PREVALENCE AND CORRELATES OF ALPHA-DELTA SLEEP
IN MAJOR DEPRESSIVE DISORDERS

by

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List of Abbreviations

AASM: American Academy of Sleep Medicine
AHI: Apnea Hypopnea Index
ANOVA: Analysis of variance
BMI: Body mass index
BZD: Benzodiazepine
DSM-IV: Diagnostic and Statistical Manual for Mental Disorders, 4th Edition
ECG: Electrocardiogram
EEG: Electroencephalogram
EMG: Electromyogram
EOG: Electrooculogram
ESS: Epworth Sleepiness Scale
MDD: Major Depressive Disorder
NREM: Non-Rapid Eye Movement
PAP: Positive Airway Pressure
PLMAI: Periodic limb movement arousal index
PLMI: Periodic limb movement index
PSG: Polysomnogram
REM: Rapid Eye Movement
SAD: Seasonal affective disorder
SE: Sleep efficiency
SSRI: Selective Serotonin Reuptake Inhibitor
SNRI: Serotonin and Norepinephrine Reuptake Inhibitor
**SpO2:** Arterial oxygen saturation

**SPSS:** Statistical package for social sciences

**SWS:** Slow wave sleep

**TCA:** Tricyclic antidepressants

**TST:** Total sleep time

**VIF:** Variance inflation factor

**WASO:** Wake time after sleep onset
Glossary

**Alpha-delta sleep**: alpha waves superimposed over delta wave sleep (also known as slow wave sleep or deep sleep)

**Alpha waves**: Trains of sinusoidal 8-13 Hz activity recorded predominantly over the occipital region.

**Apnea**: An apnea is a period of time lasting for ten seconds or more during which breathing stops during sleep.

**Apnea Hypopnea Index**: Total number of apneas and hypopneas per hour of sleep.

**Body Mass Index (BMI)**: Body mass index is derived from weight and height measurements and expressed as kg/m$^2$ units.

**CPAP (continuous positive airway pressure)**: A very effective treatment for sleep apnea, it delivers air at a higher pressure to prevent collapse of airways when asleep.

**Delta waves**: Waves of frequency 0.5 to 2 Hz and peak to peak amplitude $>$ 75 microvolt predominantly over the frontal regions

**Epworth Sleepiness Scale (ESS)**: A self administered questionnaire used to determine the severity of daytime sleepiness in day-to-day situations. Total score range from 0 to 24. A cut-off of 10 is used to indicate excessive daytime sleepiness (higher scores indicate increased severity of daytime sleepiness).

**First night effect**: Altered quality and duration of sleep observed on the first night of a sleep study and attributed to sleeping in an unfamiliar environment with electrodes, video monitoring, etc
**Hypopnea:** A respiratory event associated with oxygen desaturation and/or EEG arousal resulting from a reduction in oro-nasal airflow, accompanied by evidence of continued efforts to breathe based upon chest and abdominal signals and lasts for at least 10 seconds. Definitions vary for adult and pediatric events.

**Insomnia:** Difficulty with either falling asleep, staying asleep, early morning awakening or non-restorative sleep despite adequate opportunity to sleep and associated with daytime impairment.

**Major Depressive Disorder (MDD):** A major psychiatry disorder characterized by low mood and/or lack of interest for most days over a period of at least two weeks and associated with symptoms such as lack of appetite, sleep disturbances, lack of energy, feelings of hopelessness, helplessness, suicidal ideation, etc.

**Non-rapid eye movement (NREM) sleep:** One of the two basic states of sleep. It consists of stages 1, 2 (light sleep) and 3 (deep sleep).

**Periodic limb movement disorder (PLMD):** A disorder in which rhythmic jerking of the legs interrupts sleep, causing insomnia and/or excessive daytime sleepiness and daytime impairments.

**Polysomnography:** A sleep test that records sleep architecture and a variety of other body functions during sleep, including breathing patterns, heart rhythms, and limb movements.

**Rapid eye movement (REM) sleep:** This is one of the two basic states of sleep. Also known as "dream sleep," it is characterized by rapid eye movements, and more irregular breathing and heart rate compared to NREM sleep.
Seasonal Affective Disorder (SAD): Also known as winter depression, it is a variant of major depressive disorder characterized by excessive sleepiness, increased appetite, fatigue and carbohydrate craving.

Sleep efficiency: Total number of hours of sleep divided by the total number of hours spent in bed expressed as a percentage (i.e. multiplied by 100)

Sleep apnea: A sleep disorder that occurs when a person’s breathing is interrupted during sleep.

WASO (wake time after sleep onset): The amount of time spent awake after sleep onset and before the final wake-up in the morning.
Objective: Major depressive disorder (MDD) is associated with sleep disturbances. An electroencephalographic (EEG) pattern of alpha wave intrusion in delta wave sleep (alpha-delta sleep) is observed in some subjects with MDD. The treatment-resistant symptoms in MDD, non-restorative sleep and fatigue, are associated with alpha-delta sleep. The objective of this study is to identify the prevalence and clinical correlates of alpha-delta sleep in MDD.

Methods: Retrospective study of 150 polysomnograms of subject’s ≥ 18 years (75 each with and with no MDD). The percent of delta waves with alpha intrusion was collected and analyzed.

