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Sleep Disturbances in Pediatric Depression

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Abstract

Depressive illness beginning early in life can have serious developmental and functional consequences. Therefore, understanding its etiology and pathophysiology during this developmental stage is critical for developing effective prevention and intervention strategies. There is considerable evidence of sleep alterations in adult major depressive disorder. However, studies in children and adolescents have not found consistent changes in sleep architecture paralleling adult depression. This review article summarizes sleep polysomnography research in early-onset depression, highlighting the factors associated with variable findings across studies. In addition, potential avenues for future research will be suggested in order to develop more comprehensive theoretical models and interventions for pediatric depression.

Keywords

child; adolescent; depression; sleep; polysomnography; EEG

1. Introduction

Depression is a leading cause of morbidity and mortality in youngsters. Major depressive disorder, the most severe form of depression, occurs approximately in 2% of children up to 8% of adolescents (Kessler et al., 2001; Lewinsohn and Essau, 2002), and it is associated with significant problems in multiple social domains (Birmaher et al., 1996). Elevated risk for the disorder begins in the early teens and continues to rise in a linear fashion throughout adolescence, with lifetime rates estimated to range from 15% to 25% by late adolescence (Giaconia et al., 1994; Hankin et al., 1998; Kessler et al., 2001; Weissman et al., 1997). Numerous studies also have documented that early depressive episodes persist or recur into adult life along with ongoing psychosocial difficulties (Birmaher et al., 1996; Rao and Chen, 2009). These difficulties include, but are not limited to, disruption in interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning and unemployment, as well as increased risk for suicidal behavior, resulting in substantial socioeconomic burden (Birmaher et al., 1996; Rao and Chen, 2009). A better understanding

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of the etiology and pathophysiology of early-onset depression will be helpful in the development and implementation of more effective primary and secondary preventive strategies, thereby allowing such youth to achieve their full potential as adults.

The pathogenesis of early-onset depressive disorder involves interactions among a range of predisposing and precipitating factors, which in combination lead to alterations in psychological and biological processes (Birmaher et al., 1996; Rao and Chen, 2009). The focus of this report will be limited to sleep disturbances associated with juvenile depression. In order to better understand the sleep changes associated with juvenile depression, a summary of the literature on adult depression will be provided; in contrast to the huge wealth of information available in adult populations, empirical data in youngsters are limited by relatively modest sample sizes in very few studies.

2. Association between Sleep Regulation and Depression

There has been considerable interest in the relationship between sleep disturbances and depression, with over 2,000 publications since the 1960s. There are a number of reasons to consider the regulation of sleep as an essential component for understanding the pathophysiology and treatment of depression. There is a significant overlap in the control of sleep and mood regulation (Adrien, 2002). Sleep complaints are commonly associated with depression and form an essential criterion of the diagnosis (American Psychiatric Association, 1994).

Developmental influence(s) on the rates of depression and maturational changes in sleep regulation also imply a close connection between depressive disorders and sleep regulation. As described above, mood disorders are relatively rare prior to puberty but increase dramatically during adolescence (Giaconia et al., 1994; Hankin et al., 1998; Kessler et al., 2001; Weissman et al., 1997). There is evidence that sleep regulation at younger ages is relatively "protected" against disruptions. Specifically, pre-school and early-school-aged children demonstrate the greatest levels of deepest (Stage IV) sleep (Feinberg, 1974); (Williams et al., 1974). A more detailed description of sleep stages is described below. Prepubertal children are highly resistant to being awakened from deep sleep (Busby and Pivik, 1985). Children also demonstrate remarkable daytime alertness on objective measures of sleep (Carskadon et al., 1983). By mid-to-late puberty, however, profound changes occur in sleep regulation. In particular, there is a large drop in slow-wave sleep (Carskadon et al., 1983; Coble et al., 1987; Dahl et al., 1990), decrease in the threshold of arousal to disrupt sleep (Busby et al., 1994), and a dramatic increase in objectively measured daytime sleepiness (Carskadon et al., 1983). There is also evidence for a shift in the circadian pattern, with a preference for late-night schedules in association with puberty (Carskadon et al., 1983).

Objective sleep changes typically associated with adult major depressive disorder are rarely seen in prepubertal depression, gradually emerge after puberty, and appear as consistent biological findings in later adolescence (Kaufman et al., 2001). More details regarding these objective sleep changes are described below. Increased risk for depression during adolescent development, greater vulnerability to perturbation of the sleep system during adolescence, and relatively more robust depression-related sleep changes in older adolescents suggest a link between sleep dysregulation and increased liability to depression.

In this review, sleep disturbances associated with adult and juvenile depression will be described. Potential influential factors on sleep parameters will be discussed in the context of understanding developmental continuities and discontinuities in sleep patterns associated with depressive disorder. Additionally, an overview of the theoretical models that have

contributed to understanding the pathophysiology of depression will be provided. Finally, potential areas of future research will be suggested in order to develop more comprehensive theoretical models and interventions for pediatric depression.

3. Subjective Sleep Measures and Depression

Subjective sleep complaints can be assessed either through standardized self-report scales or clinical interviews. The information normally includes sleep/wake habits, and the duration, frequency and pattern of sleep disturbances.

3.1. Subjective sleep disturbances in adult depression

Sleep disturbance is a characteristic symptom of depressive disorders (American Psychiatric Association, 1994; Zimmerman et al., 2006), with subjective sleep complaints in over 80% of depressed patients (McCall et al., 2000; Reynolds and Kupfer, 1987). Typically, depressed patients suffer from difficulties in falling asleep, frequent nocturnal awakenings, and early morning awakening. While delayed sleep-onset and frequent awakenings accompany almost any kind of insomnia, early morning awakening was considered to be specific for endogenous depression but this hypothesis was not confirmed (Reynolds and Kupfer, 1987). Although insomnia is the most frequent complaint, hypersomnia also has been observed (Garvey et al., 1984; Hawkins et al., 1985), particularly in individuals with bipolar depression (Parker et al., 2006; Thase et al., 1989).

In a relatively recent study, insomnia was measured simultaneously by clinician ratings (Hamilton Depression Rating Scale; HDRS) and self-report (Beck Depression Inventory; BDI) in a sample of inpatients with major depressive disorder. A high proportion of patients reported insomnia on both measures; 93% and 97%, respectively (McCall et al., 2000). However, there was only a modest correlation in the severity of insomnia between the two measures. Also, increasing severity of insomnia on the HDRS was associated with better quality of life, while increasing severity of insomnia on the BDI was associated with worse quality of life. These data suggest that these two measures tap into different components of the insomnia severity in depressed patients.

