2012, an estimated 329,290 children, younger than 20, were treated in United States emergency departments for TBI [16]. Among this demographic, the rate of emergency department visits for sports and recreation-related injuries with TBI more than doubled between 2001 and 2012 [16]. In fact, approximately 20% of 8–12th grade students were identified as having had at least one concussion, with 5.5% sustaining recurrent injuries [3]. It is important to identify associated risk factors for TBI within this group, as well as contributors to successful recovery to improve incidence and reduce morbidity.

Table 3. Post-concussive symptoms and prevalence [10–14,17–23].

Post-Concussive Symptoms		Prevalence
Physical	Headache	25–47%
	Nausea	7–12%
	Dizziness	30%
	Fatigue	16–40%
	Problems with Balance and Gait	24–34%
	Light and Sound Sensitivity	1–4%
Emotional	Emotional Lability	1–40%
	Increased Anxiety	8–17%
Cognitive	Cognitive Deficits	7–22%
	Language Impairment	1–68%
	Disorientation and Amnesia	21–30%
Sleep	Sleep–Wake Disturbance	13–67%

The clinical course following TBI is influenced by multiple factors. Pre-injury behavior and functioning are strong predictors for the long-term development of behavioral problems and worsening

of symptoms of psychiatric disorders [24–26]. For instance, children experiencing a significant life stressor prior to injury have been found to be at greater risk of persistent post-concussive symptoms after TBI [13,27]. Children with behavioral problems are commonly endorsed as being at greater risk for experiencing a TBI; however, these specific behavioral disorders are not commonly well defined [4,13].

In addition to baseline behavioral and psychiatric features, sleep–wake dysfunction is also associated with TBI (Figure 1). Sleep difficulties can affect cognition (particularly attention, memory, and executive functions), behavior, and emotional problems (Table 4) [28]. Pre-existing sleep conditions enhance the likelihood of experiencing post-concussive symptoms [29]. In addition, the presence of a comorbid sleep disorder contributes to psychologic instability, resulting in increased emotional lability and behavioral problems with worsened daily executive function [28,30]. In general, symptoms from a mild TBI should disappear by 3 months, and functional status improves over the first six to twelve months without obvious regression over the first 30 months [31]. However, in patients with history of psychiatric disease and/or sleep dysfunction, recovery may be more protracted (Table 5) [10].

Table 4. TBI comorbidities and associated symptoms [4,32–40].

	Diagnoses	Signs and Symptoms
Sleep–Wake	Insomnia	Difficulty falling/staying asleep, unrefreshing sleep, insufficient number of hours of sleep despite adequate opportunity
	Sleep Apnea	Snoring, restlessness, apnea, enuresis, diaphoresis, open-mouth breathing, bruxism, sleep fragmentation
	Idiopathic Hypersomnia	Excessive daytime sleepiness, ± excessive number of hours asleep
	Narcolepsy	Excessive daytime sleepiness, cataplexy, sleep paralysis, sleep related hallucinations, sleep fragmentation
	PLMD/RLS *	PLMs >5/h on PSG; Restlessness, discomfort in arms or legs that interferes with sleep onset or maintenance, improves with movement
	CRD	Sleep difficulties that conflict with age typical circadian rhythm; When given opportunity sleeps appropriate number of hours for age
	Parasomnia	Sleep walking, sleep talking, confusional arousals, night terrors, REM behavior disorder/dream enactment behavior
Psychiatric	Anxiety	Avoidance, phobias, obsessive compulsive symptoms, generalized anxious feelings
	Depression	Fatigue, irritability, sadness, difficulty concentrating, difficulty with recall, suicidality
	ADHD	Impaired attention, hyperactivity, impaired working memory, impaired working speed
	PTSD	Headaches, decreased psychosocial recovery, sleep disturbance/nightmares, pain, flashbacks, amnesia, irritability/aggression, concentration difficulty

PLMD: periodic limb movement disorder; RLS: restless leg syndrome; CRD: circadian rhythm disorder; ADHD: attention deficit hyperactive disorder; PTSD: post-traumatic stress disorder; PLM: periodic limb movements; PSG: polysomnography; * Note: RLS is a clinical diagnosis and PLMD is a polysomnographic diagnosis.