Results: MDD patients had higher alpha-delta sleep (23.4±14.2 %; 2.3±6.7%, p<0.01). MDD patients with high alpha-delta sleep were at 3.15 greater odds to have excessive daytime sleepiness.

Conclusion: Patients with MDD have a higher prevalence of alpha-delta sleep. Alpha-Delta sleep is associated with daytime sleepiness in MDD-patients.
Major Depressive Disorder (MDD) is a common condition with a reported lifetime prevalence of up to 5-12% in men and 10-25% in women. A variety of factors have been associated with an increased risk for mood disorders, including psychosocial stress, chronic illness and pain, alcohol/substance abuse, and physical or psychological trauma. Most patients with MDD complain of insomnia, mainly difficulty falling/staying asleep, early morning awakenings and non-restorative sleep. Although a significant number of depressed patients frequently report increased daytime sleepiness/fatigue, there is little evidence to show that they have increased daytime sleepiness when measured objectively. Mood disorders and sleep disturbances have a bi-directional relationship. Not only are sleep disturbances common in patients with mood disorders, they are predictive of individuals at higher risk for the development of depression. The lifetime prevalence of MDD in subjects with sleep disturbances demonstrated a significantly higher rates of MDD in individuals with sleep complaints: 25.3% of those who had hypersomnia and 54.3% of those with both insomnia and hypersomnia had MDD, compared to 2.7% in individuals with no sleep complaints. Nevertheless, symptoms of depression tend to persist even when sleep abnormalities shows some signs of improvement. MDD has been studied polysomnographically more than any other psychiatric disorder, and the polysomnographic findings are characterized by a shift of REM sleep earlier in the night, resulting in reduction of REM latency, increase in
total REM time/REM density, disrupted sleep continuity and diminished slow wave sleep (SWS).\textsuperscript{10,14,15}

An electroencephalogram (EEG) pattern of alpha intrusion into NREM sleep was first noted in 1973 in patients with psychiatric disorders\textsuperscript{18}. The EEG appearance was that of intrusion of prominent alpha activity (frequency of 8 to 13 cycles per second) on delta waves (frequency of 0.5 to 2.0 per second with amplitude greater than 75 microvolts) [figure 11 and 12]. A similar pattern, termed alpha-delta sleep, has been found to be related to a complaint of non-restorative sleep in patients with musculoskeletal pain or fibrositis, and non-depressed patients with chronic fatigue.\textsuperscript{19,20,21} Other disorders in which alpha-delta sleep, non-restorative sleep, and pain or fatigue symptoms are evident include rheumatoid arthritis and systemic lupus erythematosus.\textsuperscript{22,23,24} Alpha-delta sleep is also reported in patients with sleep disorders such as psychophysiological insomnia and other primary sleep disorders (e.g. periodic limb movement disorder, circadian rhythm sleep disorders, sleep apnea and narcolepsy).\textsuperscript{24,25,26,27,28,29} Among these conditions, however, daytime symptoms including daytime fatigue and excessive daytime sleepiness are thought to be multi-factorial in origin and non-restorative sleep is known to contribute to daytime sleepiness and fatigue.\textsuperscript{30}

Abnormalities of sleep, as observed on polysomnogram, offer a unique insight into some of the physiological processes in the brain and the pathophysiology of the disease state. Although a lot of excitement was
generated regarding REM sleep abnormalities in MDD (short REM latency and increased REM density), these findings were by no means specific to MDD and do not have any diagnostic or therapeutic value.\textsuperscript{31,32} Alpha-Delta sleep is observed in the polysomnograms of patients with major depressive disorder and mood disorders are often diagnosed in patients known to have predominant alpha-delta sleep, for example, fibromyalgia\textsuperscript{41}. Much is known about the characteristic features of alpha-delta sleep in patients with rheumatology/pain disorder, but to-date no studies have systematically assessed alpha-delta sleep in patients with MDD using objectively defined criteria that can be considered as reliable. Ware et al were one of the first to describe alpha intrusions in sleep of patients with depression\textsuperscript{38}. They found that alpha intrusion during NREM sleep in depressed patients was “common”. They did not, however, specifically look at alpha intrusion in slow wave or delta sleep but rather considered any alpha intrusion in NREM sleep. In addition, they graded the severity of alpha intrusion in NREM sleep on a four point scale: 1 = 0 to 25\% of NREM sleep has alpha intrusions; 2 = up to 50\%; 3 = up to 75\%; and 4 = up to 100\%. Five out of twelve depressed patients had a rating of 3 or 4 (i.e. alpha intrusions in more than 50\% of the NREM sleep). Although commendable given this work was done in 1986, some of the major drawbacks include the criteria for alpha intrusion that is not considered appropriate today, small sample size, and lack of a control group. Manu et al studied alpha-delta sleep in patients with a chief complaint of chronic fatigue\textsuperscript{21}. Eight of the 30 consecutive patients had MDD and three of these eight patients (37\%) had alpha-delta sleep pattern. In this study, the criterion to detect the presence of alpha-delta sleep was “prominent alpha
frequency activity occurring tonically during non-rapid eye movement sleep”. This criterion does not have any objective measures and was not validated. This study did account for the “first-night effect” in the majority of the patients by doing sleep studies on two or even three successive nights. However, this study again lacked any control subjects.