In addition to cross-sectional evidence on the association between subjective sleep disturbances and depression, prospective studies demonstrated that sleep disturbances increase the risk for depressive disorders (Franzen and Buysse, 2008; Riemann and Voderholzer, 2003). Persistent insomnia also has been linked to increased risk of relapse and suicide (Agargun et al., 2007; Breslau et al., 1996; Wingard and Berkman, 1983).

3.2. Subjective sleep disturbances in pediatric depression

Few studies have assessed the prevalence and nature of subjective sleep complaints in children and adolescents with depression (Ivanenko et al., 2005; Lofthouse et al., 2009). In a study of prepubertal children with major depressive disorder, approximately two-thirds reported sleep-onset and sleep-maintenance insomnia, whereas almost 50% experienced terminal insomnia (Puig-Antich et al., 1982). Subsequent studies, including both children and adolescents with major depression, found that almost 75% manifested sleep disturbances, with over 50% experiencing insomnia only, approximately 10% with hypersomnia alone and 10% with both insomnia and hypersomnia (Liu et al., 2007; Yorbik et al., 2004). In an epidemiological sample of adolescents, almost 90% of those who met criteria for major depression indicated sleep disturbances, and approximately 75% of adolescents who initially reported sleep disturbances subsequently developed a depressive episode (Roberts et al., 1995). In a controlled investigation of children and younger adolescents with major depression, subjective ratings of sleep were assessed during a laboratory sleep study (Bertocci et al., 2005). Compared with controls matched on age,

gender and pubertal status, participants with depression reported poor sleep quality, increased number of awakenings, longer wake time and difficulty in waking in the morning. Even youngsters with dysthymic disorder experience sleep disturbances (Masi et al., 2003).

Sleep problems seem to be associated with greater severity of depression as well as more protracted and recurrent episodes, particularly in those who manifest both insomnia and hypersomnia (Liu et al., 2007). Additionally, sleep disturbances increase the risk for suicidal behavior in depressed youngsters (Barbe et al., 2005; Goldstein et al., 2008; Lofthouse et al., 2009; Roane and Taylor, 2008). Comorbid anxiety disorders also might be more common in depressed youth with sleep difficulties, specifically those with insomnia (Liu et al., 2007). Longitudinal studies revealed that sleep problems increase vulnerability to depressive disorders in children and adolescents (Gregory et al., 2009; Ong et al., 2006; Roane and Taylor, 2008; Roberts et al., 2002).

Taken together, subjective sleep complaints are highly prevalent in both youngsters and adults suffering from depression. Persistent sleep problems also might be associated with increased vulnerability to depression and poor clinical course.

4. Objective Measures of Sleep

Laboratory-based sleep studies examine the physiological characteristics of sleep through electroencephalographic (EEG) sleep measures or polysomnography. The traditional method of reporting EEG sleep parameters is macroarchitecture, and it refers to the visual method of scoring sleep stages; for example, proportion and time spent in rapid eye movement (REM) sleep and the four stages of non-rapid eye movement (NREM) sleep (see Figure 1). The time between sleep-onset and the appearance of the first REM sleep episode is known as REM latency. REM activity and REM density denote the number of eye movements during REM sleep. Delta or slow-wave sleep refers to stages 3 and 4 of NREM sleep. Sleep microarchitecture refers to the measures derived from all-night computerized, quantitative EEG analysis including frequency, amplitude and power in five standard EEG bands: alpha, beta, delta, sigma and theta.

In healthy subjects, the onset of sleep occurs about 10–15 minutes after switching off the lights, followed shortly thereafter by the progression of deeper stages of NREM sleep. The first REM period occurs approximately 90 minutes after sleep onset. NREM and REM sleep alternate throughout the night, with each sleep cycle lasting about 90–120 minutes. Short periods of intermittent awakenings occur throughout the night. The first REM episode is short in duration (1–5 minutes) but lengthens progressively across the night, whereas slow-wave sleep is concentrated in the early part of the night (see Figure 1).

4.1. Objective sleep disturbances associated with adult depression

Starting in the 1970s, numerous controlled studies have been conducted in adult patients with depression. Although no single EEG sleep marker is specifically associated with depressive disorders, a constellation of sleep changes has been observed consistently in patients suffering from major depressive disorder (Armitage, 2007; Benca et al., 1992; Riemann et al., 2001; Tsuno et al., 2005). The most reliable sleep macroarchitectural changes associated with major depression include sleep continuity disturbances (e.g., delayed sleep onset, and decreased sleep efficiency), shorter REM latency, increased REM activity and REM density, increased amount of REM sleep, and diminished slow-wave sleep (see Figure 1).

Sleep microarchitectural changes also have been described in relation to depression. Increased alpha and fast-frequency β activity were found both during NREM and REM

sleep, suggesting hyperarousal and sleep fragmentation in individuals with depression (Armitage, 2007; Armitage et al., 1992b; Lischke et al., 2002). Other studies reported reduced slow-wave activity (Borbely et al., 1981), particularly during the first NREM period (Kupfer et al., 1990). Also, lower temporal coherence of EEG sleep recorded from left and right hemispheres, and decreased synchronization of fast frequency activity have been observed in association with depression (Armitage, 2007; Armitage et al., 1999).

4.2. Objective sleep disturbances associated with pediatric depression

In contrast to the high frequency of subjective sleep complaints, EEG sleep studies in children and adolescents with depression have often failed to find objective evidence of sleep dysregulation (Ivanenko et al., 2005; Lofthouse et al., 2009). In fact, in the above-described study in which subjective sleep complaints were recorded in the laboratory, depressed youth with the most severe sleep quality ratings manifested significantly better sleep with respect to the number of awakenings and other objective measures of EEG sleep (Bertocci et al., 2005). These findings suggest that the subjective perception of sleep may differ from objectively measured sleep.

Among studies of sleep macroarchitecture (see Table 1), shorter REM latency, the most frequently observed marker of depression in youngsters, was observed only in 3/7 child samples (Arana-Lechuga et al., 2008; Dahl et al., 1990; Emslie et al., 1990), 8/13 adolescent samples (Dahl et al., 1990, 1996; Emslie et al., 1994; Kutcher et al., 1992; Lahmeyer et al., 1983; Rao and Poland, 2008; Rao et al., unpublished data; Riemann et al., 1995), and 0/3 studies that included both children and adolescents. Other observed EEG sleep changes in depressed youngsters included prolonged sleep latency (Arana-Lechuga et al., 2008; Armitage et al., 2000; Dahl et al., 1990; Dahl et al., 1996; Emslie et al., 1994; Goetz et al., 1987; Kutcher et al., 1992), decreased sleep efficiency (Appelboom-Fondu et al., 1988; Emslie et al., 1994; Goetz et al., 1987), and increased REM density (Cashman et al., 1986; Dahl et al., 1990; Emslie et al., 1994; Lahmeyer et al., 1983; McCracken et al., 1997; Rao and Poland, 2008; Rao et al., unpublished data). With respect to slow-wave sleep deficits, only one study revealed overall group differences (Rao et al., unpublished data) although changes were observed in certain subgroups of patients. In an investigation of prepubertal children, only a subset of the children who had more severe depression manifested reduced stage 4 sleep (Dahl et al., 1994). In a separate study that included both children and adolescents, reduced slow-wave sleep, particularly in the first NREM period, was observed only in adolescent males with depression (Robert et al., 2006).