Table 5. Risks factors associated with prolonged recovery following TBI [2,3,41–43].

Risk Factors of Protracted Recovery
Pre-injury psychiatry history
Injury Severity
Family dysfunction
Sleep–Wake Dysfunction
Re-injury
Female gender
Referral to Rehabilitation Facility
Prescription for acute headache rescue therapy
Chronic headache treatment
Presenting SCAT2 * score <80
Participation in a non-helmeted sport

* SCAT2—Sport concussion assessment tool.

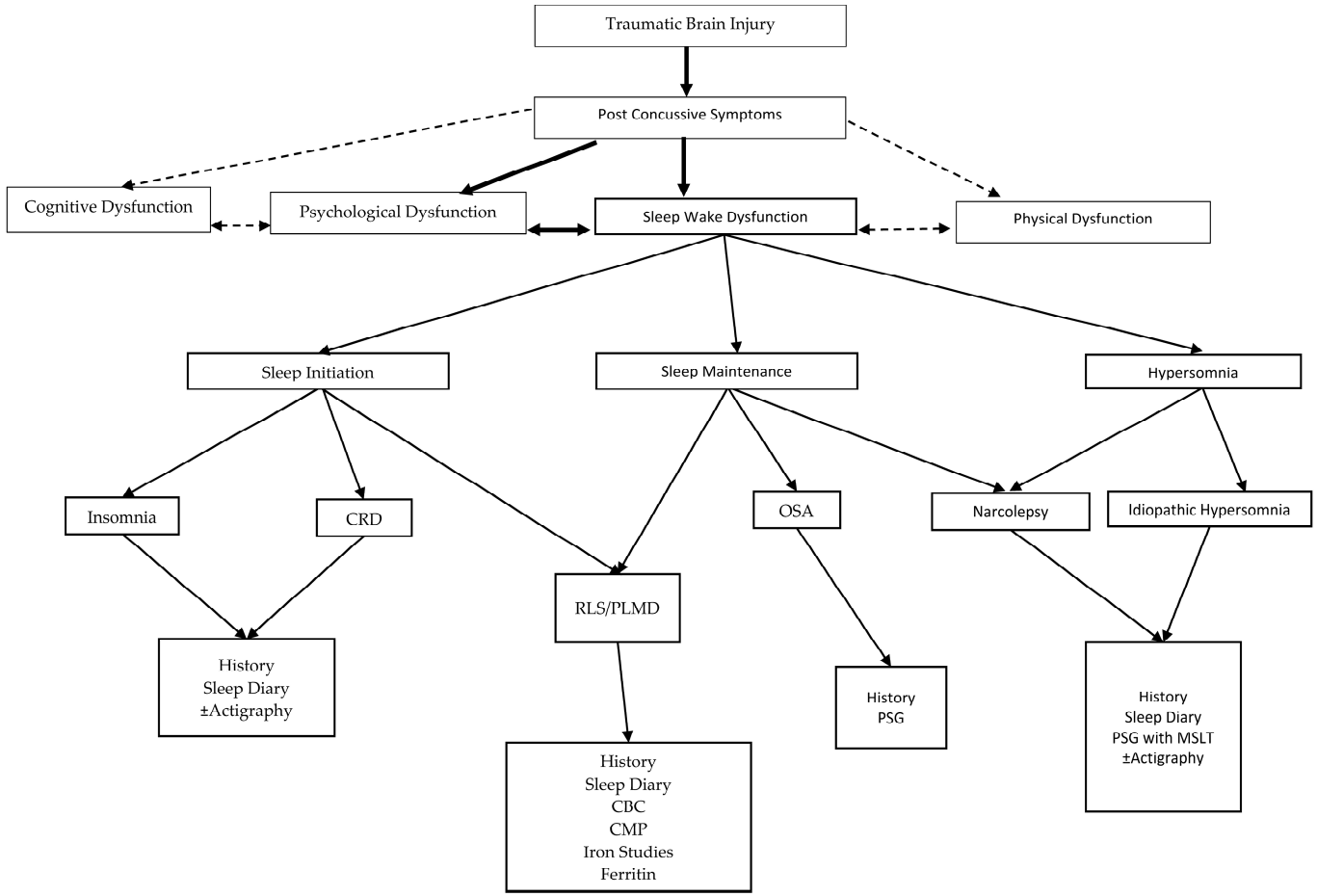

Figure 1. Traumatic brain injury and the development of post-concussive syndrome, highlighting the development of sleep wake dysfunction and its relationship to co-morbid PCS symptoms. CRD: Circadian Rhythm Disorder; CBC: Complete Blood Count; CMP: Complete Metabolic Panel; OSA: Obstructive Sleep Apnea; PSG: Polysomnography; MSLT: Multiple Sleep Latency Test; RLS: Restless Leg Syndrome; PLMD: Periodic Limb Movement Disorder.

The complexity in care of TBI patients is reflective of the multi-disciplinary needs of these patients. TBI-related morbidity may be improved with enhanced understanding of factors that not only contribute to risk for experiencing TBI, but also improved understanding and assessment of the post-concussive factors that influence the course of recovery. This manuscript will focus on the relationship of sleep and psychiatric features. It will explore the clinical relationship, examine the possible crossover in pathophysiology of TBI, sleep, and psychiatric disorders, and discuss the approaches to consider for diagnosis and treatment, highlighting the need for a comprehensive multidisciplinary evaluation to improve recovery times and outcomes [44].

2. Anxiety

Children with TBI are at a significantly higher risk than those with orthopedic injuries to present with new-onset mood and/or anxiety disorders [45]. Anxiety can be defined as the brain's response to danger causing avoidance type behavior [46]. Age at time of injury may influence the development of symptoms. Children who are younger than 10 years old are at higher risk of developing post-concussive anxiety disorders [23,47]. There is also a relation to sleep–wake dysfunction.

In general, youth with anxiety are found to have an increased rate of sleep problems with 88% of those with anxiety reporting at least one sleep problem, and 55% reporting three or more sleep problems [48]. One study also showed that sleep disturbance may vary with age, with younger children being more prone to nighttime wakings and sleep anxiety, and adolescents being more likely to experience excessive daytime sleepiness [49]. After TBI, individuals with continued symptoms of insomnia and fatigue, up to 2 years after the injury, have been found to have higher rates of depression and anxiety [50]. In fact, sleep disturbance, even in the acute post-TBI period, predicted the development of anxiety and depression in the chronic period for all severities of TBI.