Alpha-delta sleep, as measured by objectively defined and reliable criteria, if consistently found in patients with MDD, could emerge as an important feature and perhaps a biological marker. Fatigue and non-restorative sleep are often the residual symptoms in patients with MDD and these are considered to be the most resistant to the medical treatment of MDD. Since, alpha-delta sleep is also associated with similar symptoms i.e. non-restorative sleep and fatigue, treatment aimed at normalizing the alpha intrusion in slow-wave sleep could potentially benefit the MDD patients. Medications such as sodium oxybate have demonstrated normalization of alpha-delta sleep in patients with fibromyalgia and this is associated with a significant improvement in the symptoms of pain, fatigue and sleep. Similarly, selective serotonin re-uptake inhibitors (SSRIs) have shown to decrease the alpha intrusion in delta sleep. Therefore, elucidating the nature, severity and correlates of alpha-delta sleep in patients with MDD can have significant diagnostic and therapeutic implications.
Primary hypothesis:
Patients with MDD have a higher prevalence of alpha-delta sleep compared to age-matched non-MDD subjects.

Primary goal:
To compare alpha-delta sleep among MDD and non-MDD subjects

Secondary goal(s):
1. To identify various correlates of alpha-delta sleep in patients with MDD

Exploratory goal(s):
1. Evaluate if alpha-delta sleep is associated with subjective complaint of excessive daytime sleepiness in patients with MDD.
Methods

A retrospective review of 150 polysomnogram (PSG) studies, consisting of 75 subjects with major depressive disorder and 75 non-depressed subjects, who had polysomnograms done at Cleveland Clinic Sleep Disorders Center from July 2005 to October 2008 was conducted.

The Cleveland Clinic Sleep Disorders Center database had information (both raw data and interpretations) on a total of 14,549 patients for the period from July 2005 to October 2008. A total of 960 patients out of 14,549 patients (6.6%) matched the criteria for a current active medical history of MDD. Out of these 960 patients, the first 410 patient's medical charts were reviewed including the clinical interview, sleep questionnaire, polysomnographic raw data to identify 75 patients who met all the inclusion and exclusion criteria for the study. Similarly, for the on-depressed patient selection, the first 341 charts (out of 13,589 patients) were reviewed to identify 75 subjects who met all the inclusion and exclusion criteria for the study. The most common reason for exclusion of subjects in both MDD and non-MDD group was the presence of significant sleep apnea.

All the subjects included in this study had a one-night polysomnogram conducted in an accredited sleep lab and attended by a polysomnogram technician. All polysomnograms were performed according to the standard American Academy of Sleep Medicine (AASM) procedure, including video recording, left and right electrooculogram (EOG), central and occipital electroencephalogram (EEG), mental and submental
electromyogram (EMG), intercostal EMG, left and right anterior tibialis EMG, electrocardiogram (ECG), snoring sensor, continuous airflow measurement with thermistor, nasal pressure transducer, chest and abdominal effort, and oxygen saturation with pulse oximetry. Sleep stages were scored according to standard AASM 2007 criteria on 30-second epoch, which were scored as wakefulness, and sleep stage non rapid-eye-movement (NREM) 1, 2 and 3 (stage N1, N2, N3, respectively) and rapid-eye-movement (REM) sleep.\textsuperscript{33}

Given that the sleep studies done prior to 2007 were scored according to the “old” PSG scoring criteria, all the identified polysomnograms of patients who met the inclusion and the exclusion criteria were then rescored in accordance with the AASM scoring criteria 2007. Rescoring of the polysomnograms was accomplished by the principal investigator. In addition, the standard sleep definitions as in International Classification of Sleep Disorders, 2\textsuperscript{nd} Edition (ICSD-2) and standard mental disorders definitions as described in Diagnostic and Statistical Manual of Mental Disorders, 4\textsuperscript{th} Edition (DSM-IV) were applied for the purpose of this study.\textsuperscript{41,42} Specifically, Insomnia was defined as either difficulty falling asleep, staying asleep, maintaining sleep or non-refreshing sleep despite adequate opportunity to sleep and associated with daytime impairments such as fatigue, headaches, tension, anxiety, lack of concentration, etc.\textsuperscript{39}

Alpha-delta sleep, the most important parameter for our study has unclear criteria. As discussed previously, most researchers have defined alpha-delta sleep as “prominent” alpha frequency occurring during slow wave sleep. None of the published studies until now have used objective criteria to define alpha-delta sleep. Manu et al evaluated the correlation of alpha-delta
sleep and various other medical conditions that can cause fatigue (including depression), but the criteria used to identify alpha-delta sleep was “prominent alpha sleep during slow wave sleep”\(^{31}\). Similarly, Ware et al did not specifically look at alpha intrusion in slow wave or delta sleep but rather considered any alpha intrusion in NREM sleep\(^{38}\).