Even fewer studies examined sleep microarchitectural changes in depressed youth. In one investigation, depressed youngsters exhibited lower intra- and inter-hemispheric coherence than controls (Armitage et al., 2000). In a subsequent investigation, lower delta amplitude and power was observed in adolescent females with depression (Armitage et al., 2001).

In summary, EEG sleep changes have been observed quite consistently in association with adult depression. In contrast to this, there is significant heterogeneity in EEG sleep findings in studies investigating pediatric depression. Potential factors that might contribute to these discrepancies will be described below.

4.3. Factors influencing sleep abnormalities in depression

Chronological age seems to have a significant influence on EEG sleep parameters. Even among healthy adults, increased number of nocturnal awakenings, early morning awakening, reduced slow-wave sleep and shortened REM latency are more predominant in older individuals (Bliwise, 1993; Miles and Dement, 1980; Williams et al., 1974). Sleep continuity disturbances, shortened REM latency and diminished slow-wave sleep seem to be

more robust in older patients with depression (Benca et al., 1992; Knowles and MacLean, 1990; Lauer et al., 1991), although one research group reported more robust changes in slow-wave activity among younger adults than older subjects (Armitage et al., 2000). Age does not appear to influence REM density (Lauer et al., 1991). Among pediatric samples, both macro- and microarchitectural changes are more prevalent in adolescents (Armitage, 2007; Armitage et al., 2006; Ivanenko et al., 2005; Robert et al., 2006).

Some studies examined the impact of gender on sleep. Healthy males have less slow-wave sleep than females (Williams et al., 1974). Among adults, both macro- and microarchitecture analyses indicated that slow-wave sleep deficits are more prevalent in depressed males than females (Armitage et al., 2000; Reynolds et al., 1990). Among youngsters, age, gender and depression diagnosis interacted, with depressed adolescent males exhibiting most severe sleep problems including highest proportion of stage 1 sleep, shortest REM latency and lowest percentage of slow-wave sleep (Robert et al., 2006). However, adolescent females had the lowest temporal coherence (Armitage et al., 2006). Summarizing the data on gender differences, Armitage (2007) has hypothesized that low slow-wave activity and impaired sleep homeostasis might be a primary biological risk factor for depression in males, whereas low temporal coherence serves as a vulnerability marker specifically in females.

Ethnicity/race also plays a role in sleep regulation. Evidence suggests that healthy adult African-Americans have more frequent sleep continuity disturbances and less proportion of slow-wave sleep compared with Hispanics or Non-Hispanic Whites (Mezick et al., 2008; Profant et al., 2002; Rao et al., 1999a; Redline et al., 2004; Stepnowsky et al., 2003). In contrast to the ethnic differences in sleep continuity disturbances and NREM sleep, few studies reported variations in REM sleep. In one investigation, Hispanics had increased phasic REM sleep compared to African-Americans and Non-Hispanic Whites (Rao et al., 1999a). These cross-ethnic differences in NREM and REM sleep also were replicated in a group of healthy adolescents (Rao et al., 2009a). Similar patterns of cross-ethnic differences in sleep profiles were observed in adult patients with depression. African-American patients with depression had less efficient sleep and NREM sleep changes, whereas Hispanic and Non-Hispanic White patients manifested predominantly REM sleep changes, although the ethnic groups were comparable on clinical symptoms and severity of depression (Giles et al., 1998b; Poland et al., 1999).

Depression severity and symptom patterns (e.g., depression subtype) also might affect sleep profiles. Among adults, some studies demonstrated that greater depression severity is associated with more impaired sleep including sleep continuity disturbances (Kerkhofs et al., 1988; Thase et al., 1986), reduced slow-wave sleep (Armitage, 2007; Thase et al., 1986), shortened REM latency (Akiskal et al., 1982; Cartwright, 1983; Thase et al., 1986), and increased REM density (Cartwright, 1983; Thase et al., 1986). In a pediatric study, a subgroup that exhibited shorter REM latency, more REM time and less stage 4 sleep had more severe depression (Dahl et al., 1994). In a separate investigation, although depression severity itself did not affect EEG sleep measures, delayed sleep onset, reduced REM latency and higher REM density was observed only in a subgroup of depressed adolescents with inpatient and suicidal status (Dahl et al., 1990).

Several investigators examined the relationship between different subtypes of depression and EEG sleep changes. Although majority of the studies failed to show significant associations (Riemann et al., 2001; Tsuno et al., 2005), some studies reported shorter REM latency in adult patients with endogenous depression than in those with non-endogenous depression (Giles et al., 1986a; Kerkhofs et al., 1988; Rush et al., 1982). It is important to note that the endogenous groups of patients in these studies had greater depression severity than the non-endogenous groups. Reduced REM latency also was observed in adolescents

with endogenous depression (Kutcher et al., 1992). Some investigations described more pronounced abnormalities in REM sleep in adolescent and adult patients with psychotic depression (Kupfer and Foster, 1972; Kupfer et al., 1986; Naylor et al., 1990), whereas other studies did not detect such differences (Ivanenko et al., 2005; Kerkhofs et al., 1988; Riemann et al., 2001). Several studies examined EEG sleep profiles in adult patients with seasonal affective disorder, and none of them found the typical sleep patterns observed in major depression (Anderson et al., 1994; (Brunner et al., 1993, 1996; Partonen et al., 1993; Rosenthal et al., 1989).

In conclusion, there is substantial evidence for developmental differences in sleep regulation. Gender and ethnicity/race also have an impact on sleep. There is little evidence that depression severity and sub-types of depression have a significant influence on EEG sleep parameters.

4.4. Stability of EEG sleep measures

An important question is whether the sleep “abnormalities” observed during the acute episode of depression normalize when the symptoms remit (“state” marker), or if they persist even during clinical remission (“scar” marker). From various adult samples with depression, including cross-sectional comparison of remitted patients with healthy controls, single episode cases versus those with recurrent illness, and prospective follow-up of individual patients through recovery, there is emerging consensus that EEG sleep disruptions associated with major depressive illness are remarkably stable from episode to recovery (for a review, see (Rao and Poland, 2008; Riemann et al., 2001; Tsuno et al., 2005). A few investigations, however, demonstrated normalization of certain EEG sleep measures during remission, particularly sleep continuity disturbances (Buysse et al., 1997; Cartwright, 1983; Riemann et al., 2001). Also, it appears that some EEG sleep changes during remission might be too subtle to be detected by visual scoring methods (Buysse et al., 1992a).