3. Major Depressive Disorder

Depressive disorders occur in 10–25% of children post TBI [39,51,52]. Children greater than 12 years of age are five times more likely to experience post-traumatic depressive symptoms [51]. In general, depressed patients may have problematic sleep, as well cognitive difficulties and energy loss. Insomnia or hypersomnia is frequently one of the defining characteristics for depression. The development of depressive symptoms has been suggested to be due to either the injury itself, or as a result of other post-concussive comorbidities, such as anxiety, aggression, and sleep disturbance [53,54].

Due to their intimate relationship, the symptoms of depression and sleep–wake dysfunction influence the development and prognosis of one another. Patients identified to have a sleep disturbance ten days post TBI were 6 times more likely to have depression [54]. Sleep deprivation, defined as 6 h of sleep or less a night, in adolescents at baseline, had a 25–38% increased risk of developing depressive symptoms at follow up exams [55]. On the other hand, major depression and depressive symptoms increase the risk for the development of insomnia [56]. There is a suggestion that early onset depression may be related to the direct injury, whereas late onset depression may be due to a psychological reaction to the injury [57]. However, when including sleep symptoms as part of the evaluation, the pattern of development is less clear.

4. ADHD

ADHD has not only been shown to increase the likelihood to experience TBI, but a preexisting diagnosis of ADHD may also lead to worse outcomes after TBI [58–60]. ADHD that develops as a result of head injury is referred to as secondary ADHD or S-ADHD [61]. S-ADHD has been shown to develop in about 10–20% of patients post TBI. In one study, 15% of S-ADHD cases developed after one year and 21% after two years [9]. Increased TBI severity also increases the incidence of S-ADHD from 7–46% going from mild to severe TBI respectively [51]. Children with TBI, less than 2 years old, have double the risk for the development of S-ADHD as compared to the general population [62], thus raising the questing as to whether S-ADHD is a direct result of injury versus a biased population

of children with poor self-regulation who may be more likely to participate in risk-taking behaviors resulting in injury [62].