In view of the lack of objective criteria for alpha-delta sleep and a lack of guidance from any of the major sleep or psychiatry professional bodies (including American Academy of Sleep Medicine, American Sleep Research Society and American Psychiatry Association), it was decided to define an objective criteria that is straight-forward to score and reproducible. Accordingly, we specified alpha-delta sleep as the duration of delta waves with superimposed alpha rhythm divided by the total duration of slow wave sleep multiplied by 100 (i.e. percent of slow wave sleep duration). Alpha rhythm was defined as trains of sinusoidal 8-13 Hz activity recorded predominantly over the occipital region and delta (slow) wave activity was defined as waves of frequency 0.5 to 2 Hz and peak to trough amplitude > 75 microvolt predominantly over the frontal regions, consistent with the AASM guidelines\(^{33}\). This criterion was used to determine the presence and extent of alpha-delta sleep in all of the polysomnograms reviewed in this study. Of note, the principal investigator who scored and interpreted the studies was also involved with the selection of the subjects who fulfilled the inclusion/exclusion criteria i.e. the principal investigator was not blinded.

To ensure reproducibility of the criteria used in this study, a sample of 15 polysomnograms were randomly selected from the 150 studies identified
for our study. A board certified sleep specialist who was not involved in this study scored alpha-delta sleep using the above criteria.

**Inclusion and Exclusion criteria**

**Inclusion criteria:**

(1) age ≥ 18 years old

(2) apnea-hypopnea index (AHI) < 5/hour (apnea was defined as airflow cessation for at least 10 seconds and a hypopnea was defined as the nasal pressure signal excursions (or those of the alternative hypopnea sensor) drop by ≥ 50% of baseline for at least 10 seconds and was associated with an oxygen de-saturation of at least 3% and/or followed by a cortical arousal)

(3) subjects with adequate polysomnogram (PSG) data, defined as total sleep time (TST) of more than 6.5 hours and a sleep efficiency (SE) of ≥ 65%.

**Exclusion criteria:**

(1) Subjects with co-morbid disorders that are known to be associated with alpha-delta sleep including Fibromyalgia, Systemic lupus erythematos, Rheumatoid arthritis, Polymyalgia rheumatica, Fibrosis, Myositis, chronic pain syndrome and chronic fatigue syndrome.

(2) Subjects with significant sleep disorders: Sleep apnea syndrome (both obstructive and central), Narcolepsy, Circadian rhythm sleep disorders, Restless legs syndrome and Periodic limb movement disorders.

(3) Positive airway pressure (PAP) titration studies or split-night studies.
Statistical analyses

Data on the following demographic and disease characteristic variables were collected: age, sex, body mass index (BMI), neck circumference, past medical history and Epworth Sleepiness Scale (ESS) scores. Data on polysomnographic variables of interest were also collected including: sleep efficiency, sleep and rapid eye movement (REM) latencies, sleep stage distribution, arousal index, apnea-hypopnea index (AHI), periodic limbs movements index (PLMI), periodic limbs movements arousal index (PLMAI), nadir oxygen desaturation and alpha-delta sleep (as percentage of delta wave sleep).

Variables of interest with normal distribution were summarized and expressed as mean but otherwise as median or ratio (%). To ascertain the normal distribution of all continuous variables, a Kolmogorov-Smirnov test was performed. Independent sample t-tests were performed so as to compare a basic demographic, sleep parameters and alpha-delta sleep between MDD and non-MDD subjects. The effect of comorbid disorders, medication, gender, age groups on the prevalence of alpha-delta sleep was determined using univariate ANOVA. The relationship between alpha-delta sleep and ESS was qualified using Pearson correlation.

Upon data review we observed a tendency for subjects with a relatively lower percentage of alpha-delta sleep to be associated lower ESS scores. In the post-hoc analysis, the subjects with MDD were divided into two groups (high and low alpha-delta sleep) by means of a median split method (greater
than or less than 15% of alpha delta sleep) and the basic demographic data, sleep parameters as well as ESS in both groups were compared using independent sample t-test.

Multiple linear regression analyses and scatter plot were performed to evaluate the contribution of each basic demographic and sleep variable to models predicting the percentage of alpha-delta sleep. In addition, the impact of collinearity among the variables in the regression model was measured by means of tolerance and the Variance Inflation Factor (VIF). The multiple logistic regression analysis was subsequently performed to determine whether alpha-delta sleep correlates with excessive daytime sleepiness (defined as ESS ≥ 10) after adjusting for other factors. The statistical significance was defined as p ≤ 0.05 for all statistical tests.

The sample size was estimated to detect a 10% difference in the alpha delta sleep in patients with MDD and non-MDD. A total sample size (n) of 138 subjects (69 in each group) gives an alpha of 0.5 and a power of 90%.

The above statistical computations were performed using the SPSS version 11.5 and JMP version 6.1.
Results

The scoring criterion for alpha-delta sleep was validated in the study. A sample of 15 polysomnograms were randomly selected from the 150 studies identified and a board certified sleep specialist who was not involved in this study scored alpha-delta sleep using the criteria defined in the study. The random sample had six studies with a history of MDD and nine studies with no history of MDD. The alpha-delta sleep scoring was similar and mean alpha-delta score was slightly higher in the studies scored by the PI. The variation was 2.66 ±1.82% (mean±SD).