The discrepant findings among adult depressed patients on the stability of EEG sleep measures from episode to recovery suggest potential differences in the risk for relapse. Sleep measures might normalize in depressed patients with a low risk for relapse, whereas those prone to relapse tend to exhibit sleep abnormalities even during remission (Riemann et al., 2001; Thase et al., 1998). For instance, persistence of shortened REM latency during remission was associated with increased risk for relapse (Giles et al., 1987). Also, depressed patients with lower slow-wave sleep intensity during the first NREM period than the second one (“low delta ratio”) were five times more likely to develop a recurrent episode over the 2-year follow-up period than those with higher delta ratio (Kupfer et al., 1990).

To the best of my knowledge, there are only two reports of repeated EEG sleep assessments performed during the depressive episode and remission in youngsters (Rao and Poland, 2008; Rao et al., 1997). Both studies demonstrated persistent sleep abnormalities during remission in depressed adolescents.

4.5. EEG Sleep measures as vulnerability markers for depression

It is also important to know whether depression-related EEG sleep changes are already present before the clinical manifestation of the disorder (i.e., “trait” or “vulnerability” marker). A higher concordance in sleep macro- and micro-architecture has been observed in monozygotic twins compared to dizygotic twins (Ambrosius et al., 2008; Kimura and Winkelmann, 2007). There is also evidence that shortened REM latency and related sleep characteristics are familial and might be associated with increased risk for depression, beyond the risk conferred by depressive illness in relatives (Giles et al., 1992, 1998a).

Specific depression-related EEG sleep markers were observed in healthy adolescents and adults who were at high familial risk for depression (Friess et al., 2008; Fulton et al., 2000; Giles et al., 1998a; Lauer et al., 1995; Morehouse et al., 2002; Rao et al., 2009b; Schreiber et al., 1992; Sitaram et al., 1987). These EEG sleep markers predicted the subsequent onset of depression (Giles and Kupfer, 1994; Lauer et al., 2004; Modell et al., 2005; Morehouse et al., 2002; Rao et al., 2009b). In addition to identifying highly vulnerable persons, familial aggregation of specific EEG sleep abnormalities might delineate a valid subtype of the depressive illness. For instance, familial aggregation of short REM latency was associated with similar clinical features and psychological profiles of depression among relatives (Giles et al., 1988, 1990).

These results confirm that EEG sleep measures can serve as vulnerability markers for identifying individuals who are at significant risk for developing depressive disorder in order to target them for primary prevention. They also might serve as suitable endophenotype measures for identifying more homogeneous subgroups of depressed patients as well as detecting the mode of inheritance, thereby aiding in developing more specific and effective interventions for the different subgroups (Gottesman and Gould, 2003).

4.6. EEG sleep measures as predictors of clinical course of depression

Among adults, certain EEG sleep measures, including reduced REM latency and diminished slow-wave sleep, have been shown to predict early relapse following the successful treatment of depressive episodes (Giles et al., 1987; Grunhaus et al., 1994; Kupfer et al., 1990; Reynolds et al., 1989).

Although EEG sleep measures did not discriminate depressed youngsters from controls in some cross-sectional studies, these same variables were helpful in predicting differential clinical course over time. For instance, adolescent healthy controls that manifested reduced REM latency and higher REM density at baseline were more likely to develop a depressive episode subsequently (Rao et al., 1996). In the same study, depressed adolescents who had a normal REM sleep profile but a tendency for reduced slow-wave sleep developed bipolar disorder (Rao et al., 2002). Although the depressed adolescents, as a group, did not exhibit EEG sleep changes at baseline (Dahl et al., 1990), after separating these latent depressive and bipolar groups from their respective cohorts, the sleep profile of the depressed youth with unipolar course was similar to the pattern seen in adult depression (Rao et al., 2002). Also, depressed adolescents who subsequently developed substance use disorders had relatively normal EEG sleep patterns compared to those who did not develop the disorder (Rao et al., 1999b).

In a separate investigation, longer sleep latency and decreased sleep efficiency predicted recurrent depression (Emslie et al., 2001). In a subset of this cohort, depressed youth who exhibited lower hemispheric coherence, particularly boys, were less likely to recover from the index depressive episode or were at increased risk for a recurrent episode after recovery (Armitage et al., 2002). Another study identified longer sleep latency and sleep period time as predictors of lifetime depression at follow-up in adulthood, whereas the combination of reduced REM latency and diminished slow-wave sleep predicted suicidality (Goetz et al., 2001).

The observed variability in EEG sleep changes in depressed youngsters may reflect, at least in part, heterogeneity in the longitudinal clinical course of these disorders. For example, sleep data in adults suggest distinct biological substrates in unipolar and bipolar mood disorders. REM latency changes were observed less frequently in bipolar depression (Giles et al., 1986b; Rao et al., 2002; Thase et al., 1989). Sleep loss can effectively trigger the onset

of mania in patients with bipolar illness (Barbini et al., 1996; Wehr et al., 1987), but it has minimal euphorogenic effect in unipolar depression. Therapeutic sleep deprivation also appears to have different clinical effects in unipolar and bipolar patients (Barbini et al., 1998). A substantial minority of youngsters initially identified as having unipolar depression subsequently develop bipolar disorder, and those with early-onset illness in particular (Geller et al., 2001). Among pediatric samples, studies that excluded depressed patients with a family history of bipolar disorder were more likely to demonstrate EEG sleep changes compared with controls (Armitage et al., 2000; Emslie et al., 1990; Rao and Poland, 2008; Rao et al., unpublished data).

These findings together with the observation that EEG sleep markers are evident prior to the clinical manifestation of depressive illness emphasize the need for careful selection of experimental and control groups based on both family and personal history.

5. Antidepressant Treatments and Sleep

5.1. Sleep deprivation therapy

One of the most striking links between depression and sleep regulation is the observation that depressive symptoms are alleviated by acute sleep deprivation for a night and that the initial symptoms reemerge after recovery sleep the following night (Pflug and Tolle, 1971; Svestka, 2008). A meta-analysis of sleep deprivation studies in adults concluded that approximately 50% to 60% of depressed patients show a transient improvement in mood after total sleep deprivation (Wu and Bunney, 1990). This is the only known intervention that has proven anti-depressive benefits within 24 hours. Because majority of the un-medicated patients (up to 80%) relapse after the next night of sleep, the clinical utility of this intervention is limited. However, from a research perspective, sleep deprivation offers a unique opportunity to relate rapidly occurring changes in mood to simultaneous changes of neurobiological measures (Benedetti and Smeraldi, 2009; Gillin et al., 2001; Wirz-Justice and Van den Hoofdakker, 1999).