The relationship between sleep and ADHD has a significant bidirectional effect, which is exaggerated in children following TBI [63]. Children with TBI and ADHD have a poorer sleep quality and quality of life than children with primary ADHD without TBI [64]. Evaluation of comorbid sleep dysfunction in secondary ADHD is lacking, but likely has a similar deleterious effect.

5. Post-Traumatic Stress Syndrome

Post-traumatic stress disorder (PTSD), as a part of PCS, has been well described in adults with TBI [65]. Data is lacking, however, to demonstrate the same relationship in children. Specific symptoms of PTSD present after TBI have been poorly defined in pediatric studies. There is a suggestion that children with orthopedic injuries more frequently display PTS symptoms than those with mTBI and met more symptom criteria at 12 months [40]. On the other hand, there is also a report of children with severe TBI exhibiting higher levels of PCS symptoms than those with moderate TBI or orthopedic injury [66]. Furthermore, another study demonstrated that childhood PTSD after traffic injuries was associated more with increasing age and parental PTSD, and no relationship to severity of injury [67]. The evolving anatomy and age-specific biomechanical properties of the developing child increase risk for distinct types of injuries that rarely occur in adults [68]. This may contribute to the differences observed in the development of PTS symptoms between adults and children.

Another ill-defined parameter in the literature is what symptoms of PTSD are present post TBI [69]. Persistent attention deficits at 3 months post injury have been identified as a risk factor for continued PTS symptoms at 6 months [70]. On the other hand, working memory and verbal learning deficits were found to be protective [70]. This may suggest that patients with impaired working memory and verbal learning, have impaired ability to recall the event, lending to reduced PTS symptoms [65]. Many comorbid conditions often present with TBI and can lead to shorter life expectancy, poor academic performance, and neurocognitive deficits [71]. It has been suggested in adults that sleeping difficulties may be an earlier indicator for risk of PTS disorder [72]. Another study with veterans notes that nightmares are commonly comorbid with TBI [73]. Those with insomnia and PTSD post TBI were found to have a subjective increase in sleepiness as compared to those with just PTSD and insomnia [73]. Literature evaluating sleep-specific risks associated with PTSD in pediatrics is lacking for comparison.

6. Crossover Pathophysiology of TBI, Sleep, and Psychiatric Disorders

TBI can be the result of diffuse or focal injury and frequently can be a combination of both. Diffuse injury occurs when the mechanism causes non-specific global damage, as in diffuse axonal injury or concussion. Focal injury occurs when the mechanism causes a specific targeted area of damage, such as with hematoma or contusion. These injuries may be a result of direct linear force (coup), acceleration deceleration forces (contra-coup) or a combination of both, causing shearing injuries and axonal damage [68]. In addition, there are secondary brain injuries that develop over hours to days that may result from perfusion abnormalities, neuroinflammation, excitotoxicity and dysregulated cell signaling [74,75].

The frontal–striatal circuits, which can affect executive function and wakefulness are particularly vulnerable [76]. Damage to this system is found in 18–38% of children who have suffered a TBI between the ages of 5–15 and may be related to the impaired executive function identified in the first year after injury [77]. Emotional dysregulation can also be common after TBI; this combined with executive dysfunction and hormonal imbalance can make adolescents who experience TBI more susceptible to impulsive decisions and poor choices in social situations [78]. This also may indicate why performance on neuropsychological testing may be normal; however, patients still experience significant functional impairment in real-world situations [78].

Sleep–wake dysfunction following TBI is common, affecting up to 70% of patients. The sleep–wake cycle is tightly controlled via cooperation between circadian rhythms, sleep–wake homeostasis, and external environmental factors such as medication, diet, stress, and surroundings [37]. The main sleep-promoting pathways are found in the ventrolateral (VLPO) and median preoptic nuclei (MnPO), which inhibit ascending arousal pathways in the brainstem and hypothalamus [79]. The arousal areas include histaminergic tuberomammillary nucleus, orexinergic lateral hypothalamus, noradrenergic locus coeruleus, serotonergic dorsal raphe, and the cholinergic laterodorsal tegmental and pedunculopontine tegmental nuclei [80].