One hundred and fifty subjects were included in this study, of which 75 (50%) were subjects with MDD and the other 75 (50%) were non-MDD subjects (Figure 1). When stratified by age groups (18-29, 30-39, 40-49, 50-59 and > 60), the distribution of subjects was again similar in the two groups (Figure 2). The baseline demographic and disease characteristics of subjects in MDD and non-MDD groups were not significantly different except for gender and ESS score. The majority of subjects with MDD were female, somewhat consistent with the higher prevalence of depression in women (78.67% vs. 54.67%, p<0.05); in addition, compared to non-MDD subjects, subjects with MDD reported more sleepiness although the ESS score remained within normal limits (9.09±4.09 vs. 6.01±4.55, p<0.001)[Table 1].

Compared to non-MDD subjects, subjects with MDD had significantly higher sleep efficiency (p=0.01), shorter REM sleep latency (p < 0.001), higher REM sleep time (p < 0.001) and less slow wave sleep distribution (p < 0.001) [Table 2]. Furthermore, leg movements were more predominant in
subjects with MDD compared to non-MDD subjects (p=0.02). Between group difference in percent alpha delta sleep is illustrated in Figure 3. Alpha delta sleep was significantly higher in MDD subjects compared to non-MDD subjects (p<0.01). This difference persisted even after stratifying each of the groups into five different age groups (Table 3). Gender did not significantly affect the prevalence of alpha-delta sleep but female subjects with MDD had a relatively higher alpha-delta sleep compared to male subject with MDD (p=0.057); even within non-MDD group, female subjects had a relatively higher alpha-delta sleep than male subjects (Figure 4).

Within the MDD group, increasing age had an inverse correlation with alpha-delta sleep, particularly at age 60 and higher (p < 0.001, Figure 5). On the other hand, history of comorbid insomnia or comorbid psychiatric disorders (other than MDD) did not significantly affect the prevalence of alpha-delta sleep in subjects with MDD (Figure 6 and 7).

Of the 75 MDD subjects in this study, 30 patients had been never prescribed any medication, 26 were on selective serotonin reuptake inhibitor (SSRI), 9 on tricyclic anti-depressant (TCA), 4 were on benzodiazepine (BZD), 3 on BZD and SSRI, and 3 on BZD plus SSRI and TCA. Use of SSRI in patient with MDD was associated with a significant decrease in alpha delta sleep compared to subjects with MDD who were not on any medicines (p<0.001) [Figure 8].

Of all the demographic and disease characteristic variables of interest, alpha-delta sleep showed a statistically significant but a weak association with ESS scores (r = 0.246, p=0.034). A scatter plot generated according to the multiple linear regression model also demonstrated somewhat linear
correlation between ESS and percentage of alpha-delta sleep \( (r^2 = 0.06, p<0.05) \) [Figure 9].

In post-hoc analysis, within the MDD group, a median split was performed on the percentage of alpha-delta sleep in delta wave sleep to examine whether a high percentage of alpha-delta sleep (defined as \( \geq 15\% \) of alpha-delta sleep) have any unique characteristics compared to subjects with low percentage of alpha-delta sleep (defines as \( < 15\% \) of alpha-delta sleep). The demographic and disease characteristics (Table 4) and polysomnographic characteristics (Table 5) were examined among patients with high and low alpha-delta sleep within MDD group. The mean age of MDD patients with high alpha-delta sleep was significantly lower than that of MDD patients with low alpha-delta sleep (36.92±10.65 vs. 47.36±15.77, \( p=0.001 \)). Interestingly, although the mean ESS score of all MDD patients remained within normal limits (9.09±4.09, Table 1), the MDD patients with high alpha-delta sleep had a significantly increased ESS score compared to the MDD patients with low alpha-delta sleep (10.36±4.09 vs. 7.92±3.79, \( p=0.009 \)). Furthermore, multiple logistic regression analysis also demonstrated that the MDD patients with high alpha-delta sleep had a 3.15 greater odds of having excessive daytime sleepiness, as defined as ESS \( \geq 10 \), compared to the MDD patients with low alpha-delta sleep (Table 5).
Discussion

This polysomnogram based study was conducted to evaluate the prevalence of alpha-delta sleep in patients with MDD, as well as to determine various demographic and clinical correlates of alpha-delta sleep in patients with MDD. In this study, we found that MDD subjects (compared to subjects with no MDD) had a higher prevalence of alpha-delta sleep. In addition, MDD subjects compared to subjects with no MDD, had higher sleep efficiency, shorter REM sleep latency, less slow wave sleep, higher REM sleep as percentage of total sleep, and more frequent leg movements.