Functional neuroimaging studies have revealed that responders to sleep deprivation have elevated glucose metabolism in the ventral portion of the cingulate cortex at baseline, which normalizes after total sleep deprivation (Gillin et al., 2001). Evidence suggests that signal transduction in the cingulate gyrus is dominated by cholinergic neurotransmission, which is involved in REM sleep regulation (McCarley, 2007; Nofzinger, 2005). Additionally, single photon emission computed tomography (SPECT) studies using a radioactively labeled dopamine (D2) receptor antagonist suggest that the antidepressant benefits of sleep deprivation are correlated with endogenous release of dopamine (Gillin et al., 2001; Nofzinger, 2005). Another model focuses on the role of the neuromodulator adenosine, which is now known to be involved in sleep regulation (McCarley, 2007).

Variations of total sleep deprivation have been developed for therapeutic intervention in depression. Because of the changing direction in circadian rhythm of several bodily functions, it has been proposed that staying awake in the early morning should be the central target for maximizing the therapeutic efficacy of total sleep deprivation (Schilgen et al., 1976). Although an early study reported that late partial sleep deprivation was as effective as total sleep deprivation (Schilgen et al., 1976), recent investigations concluded that total sleep deprivation was indeed more effective than partial sleep deprivation (Giedke et al., 2003; Svestka, 2008).

Almost all antidepressant drugs inhibit REM sleep, although the magnitude of effect varies between compounds within antidepressant classes (Mayers and Baldwin, 2005; Sandor and Shapiro, 1994). In order to examine whether the underlying mechanism of action of

antidepressant drugs occurs via REM sleep suppression, some investigators utilized the selective REM sleep deprivation strategy (Svestka, 2008; Vogel, 1983). In a controlled study, although selective REM sleep deprivation improved mood, the NREM sleep deprivation group exhibited an even stronger antidepressant effect (Grozinger et al., 2002). Both experimental conditions increased the duration of NREM sleep cycles and, therefore, it was postulated that this might be the underlying mechanism of action.

Several techniques have been used to try to reduce the relapse of depressive symptoms following sleep deprivation. Although antidepressant drugs have little influence on the rate of response to single-night sleep deprivation, they might increase the response to multiple nights of sleep deprivation (Wirz-Justice and Van den Hoofdakker, 1999). Several investigators examined the effects of adjunctive pharmacotherapy or bright light therapy with multiple days of sleep deprivation, and these strategies resulted in more sustained improvement in depressive symptoms (Colombo et al., 2000; Giedke and Schwarzler, 2002; Smeraldi et al., 1999; Wehr et al., 1985; Wu et al., 2009).

In pediatric depression, only three studies examined the effect of sleep deprivation. The first study described the case of a 12-year-old boy who received combined partial sleep deprivation and antidepressant agent, which resulted in significantly improved mood for 1–2 days (King et al., 1987). A subsequent investigation examined the effect of sleep deprivation in four adolescents with major depression and attention-deficit hyperactivity disorder, and it reported improved mood and psychomotor activity for 3 days following treatment (Detrinis et al., 1990). The final study employed sleep deprivation for 36 hours in 17 patients (Naylor et al., 1993). Severely depressed adolescents showed a decrease in depression severity, whereas remitted depressed patients and psychiatric controls showed a worsening of symptoms after sleep deprivation.

Taken together, these findings suggest that sleep deprivation can have therapeutic utility in depression, particularly in conjunction with chronobiological or pharmacological treatment. Moreover, sleep deprivation is a useful tool for understanding the pathophysiology of mood disorders.

5.2. Pharmacological Interventions

Almost all antidepressant drugs have been shown to impact sleep architecture, notably delayed onset of REM sleep, reduced amount of REM sleep and increased slow-wave sleep (Mayers and Baldwin, 2005; Winokur et al., 2001). A large body of evidence indicates robust suppression of REM sleep immediately after antidepressant administration (Mayers and Baldwin, 2005; Winokur et al., 2001). Exceptions to this rule are trimipramine (Dunleavy et al., 1972; Wiegand et al., 1986) and trazodone (Ware and Pittard, 1990), where no REM sleep suppression occurs. Nefazodone and bupropion, both atypical antidepressants, actually enhance REM sleep (Nofzinger et al., 1995; Sharpley et al., 1992). Also, REM sleep suppression is less pronounced with the selective and reversible monoamine oxidase inhibitor (MAOI), moclobemide (Steiger et al., 1994). The effect of antidepressants on NREM sleep is less evident and less consistent. In general, tricyclic agents and antidepressants having significant 5-HT_{2A/2C} receptor antagonist properties (e.g., trazodone, mianserin) increase slow-wave sleep, whereas other drugs, such as SSRIs or MAOIs, either lower slow-wave sleep or produce no change (Sharpley and Cowen, 1995). Antidepressants with sedating properties, such as certain tricyclic agents, trazodone and mianserin, improve sleep continuity variables. Some non-sedating drugs (e.g., ritanserin and nefazodone) also improve sleep continuity measures, possibly through 5-HT_{2A/2C} receptor blockade (Sharpley and Cowen, 1995).

In contrast to the relatively strong influence of antidepressant drugs on REM sleep, mood stabilizers exhibit only minimal effects on REM sleep but enhance slow-wave sleep (Alfaro-Rodriguez et al., 2002; Friston et al., 1989; Harding et al., 1985; Yang et al., 1989). Preliminary data on lamotrigine and gabapentin suggest that they, in fact, increase REM sleep and reduce slow-wave sleep (Placidi et al., 2000).

A temporal discordance between REM sleep suppression and clinical response to antidepressants has been reported. For instance, clomipramine produces immediate suppression of REM sleep but clinical response is seen approximately 10 days later (Goldenberg, 1994). In contrast to this, although suppression of REM sleep in response to MAOIs is significantly delayed (about 10 days), this coincides temporally with clinical improvement (Kupfer et al., 1972). It is also not clear how long REM sleep suppression persists during long-term treatment with antidepressants. Some studies reported an attenuation of REM sleep suppression within 3–5 weeks of treatment (Berger et al., 1986); (Riemann et al., 1990), whereas another investigation demonstrated a persistent effect of antidepressants on REM sleep that persisted for up to 3 years (Kupfer et al., 1994).