Post-mortem evaluations of the brains of patients with and without TBI demonstrated a significant reduction in hypocretin neurons [81,82]. Impaired hypocretin (orexin) signaling causes excessive daytime sleepiness [37,83,84]. It has been shown that reduced cerebrospinal fluid (CSF) orexin levels are associated with a worse clinical outcome with greater likelihood for depression and sleep–wake dysfunction [85,86].

Impaired melatonin production has also been suggested to be contributory [81]. Melatonin directs this circadian regulation of sleep and wakefulness, but also has been found to have anti-inflammatory properties [37]. Melatonin may repress TBI-induced inflammation by activating mitophagy and removing damaged mitochondria [87], although it secretes directly into the third ventricle and levels can be much higher in the CSF than in the peripheral blood [88]. Peripheral sampling does provide an accurate surrogate. Melatonin production can be impacted by TBI. CSF melatonin may vary depending on time from TBI. Acutely, there is evidence of increased melatonin with decreased levels as time progresses [81,89]. These findings, however, have been inconsistent. The acute increase is suggested to be related to the anti-inflammatory properties, which may contribute to neural recovery [89,90]. Additionally, this variation may be related to the spectrum of post-traumatic sleep disorders seen (i.e., hypersomnolence to delayed sleep phase disorder) [81,91].

Circadian rhythm is associated with mood regulation, and disturbances can be linked to the development of psychiatric symptoms [37,92]. There has been the suggestion that this may be related to clock genes, which regulate circadian entrainment. Certain clock genes have been implicated in altering the homeostasis of individuals leading to psychiatric disorders such as autism, ADHD, anxiety, major depressive disorder, bipolar disorder, and schizophrenia [93]. This may represent an increased genetic susceptibility for the development of comorbid post-traumatic sleep dysfunction and mental illness.

7. Evaluation and Treatment Options

A multi-disciplinary approach should be taken in the clinical evaluation of patients following TBI. The consideration of specialties to be involved include neurology, psychiatry, sleep medicine, rehab services, social work and sports medicine, depending on the mechanism of injury. There should be a standardized intake, such as the acute concussion evaluation [10], to ensure a comprehensive evaluation of symptoms. Establishing a pre-morbid baseline may be helpful in stratifying risk for the development of PCS. In addition, it is important to identify patient-perceived impact of head injury and goals for recovery.

Treatment of sleep or psychiatric disorders post TBI is mainly based on adult studies, with limited information on treatment in pediatrics. Frequently, the treatment applied is based on recommendations that have been successful in the relevant psychiatric and sleep disorder in the non-traumatic brain injury population [94]. The approach to treatment in patients with comorbid sleep and psychiatric dysfunction should address symptoms of both processes.

In general, psychiatric medications in pediatrics are started with the lowest dosing and titrated slowly, as pediatric patients may be more susceptible to side effects of these medications [94–97]. The selection of medication is based on the psychiatric symptoms present (Table 6). Selective serotonin reuptake inhibitors are considered first-line treatment for anxiety and depression [94]. S-ADHD treatment with stimulant medication has been shown to likely be beneficial; however, there seems to be a more attenuated

response for S-ADHD than that of primary ADHD [2,98,99]. Of note, those treated with psychostimulant medication prior to TBI, have been noted to have a lower risk of TBI [100]. In fact, retrospectively it was identified that most ADHD patients who sustained TBI were not pharmacologically treated prior to the injury [61,101].

PTS disorder patients with nightmares have been shown to have improvements with prazosin and/or image-rehearsal therapy with or without cognitive behavioral therapy (CBT) for insomnia [102]. CBT, for those with insomnia, has also been shown to decrease total wake time and improve sleep efficiency [103].

Table 6. Psychiatric disorders and treatments [104–110].