Interestingly, we found that MDD subjects have significantly higher sleep efficiency compared to non-MDD subjects in this study. In general, subjects with MDD complain of decreased amount and poor quality of sleep. However, a minority of patients with MDD, perhaps 10-15%, demonstrate high sleep efficiencies and report spending more time in bed. This finding is often associated with complaints of anergia and psychomotor slowing and the nature of depression in these patients is sometimes described as seasonal affective disorder and it is more prevalent in higher latitude places where winters are longer and severe\textsuperscript{38}. Given that the majority of the patients at Cleveland Clinic come from Northeast Ohio, which has cold climatic conditions, the prevalence of seasonal affective disorder is relatively higher, and therefore the finding of high sleep efficiency, although unexpected is not completely surprising\textsuperscript{39}.\HOLD
Regarding alpha-delta sleep, we found that MDD subjects had significantly higher alpha-delta sleep compared to non-MDD subjects, according to our criteria for alpha-delta sleep. As discussed earlier in the background section, previous studies have demonstrated inconsistent findings regarding the association between MDD and alpha-delta sleep. However, most studies defined alpha-delta sleep as “prominent” alpha frequencies occurring during slow wave sleep. Since the previous studies had not used objective criteria (as was done in the current study), this may have contributed to the inconsistent findings. When alpha-delta sleep in patient with MDD was first described, it was thought to be associated with a heterogeneous group of psychiatric patients with somatic malaise and fatigue. Subsequently, alpha-delta sleep was noted to occur in a majority (70%) of patients with fibromyalgia, and among healthy subjects deprived of non-REM sleep. Interestingly, in the later group, alpha-delta sleep also correlated with the presence of depression and irritability. Ware et al found that alpha-delta sleep was present in 42% of patients with major depression. In addition, Hudson et al showed that mood disorders are often diagnosed in fibromyalgia patients who are known to have alpha-delta sleep. Although Manu and colleagues found no correlation between alpha-delta sleep (criteria for alpha-delta sleep defined as “prominent alpha frequencies in slow wave sleep”) and chronic fatigue syndrome, fibromyalgia, major depression, primary sleep disorders, or Lyme disease, they did find that alpha-delta sleep was more evident among subjects with chronic fatigue but without major depressive disorders. However, that study had several limitations including a small sample size of just 30 patients and lack of a control group. The current study with its larger
sample size revealed for the first time that MDD subjects have higher prevalence of alpha-delta sleep compared to non-MDD subjects at least according to the newly proposed criteria for alpha-delta sleep (duration of delta wave sleep with superimposed alpha frequency divided by the total duration of slow wave sleep multiplied by 100).

Compared to non-MDD subjects, MDD subjects had significantly higher alpha-delta sleep in every age group. Within the MDD group, increasing age, particularly 60 and higher, and the use of SSRIs are associated with decreased alpha-delta sleep. On the other hand, among different age groups of non-MDD subjects there were no significant difference in terms of the prevalence of alpha-delta sleep. Therefore, it is likely that differences between the sleep of patients with MDD and normal controls is not just influenced by age but also other factors. Age strongly affects the relationship between sleep parameters and mood disorders, and the interaction of depression and age on sleep parameters suggests that depression may accelerate the effects of aging on sleep.\textsuperscript{14,44} The relationship between a generalized decrease in alpha-delta sleep and aging in MDD subjects but not in non-MDD subjects is not clearly understood. One possible explanation for this finding probably comes from the findings in a previous study which showed that some sleep parameters that change with age do not change in patients with depression, for example, elderly patients with depression do not tend to have significant reduction in slow wave sleep compared to control subjects.\textsuperscript{2,6}

Although there were limited number of MDD subjects using tricyclic antidepressant (n=9), and benzodiazepine (n=4), the number of patients using
SSRI (n=26) was comparable to the number patients not using any medications (n=30; p=0.085). A history of SSRI medication was associated with decreased alpha-delta sleep. This relationship is probably attributed to effects of SSRIs on MDD disease activity or on sleep architecture itself. However, duration of treatment may also contribute to these findings and several studies have identified various changes in sleep architecture associated with SSRIs/SNRIs. Knott and associates demonstrated that acute paroxetine (SSRI) did not alter EEG in MDD patients but chronic treatment was associated with significant alterations as shown by diffuse decrease in alpha power and increases in slow (delta and theta) and anterior fast (beta) wave power. Kluge et al found that duloxetine (SNRI) increases stage 3 sleep and suppresses REM sleep in patients with major depression. McClelland et al studied the acute effects of paroxetine (6 hours) on EEG in normal subjects which revealed a reduction in alpha waves and increases in delta waves. However, data on chronic effects of SSRI/SNRI on EEG in otherwise healthy subjects is lacking. Therefore, in addition to effect on disease severity, effects of SSRI/SNRI on EEG power itself may play an important role in decreasing alpha-delta sleep in MDD subjects found in the present study.

Alpha-delta sleep was not significantly affected by gender or comorbid insomnia. This finding is somewhat surprising in that women with depression, in general have a relatively higher prevalence of insomnia, fatigue and pain related symptoms. These symptoms, especially fatigue and pain, were found to be associated with alpha-delta sleep. Based on this association, we had expected a higher prevalence of alpha-delta sleep in women with depression.
MDD is often associated with other co-morbid psychiatric disorders, especially anxiety disorders. In addition, MDD episode could be part of a Bipolar disorders spectrum. We found that patients with MDD and no history of other co-morbid psychiatry disorder had a relatively higher alpha-delta sleep compared to MDD subjects with a history of other co-morbid psychiatry disorders such as bipolar disorder and anxiety disorders (Figure 7). However, none of these differences were statistically significant (p=0.776). The differences in the amount of alpha-delta sleep observed between these groups are hard to explain given that more than 80% of MDD subjects have co-morbid anxiety. In fact, what was surprising was a relatively large number of MDD subjects with no co-morbid anxiety.