Some investigators indicated that EEG sleep measures might be helpful in predicting clinical response to antidepressant therapy. Baseline REM latency (prior to treatment initiation) predicted response to antidepressant treatment (Akiskal et al., 1980); (Coble et al., 1979); (Rush et al., 1989); (Svendsen and Christensen, 1981), although some studies failed to replicate this finding (Berger et al., 1986); (Riemann et al., 2001). Additionally, the magnitude of REM sleep suppression during the early stages of antidepressant treatment predicted clinical response to antidepressant drugs (Gillin et al., 1978; Hochli et al., 1986; Kupfer et al., 1981; Ott et al., 2002; Reynolds et al., 1991; Vogel et al., 1990).

Compared with the rich data source examining the effects of pharmacological treatments on depression-related sleep problems in adults, only few studies examined this issue in pediatric samples. The first report involved the effect of a 3-week course of imipramine in 12 hospitalized children with depressive symptoms (Kupfer et al., 1979). REM sleep suppression was most pronounced in those whose depression improved significantly. Imipramine also increased wakefulness and stage 2 sleep but decreased sleep efficiency and slow-wave sleep. In a subsequent study, robust REM sleep suppression occurred in response to acute administration of imipramine in 10 hospitalized adolescents with unipolar depression (Shain et al., 1990). Consistent with the effects in adults, fluoxetine treatment was associated with poor sleep quality in both subjective and objective sleep measures in 6 youngsters, and the drug had minimal effect on REM latency (Armitage et al., 1997).

5.3. Somatic treatments

Electroconvulsive therapy (ECT) affects many EEG sleep parameters, most notably REM sleep suppression (Coffey et al., 1988; Grunhaus et al., 1988). Persistent short REM latency following ECT predicted poor clinical response to ECT as well as increased vulnerability to relapse in adults (Bourgon and Kellner, 2000; Grunhaus et al., 1994, 1997). Repetitive transcranial magnetic stimulation (rTMS) also was shown to suppress REM sleep (Cohrs et al., 1998).

5.4. Psychotherapy

Baseline EEG sleep measures, such as sleep continuity measures and reduced REM latency, predicted clinical response to cognitive-behavior therapy (CBT) and interpersonal therapy (IPT) in adult patients with depression (Buysse et al., 1992b; Jarrett et al., 1990b). However, no significant changes in EEG sleep macroarchitecture occurred in response to IPT although modest changes occurred in automated measures of delta sleep activity and REM sleep

activity (Buysse et al., 1992a). Also, subsequent quantitative analysis indicated that increased number of REM counts was a robust predictor of non-response to IPT (Buysse et al., 2001). In a separate investigation, a group of depressed patients were categorized based on sleep profiles (including sleep efficiency, REM latency and REM density), and clinical response to IPT was examined. Patients with an “abnormal” sleep profile responded poorly to IPT compared to patients with a “normal” sleep profile (Thase et al., 1997). Furthermore, a substantial proportion of the poor responders to psychotherapy responded well to subsequent pharmacotherapy, suggesting that an abnormal sleep profile reflects a more marked disturbance of the central nervous system (CNS) arousal and warrants pharmacotherapy (Thase et al., 1997).

In summary, the literature on the impact of antidepressant treatment on REM sleep suggests that the majority of the successful treatment modalities suppress REM sleep. It is, however, not clear whether the EEG sleep changes associated with a given treatment are just epiphenomena of the normalization of psychopathological process or reflect a real effect on relevant underlying mechanisms. Also, some successful treatment strategies do not suppress REM sleep, thereby challenging the notion that REM sleep suppression is a necessary prerequisite for the antidepressant properties of an effective intervention.

It has been hypothesized that differential effects of antidepressants on sleep may reflect differences in receptor pharmacology, and thereby signal different pathways to treatment response (Reynolds, 1998). One pathway might involve REM sleep suppression, whereas the alternate pathway might involve the augmentation of slow-wave activity in the first sleep cycle. Both types of EEG sleep changes might reflect the amelioration of increased CNS arousal associated with depression. Consistent with this notion, greater beta power during NREM sleep was related to increased glucose metabolism in the ventromedial prefrontal cortex in depressed patients (Nofzinger et al., 2000).

6. The Functional Neuroanatomy of Sleep

In the past decade, a variety of studies have advanced our understanding of the functional neuroanatomy of the two primary sleep states, REM and NREM sleep (Nofzinger, 2005). Positron emission tomography (PET) studies, using regional cerebral flow as an index of neuronal activity, revealed that the intense and widespread cortical activation observed during sleep was not uniform (Nofzinger, 2005); (Braun et al., 1997); (Maquet et al., 1990). Several studies in healthy participants demonstrated that there is increased metabolic activity during REM sleep, particularly in the pontine tegmentum, thalamus, limbic regions and temporo-cortical areas (Buchsbaum et al., 2001); (Maquet et al., 1996); (Meyer et al., 1981); (Nofzinger et al., 1997). In contrast, the dorsolateral prefrontal cortex and parietal cortex, as well as the precuneus and posterior cingulate cortex, are least active during this sleep phase.

Globally, NREM sleep is functionally less active than either waking or REM sleep (Braun et al., 1997; Maquet et al., 1990). Several investigations demonstrated that, during the transition from waking to NREM sleep, there are regional reductions in heteromodal association cortex in the frontal, parietal and temporal lobes as well as the thalamus (Nofzinger, 2005); (Braun et al., 1997; Maquet et al., 1990). These findings are consistent with disfacilitation and active inhibition of the thalamocortical relay neurons in association with delta and spindle wave generation (Andersson et al., 1998; Braun et al., 1997; Hofle et al., 1997; Maquet et al., 1997).

Functional neuroimaging studies also have been helpful in clarifying some basic functions of sleep, such as sensory processing between waking and NREM sleep (Born et al., 2002), consolidation of memory during REM sleep (Laureys et al., 2001; Maquet et al., 2000),

alertness and attention (Paus et al., 1998; Thomas et al., 2000), and the effects of sleep deprivation on cognitive performance (Thomas et al., 2000; Wu et al., 1991).

Utilizing [18F] FDG PET method, investigators have measured cerebral metabolism in 10 patients with depression and 10 controls during the first NREM period (Ho et al., 1996). They detected increased whole-brain metabolism in depressed patients, but most notably in the posterior cingulate, the amygdala, hippocampus, occipital and temporal cortex, and the pons. In contrast, depressed patients exhibited hypometabolism in the medial orbital prefrontal cortex, anterior cingulate, caudate and medial thalamus compared with controls. They concluded that this hypofrontality pattern supports the hyperarousal hypothesis of depression.