Psychiatric Disorder	Treatment Options
Depression	
Mild	CBT ± Exercise
Severe	CBT + SSRI ± Exercise
Suicidality	CBT + SSRI ± Hospitalization ± Exercise
With psychotic features	CBT + Antidepressant + Antipsychotic ± Exercise
Refractory	CBT + Antidepressant + Antipsychotic ± Exercise ± ECT
Anxiety	First Line: CBT ± SSRI, SNRI Second Line: CBT + SSRI, ± SNRI Third Line: CBT + SSRI + different SSRI or SNRI with Benzodiazepines used as a bridge until SSRI becomes effective.
ADHD	Stimulants [111,112] (methylphenidate, amphetamine), ± CBT, non-stimulants (atomoxetine, guanfacine, clonidine)
PTSD	CBT, Ensure Safety, Treat Comorbidities, ± Antiadrenergic medications (clonidine, guanfacine, or prazosin *)

* Prazosin is preferred in patients with PTSD nightmare disorder. CBT: cognitive behavioral therapy; ECT: electroconvulsive therapy; SSRI: selective serotonin reuptake inhibitor; SNRI selective serotonin norepinephrine reuptake inhibitor.

The approach to treating sleep–wake dysfunction is dependent on the specific sleep disorder present (Figures 1 and 2). Melatonin has also been studied for sleep disorders post TBI and although no statistical difference was found with daytime alertness, patients subjectively reported improved daytime alertness compared to baseline [113]. Amitriptyline has also been subjectively reported by patients to help with sleep disorders by increasing their sleep duration, despite any statistical difference being shown [113]. Other adult studies have shown that modafinil and armodafinil significantly improve sleep latency for those with excessive daytime sleepiness (EDS) due to mild or moderate TBI [114,115].

Studies evaluating non-pharmacological treatment are also limited. CBT has been shown to improve children's behavior post TBI [116]. Similarly, adolescents who participated in an online counselor-assisted problem solving therapy during their post-TBI hospitalization, showed less impaired functioning after [117]. In adults, blue light exposure, as a form of chronotherapy, was shown to reduce fatigue and daytime sleepiness following TBI [118]. Alternative therapies, such as acupuncture, have even demonstrated subjectively improved sleep quality, cognitive function, and the ability to taper sleep medication use [119]. Earlier recommendations include the importance of transition support including alerting school of injury and potential consequences, monitoring students for any increased needs, and offering assistance or adjusting requirements for a couple of weeks post injury [11].

A negative approach to problem solving and depression symptoms has been associated with elevated PTS symptoms and suggests that targeting negative aspects may help mitigate PTS symptoms [120]. This becomes important because adult and childhood survivors of TBI are already at elevated risk of suicidal behavior [121–123]. Symptom checklists are not adequate screening tools for all potential psychiatric outcomes, which highlights the importance of the physician's role in screening for psychiatric disorders and suicidal ideation post injury [26].