Alpha-delta sleep is thought to be associated with a state of hypervigilance (and hence difficulties with initiating and maintaining sleep and non-restorative sleep associated with daytime fatigue but not necessarily excessive daytime sleepiness, similar to patients with psychophysiological insomnia). Similarly, most of the patients with major depressive disorders complain of insomnia and increased daytime fatigue and sometimes sleepiness; however, they do not consistently show evidence of increased daytime sleepiness, when tested objectively.\textsuperscript{10,11,12} Although the present study revealed significant differences between ESS scores of MDD and non-MDD subjects (9.09 ± 4.09 vs. 6.01 ± 4.55, p<0.001) the total ESS score remained within normal range (<10). This is consistent with what we had expected based on studies done in patients with MDD, and other studies that evaluated the effects of alpha-delta sleep. The reason why some MDD subjects experience daytime sleepiness but the others do not is not resolved. As
mentioned above, alpha-delta sleep is thought to be related with nonrestorative sleep which, in turn, may result in daytime sleepiness or a perception of excessive sleepiness (since it is not uncommon for patients to perceive fatigue as sleepiness). The post-hoc analysis offers some insight if the severity of alpha-delta sleep has any influence on the symptoms of excessive daytime sleepiness. Subjects with MDD were divided into two groups: high alpha-delta sleep (defined as ≥15% of alpha-delta sleep) and low alpha-delta sleep (defined as <15% of alpha-delta sleep) by a median split method. We found that MDD subjects with high alpha-delta sleep had higher ESS scores and they were at 3.15 greater odds to have excessive daytime sleepiness (ESS≥10) compared to MDD subjects with low alpha-delta sleep. The influence of alpha-delta sleep on daytime sleepiness in MDD subjects persisted even after controlling for age, neck circumference, BMI, sleep efficiency, AHI, and arousal index. The cause-effect relationship between alpha-delta sleep and excessive sleepiness is not well understood. One interesting hypothesis proposed by Englebienne and De Meirleir is that acquired channelopathy with loss of intracellular potassium should lead to metabolic and intracellular abnormalities, including central fatigue and sleep disturbance such as alpha-delta intrusion found in fibromyalgia patients. However, data from Hoof and associates did not support the inclusion of sleep disturbances including alpha-delta intrusion in the list of potential consequences of the suggested channelopathy. Since the etiology of alpha-delta sleep itself is not understood, any possible explanation on the association/causation of alpha-delta sleep and excessive daytime sleepiness is likely to be only speculative.
In the post-hoc analysis, one interesting finding was the slightly higher AHI in MDD subjects with low alpha-delta sleep compared to MDD subjects with high alpha delta sleep. The AHIs in low and high alpha delta sleep groups were 2.46 ± 1.53 and 1.62 ± 1.17, respectively. This difference was statistically significant at p=0.009 and 95% CI 0.22 to 1.47. This difference may be mediated by the age difference in the two groups of subjects. The mean age in low and high alpha delta sleep groups were 47.36 and 36.92 years, respectively. It is well known that age is a risk factor for sleep apnea and increasing age in general is associated with an increase in the AHI\textsuperscript{40}.

Some of the unique features of this study include: We studied patients with MDD with non-MDD subjects as controls. None of the subjects in our study had any other disorders (other than MDD) that are known to be associated with alpha delta sleep. This is in contrast to the previous studies that had a significant number of MDD patients with co-morbid conditions that are known to have prominent alpha-delta sleep such as fibromyalgia and chronic fatigue syndrome. We rescored all polysomnograms with AASM 2007 criteria, which is supposed to reduce inter-reader variability. Finally, we proposed a new objective criteria for alpha-delta sleep (and validated it) instead of using a highly subjective and non-reproducible “prominent” alpha-delta sleep criteria that was used in almost all of the studies thus far.

However, our study does have some limitations. This is a retrospective study with it’s associated deficiencies and inabilities to influence the data collection such as any sleep deprivation prior to sleep study, etc. Only 960 out of 14,549 subjects (6.6%) in the sleep center database has a current active
diagnosis of MDD, which is less than what is observed in the general population. It is possible that only patients who had significant depression got diagnosed and hence studied. The other possibility is that a number of subjects in the non MDD group may have had mild or moderate depression that was not clinically diagnosed. In addition, it is important to realize that the “first-night” effect (the altered quality and duration of sleep observed on the first night of a sleep study and attributed to sleeping in an unfamiliar environment with electrodes, etc) should be taken into consideration. Ideally, each of these patients should have had two nights sleep study and data obtained from the second used for the analysis. This will minimize the effect of first night but it will be a prohibitively expensive study. However, it is probably safe to assume that both MDD and non-MDD subjects are equally affected by the first night effect. There is also some evidence to show that depressed patients often do not show evidence of the “first night effect”. This absence of the “first night effect” may be related to the decreased adaptability of depressed patients or their abnormal sleep tends to conceal the first night effect. The principal investigator was not blinded as to the MDD or non-MDD status of the subjects when the PI scored the studies and did the interpretation. This may introduce a bias. However, when the alpha-delta criteria were validated by using a sample of studies by another scorer (board certified in sleep medicine and blinded to the disease status of the subjects), scores/interpretations similar to those obtained by the PI were observed. Therefore, PI un-blinding is unlikely to have impacted the study. We had not planned (and hence did not have enough sample size) to analyze the association of alpha-delta sleep with various comorbidities, medication, as
well as with daytime sleepiness and therefore a relatively small sample size was available for analyses in these subgroups. Using median split method to classify MDD subjects into two groups is not ideal as a great deal of information is lost when a continuous variable is converted into binary categorical variables.