In order to further clarify the neurobiology of dysfunctional arousal in depression, Nofzinger et al. (2000) examined the relationship between β EEG power and regional cerebral glucose metabolism during NREM sleep. In both healthy and depressed participants, β power negatively correlated with subjective sleep quality. Also, significant correlations were seen between β power and metabolism in the ventromedial prefrontal cortex. At baseline, depressed patients demonstrated a trend toward greater beta power than controls. Within the depressed cohort, there was a trend for beta power to correlate with an indirect measure of absolute whole brain metabolism during NREM sleep. Given the increased electrophysiological arousal in some depressed patients and the known anatomical relations between the ventromedial prefrontal cortex and brain activating structures, they suggested that these findings raise the possibility that the ventromedial prefrontal cortex plays a significant role in mediating one aspect of dysfunctional arousal found in more severely aroused depressed patients.

As described above, the notion of hyperarousal in paralimbic structures in depression has received further support from the extensive literature describing the functional neuroanatomical correlates of the antidepressant response to sleep deprivation in depressed patients (Gillin et al., 2001).

It has been demonstrated that, while both healthy and depressed subjects showed activation in the limbic and anterior paralimbic regions during the transition from waking to REM sleep, the spatial extent of this activation was greater in depressed patients (Nofzinger et al., 2004). Additionally, depressed patients showed relatively greater activation in bilateral dorsolateral prefrontal, primary sensorimotor, left premotor and left parietal cortices, as well as in the midbrain reticular formation. The findings indicated that the altered function of limbic/anterior paralimbic and prefrontal circuits in depression may be accentuated during the REM sleep state and that this is characteristic of the observed REM sleep dysregulation in EEG sleep studies (Benca et al., 1992; Nofzinger et al., 2004; Reynolds and Kupfer, 1987). This group of authors also reported that REM density correlated positively with cerebral metabolic rate in the striatum, the posterior parietal cortices and medial and ventromedial prefrontal cortices in patients with depression (Germain et al., 2004). In contrast, REM density correlated negatively with metabolism in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortex and parahippocampal gyrus. The areas where REM density was positively correlated with glucose metabolism appear to constitute a diffuse cortical system involved in the regulation of emotion-induced arousal, and that the observed pattern might be a marker of hypofrontality during REM sleep in depressed patients (Germain et al., 2004).

Taken together, these findings suggest that the neuronal processes underlying sleep differ between brain regions and depression is associated with hyperarousal. However, it is

important to determine the extent to which the observed activation of brain regions is specific to depression or characteristic of psychiatric disorders in general.

7. Theoretical Models of Sleep Abnormalities in Depression

Current theories regarding the mechanisms underlying sleep disturbances in depression suggest that there is a reciprocal relationship between REM sleep and slow-wave sleep, such that a shorter latency to the first REM period results in reduced slow-wave sleep time in the first NREM period. It is, however, not clear whether the primary disturbance in depression is REM or slow-wave sleep regulation.

7.1. Two-process model of sleep regulation

Borbely (1982) proposed a model of sleep regulation based on the theoretical assumption that sleep is dependent on two processes: a homeostatic, sleep-inducing process (process “S”), and a circadian process (process “C”) (Borbely, 1982). According to this model, the interaction between process S and process C determines sleep propensity. Process S increases gradually during waking, resulting in an elevated initial level of slow-wave activity, which then decreases exponentially during sleep (Daan et al., 1984). Process C modulates the threshold of awakening and that of falling asleep. When process S declines to the level of process C, sleep is terminated. In accordance with this model, experimental studies demonstrated that the time course of slow-wave sleep activity is dependent on prior wakefulness (Dijk et al., 1990, 1992). Furthermore, slow-wave sleep activity is not influenced by the circadian phase, nor is its time correlated with that of core body temperature (Dijk et al., 1991).

According to the two process model, process S is deficient in depression, which is reflected by a reduction in delta-wave activity and slow-wave sleep (Borbely and Wirz-Justice, 1982). Studies utilizing frequency analysis of EEG sleep demonstrated reduced delta sleep in depression (Borbely et al., 1984; Kupfer et al., 1984). As a consequence of reduced slow-wave sleep (particularly in the first NREM period), REM sleep occurs earlier (Kupfer and Ehlers, 1989). This model accounts for the anti-depressive effect of sleep deprivation in the sense that prolonging wakefulness increases process S and slow-wave sleep, resulting in improvement in depressed mood. However, several studies failed to show significant differences in the proportion or activity of slow-wave sleep in the first NREM period, or over the entire night, between depressed patients and controls (Armitage et al., 1992a; Knowles and MacLean, 1990).

7.2. The reciprocal interaction model of REM and NREM sleep

It has been postulated that the regulation of REM sleep depends on the balance between cholinergic (REM “on” neurons) and aminergic (REM “off” neurons) systems (Hobson et al., 1975). Thus, the neurotransmitter systems involved in REM sleep control are reciprocal and are responsible, in part, for subsequent REM/NREM sleep cycle oscillations. An early onset of REM sleep in depression reflects an imbalance in the normal cholinergic/aminergic neurotransmission that produces disinhibition of REM sleep (McCarley, 1982). In support of this theory, administration of cholinergic agonists triggers an earlier onset of REM sleep (Riemann and Berger, 1992; Riemann et al., 1994b). Several studies have shown an enhanced shortening of REM latency in response to cholinergic challenge in depressed patients compared to healthy controls (Riemann et al., 1994a, 1994b). One investigation in children also demonstrated greater shortening of REM latency in depressed youth than in controls (Dahl et al., 1994).

7.3. Abnormalities in the circadian rhythm

The periodic nature of depression, with a tendency for relapse and remission, indicates that mood changes might be regulated by an endogenous biological clock (Mendlewicz, 2009; Monteleone and Maj, 2008; Soria and Urretavizcaya, 2009). Recent advances in molecular genetics have implicated some “clock” genes in the regulation of circadian and seasonal rhythms in humans (Mendlewicz, 2009; Monteleone and Maj, 2008; Sangoram et al., 1998; van der Horst et al., 1999). In addition, mutations in clock genes have been related to disruptions in circadian cycles (Jones et al., 1999; Katzenberg et al., 1998; Mendlewicz, 2009). Some depressed patients manifest circadian abnormalities in mood, sleep, temperature and neuroendocrine secretion (Bunney and Bunney, 2000; Mendlewicz, 2009; Monteleone and Maj, 2008; Soria and Urretavizcaya, 2009). Abnormalities in clock-gene function are speculated to be associated with the circadian abnormalities of depression (Bunney and Bunney, 2000; Monteleone and Maj, 2008; Serretti et al., 2003).