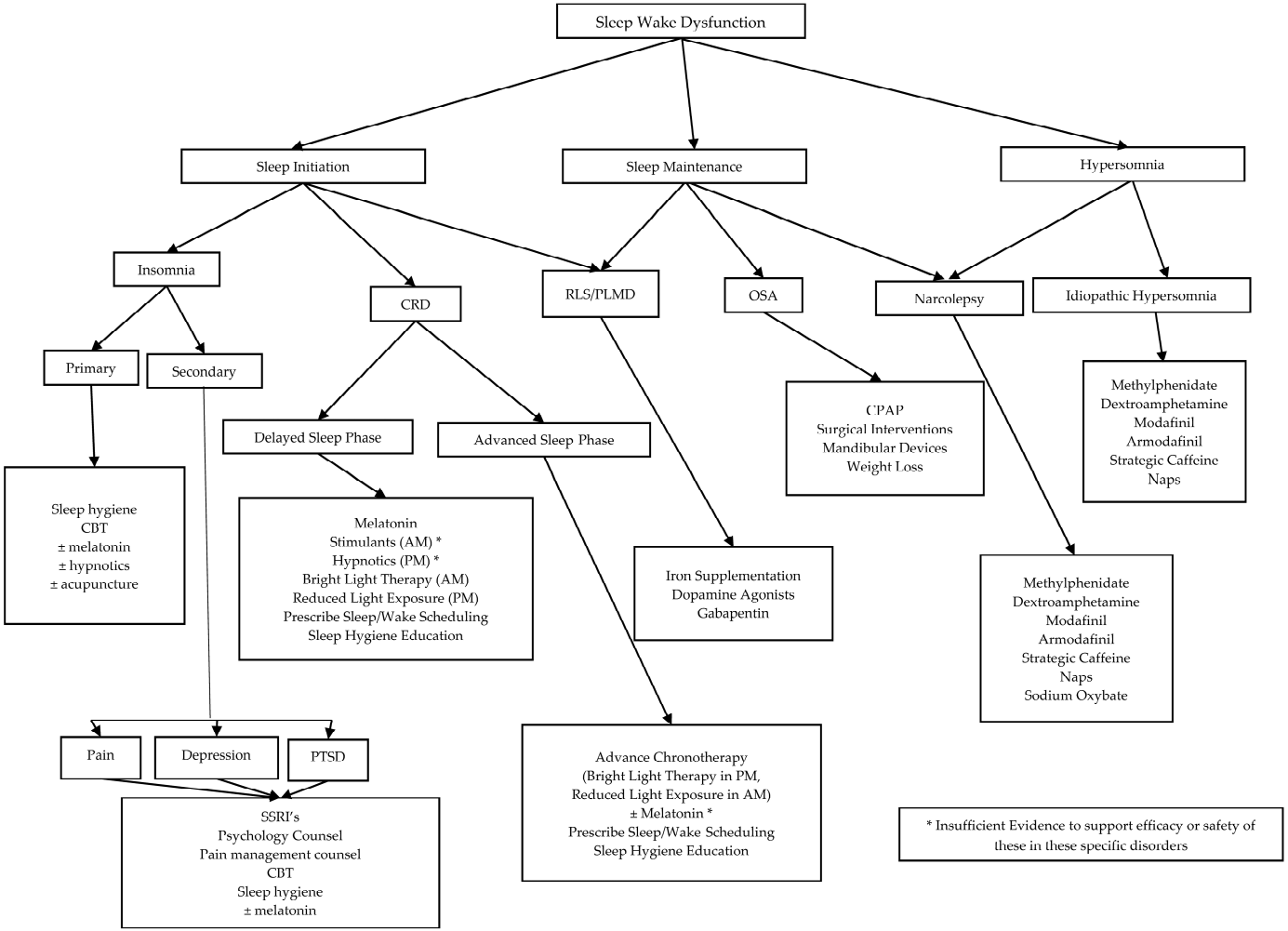

Figure 2. A disease-specific approach to treatment of sleep–wake dysfunction. CRD: Circadian Rhythm Disorder; OSA: Obstructive Sleep Apnea; RLS: Restless Leg Syndrome; PLMD: Periodic Limb Movement Disorder; CBT: Cognitive Behavioral Therapy; SSRI: Selective Serotonin Reuptake Inhibitor

8. Discussion and Future Direction

Traumatic brain injury is a significant pediatric public health concern. It is helpful to view TBI as a disease process, rather than an isolated event [38] due to the cumulative damage that can incur over time. This is evidenced by the features of post-concussive syndrome that can include evolving symptoms of physical, psychological, cognitive, and sleep–wake dysfunction. Increased comorbidity, such as co-occurrence of sleep–wake dysfunction and psychiatric illness, leads to more deleterious outcomes and a more protracted recovery. A multi-disciplinary approach is necessary to provide the comprehensive care necessary in these patients to optimize recovery.

Perception of an injury and expectations for recovery can dramatically influence patient outcomes [17]. Early incorporation of psychological support should be evaluated as a potential tool for improving outcomes in pediatrics. Adult studies have demonstrated benefit of both pharmacological treatments and non-pharmacological treatments; however, there is still a significant gap in knowledge when it comes to pediatric treatments. A targeted evaluation of these recommendations in patients by age and severity of TBI is necessary to determine whether adult treatments are appropriate and effective.

Well-defined TBI severity criteria are needed in the pediatric population. In addition, the effect of pre-morbid functioning needs to be better elucidated. Clinical studies that partner with school systems that implement baseline cognitive assessments may help in filling this data void. In order to improve understanding of how sleep and psychiatric symptoms influence recovery, longitudinal studies are needed. These studies should include well defined age at injury to better assess the effects of TBI on normal development and sleep ontogeny.

Conflicts of Interest: The authors declare no conflicts of interest.

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