7.4. Sleep-neuroendocrine relationships

In healthy humans, the first hours of sleep are characterized by peaks of slow-wave sleep and growth hormone along with a nadir in cortisol output. Ehler and Kupfer (1987) postulated that a disturbance in the interaction of two hypothalamic peptides [growth hormone-releasing factor (GRF) and corticotropin-releasing factor (CRF)] occurs in depression. They suggested that reduced GRF secretion and an increased output of CRF are involved in depression. Consistent with this hypothesis, increased nocturnal secretion of cortisol and adrenocorticotrophic hormone (ACTH) has been observed consistently in depression (Steiger, 2002). Some studies also reported reduced growth hormone secretion in individuals with depression (Jarrett et al., 1990a; Steiger, 2003). However, it is not clear whether the sleep abnormalities and neuroendocrine disturbances are causally linked or related through a third factor (e.g., circadian rhythm disturbances).

In summary, various theories have been proposed to explain the sleep abnormalities in depression. Although each of these theories is supported by empirical data, there is still no convincing model capable of explaining all the typical EEG sleep changes associated with depression.

8. Summary and Future Directions in Sleep Research

Pediatric depression is of great public health significance, with serious morbidity and mortality, thereby emphasizing the need for early identification and effective treatment strategies. In the past three decades, considerable advances have been made regarding our knowledge on the phenomenology and natural course of juvenile depression. However, additional research is needed in understanding the pathogenesis of early-onset illness. In particular, studies aimed at elucidating mechanisms and interrelationships among the different domains of risk factors are important. Such knowledge will be beneficial in developing more effective preventive and treatment strategies. Towards this end, sleep research might provide some useful insights.

Sleep disturbance is a characteristic symptom of depressive disorders in both youngsters and adults. Developmental influences on the rates of depression and maturational changes in sleep regulation also imply a close connection between depressive disorders and sleep regulation. Although a clear causal relationship between sleep disturbance and depression has not been established yet, further research in this area might play an important role in optimizing prevention and treatment. Sleep research in adult depression has provided an extensive database and fruitful theoretical considerations concerning its etiology and pathophysiology, as well as the vulnerability for developing depressive episodes. Further

studies linking the different areas of research are needed to validate such theories, also including an emphasis on developmental influences.

It is suggested that research on REM sleep may be more closely connected with the work on NREM sleep, especially slow-wave sleep, to better understand these two interdependent sleep states. Further attention is warranted on sleep-neuroendocrine interactions. Until now, the different approaches relating chronobiological, neuroendocrine and pharmacological aspects of depression have rarely been studied simultaneously. Neuroimaging studies of sleep have provided glimpses into how functional changes in the various brain regions are related to sleep abnormalities in depression. Further work is needed to clarify the reliability and specificity of these brain changes in relation to depression, as well as their association with clinical outcomes. Finally, a deeper insight into the relationship between sleep and depression might come from molecular genetic studies. Preliminary evidence suggests that sleep alterations in at-risk populations are vulnerability markers for depression. Examination of the circadian clock and circadian rhythm research in depression suggests that circadian abnormalities in depression may be related to alterations of clock genes.

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Figure 1.

Sleep profile of a medication-free depressed female patient and a healthy female control. Compared to the healthy subject, the sleep profile of this patient shows many of the typical features of sleep in depression — impaired sleep continuity, disinhibition of REM sleep and reduction of slow-wave sleep. W, Wake; REM, rapid eye movement sleep; S1–4, sleep stages 1–4; MT, Movement time; BM, body movements; EM, rapid eye movements (reprinted from Riemann et al., *Biological Psychology*, 2001;57:67–103).

EEG Sleep Studies Children and Adolescents

Table 1

Citation	Sample	Sleep latency	Sleep efficiency	REM latency	REM density	Delta sleep
Studies Conducted with Children						
21 High CDI						
Arana-Lechuga et al. (2008)	7 Low CDI	↑	=	↓	=	=
36 MDD						
Dahl et al. (1991)	18 NC	=	=	= ^a	=	= ^a
33 MDD						
Dahl et al. (1994)	15 NC	=	=	= ^b	=	=
25 MDD						
Emslie et al. (1990)	20 NC	↑	=	↓	=	=
39 MDD						
Goetz et al. (1985)	8 NC	=	=	=	=	=
54 MDD						
Puig-Antich et al. (1982)	11 NC	=	=	=	=	=
12 MDD						
Young et al. (1982)	12 NC	=	=	=	=	=
Studies Conducted with Adolescents						
9 MDD						
Appelboom-Fondu et al. (1988)	12 NC	=	↓	=	=	=
8 MDD						
Armitage et al. (2001)	8 NC	=	=	=	=	=
15 MDD						
Cashman et al. (1986)	15 NC	-	-	=	↑	=
27 MDD						
Dahl et al. (1990)	30 NC	↑	=	↓ ^c	↑ ^c	=
16 MDD						
Dahl et al. (1996)	21 NC	↑	=	↓	=	=
31 MDD						
Emslie et al. (1994)	17 NC	↑	↓	↓	↑	=

Citation	Sample	Sleep latency	Sleep efficiency	REM latency	REM density	Delta sleep
	49 MDD					
Goetz et al. (1987)	40 NC	↑	↓	=	=	=
	23 MDD					=
Kutcher et al. (1992)	28 NC	↑	=	↓	=	
	20 MDD					
McCracken et al. (1997)	13 NC	=	=	=	↑	=
	13 MDD					
Lahneyer et al. (1983)	13 NC	=	=	↓	↑	=
	16 MDD					
Rao and Poland (2008)	16 NC	=	=	↓ ^d	↑ ^d	=
	55 MDD					
Rao et al (unpublished data)	48 NC	=	=	↓	↑	↓
	10 MDD					
Riemann et al. (1995)	10 NC	=	=	↓	=	-
Studies Conducted with both Children and Adolescents						
	50 MDD					
Armitage et al (2000)	15 NC	↑	=	=	=	=
	51 MDD					
Bertocci et al (2005)	42 NC	=	-	-	-	-
	128 MDD					
Forbes et al (2008)	101 NC	=	=	=	=	=
	97 MDD					
Robert et al (2006)	76 NC	=	=	=	=	= ^e

REM = Rapid eye movement; CDI = Children's Depression Inventory; MDD = major depressive disorder; NC = Normal Controls
 = means no change; ↑ = increase; ↓ = decrease; - = no data (symbols represent data for MDD vs. NC)

^a MDD subgroup with increased depression severity had reduced REM latency and stage 4 sleep

^b Infusion of arecoline (0.5mg) during the first non-REM sleep period revealed ↓ REM Latency in MDD group

^c Differences were reported only for MDD subgroup with suicidal and/or inpatient status vs. NC

^d Sleep changes in the MDD group persisted during sustained remission

^e Adolescents with MDD had the least amount of delta sleep in the first sleep period