In summary, this study shows that MDD subjects have a higher prevalence of alpha-delta sleep (as a percentage of SWS). Compared to non-MDD subjects, MDD subjects have a shorter REM latency, more total REM sleep and less slow wave sleep and they also tend to have higher ESS scores (but within the normal range). Within the MDD group, SSRI/SNRIs and increasing age decrease alpha-delta sleep. In contrast, a history of comorbid insomnia or other comorbid psychiatric disorders did not significantly affect the prevalence of alpha-delta sleep. Alpha-delta sleep seems to be associated with daytime sleepiness in MDD subjects. Finally, MDD subjects with high alpha-delta sleep (as defined as $\geq 15\%$ of delta waves with superimposed alpha) were at 3.15 greater odds to have excessive daytime sleepiness (ESS$\geq 10$) compared to those with low alpha-delta sleep.

In terms of future directions, it may be interesting to control for gender since MDD has a higher prevalence in women and women tend to complain more about fatigue and non-restorative sleep, both of which are associated with alpha-delta sleep. In addition, further research to find an association with the severity of depression and alpha-delta sleep; fatigue and alpha-delta sleep may be helpful in further delineating the relationship between MDD and alpha-delta sleep. Finally, a longitudinal follow-up study of patients with depression and with/without SSRI treatment may help with
understanding the nature and course of alpha-delta sleep in patients with MDD.
Table 1 Baseline demographic and disease characteristics of subjects with MDD and non-MDD (n=150)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Subjects with Major Depressive Disorder (n = 75)</th>
<th>Subjects with no Major Depressive Disorders (n = 75)</th>
<th>P value&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95% Confidence interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.35±14.46</td>
<td>41.65 ± 15.37</td>
<td>p =0.78</td>
<td>-4.12 to 5.51</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>59 (78.67%)</td>
<td>41 (54.67%)</td>
<td>p &lt; 0.05</td>
<td>--</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>36.76 ± 3.75</td>
<td>38.07 ± 4.49</td>
<td>p = 0.06</td>
<td>-2.64 to 0.03</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>32.40 ± 22.06</td>
<td>30.47 ± 9.78</td>
<td>p = 0.49</td>
<td>-3.58 to 7.44</td>
</tr>
<tr>
<td>ESS</td>
<td>9.09 ± 4.09</td>
<td>6.01 ± 4.55</td>
<td>p &lt; 0.001</td>
<td>1.68 to 4.48</td>
</tr>
</tbody>
</table>

<sup>a</sup> The distributions of all continuous data are normal except for those of sex.

<sup>b</sup> All data are presented as mean ± SD except for gender which is expressed as percentage (%).

<sup>c</sup> p value was measured by means of independent sample t test. Statistical significance of the difference of mean between two groups was defined by p < 0.05.

*Abbreviations*: BMI, body mass index; ESS, Epworth sleepiness scale.
Table 2 Polysomnographic characteristics of subjects with MDD and non-MDD (n=150)

<table>
<thead>
<tr>
<th>Covariates&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Subjects with Major Depressive Disorder (n = 75)</th>
<th>Subjects with no Major Depressive Disorders (n = 75)</th>
<th>P value&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95% Confidence interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency (%)</td>
<td>83.02 ± 9.62</td>
<td>78.13 ± 8.26</td>
<td>p = 0.01</td>
<td>2.01 to 7.78</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>16.65 ± 13.25</td>
<td>16.17 ± 15.43</td>
<td>p = 0.84</td>
<td>-4.16 to 5.12</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>84.96 ± 44.55</td>
<td>189.91 ± 250.63</td>
<td>p &lt; 0.001</td>
<td>-163.03 to -46.86</td>
</tr>
<tr>
<td>N1 (% of TST)</td>
<td>8.53 ± 5.58</td>
<td>8.97 ± 6.52</td>
<td>p = 0.66</td>
<td>-2.39 to 1.52</td>
</tr>
<tr>
<td>N2 (% of TST)</td>
<td>58.43 ± 7.43</td>
<td>58.34 ± 8.79</td>
<td>p = 0.94</td>
<td>-2.53 to 2.72</td>
</tr>
<tr>
<td>N3 (% of TST)</td>
<td>8.34 ± 3.00</td>
<td>13.47 ± 6.17</td>
<td>p &lt; 0.001</td>
<td>-6.69 to -3.55</td>
</tr>
<tr>
<td>REM (% of TST)</td>
<td>24.69 ± 6.97</td>
<td>19.23 ± 8.17</td>
<td>p &lt; 0.001</td>
<td>3.01 to 7.91</td>
</tr>
<tr>
<td>Percent of Alpha-Delta in delta sleep (%)</td>
<td>23.40 ±24.16</td>
<td>2.33 ±6.66</td>
<td>P &lt; 0.001</td>
<td>15.28 to 26.86</td>
</tr>
<tr>
<td>AHI</td>
<td>2.06 ± 1.42</td>
<td>1.64 ± 1.64</td>
<td>P = 0.10</td>
<td>-0.08 to</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>P-value</td>
<td>CI</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Arousal index (events/hour)</td>
<td>13.47 ± 6.52</td>
<td>14.70 ± 8.98</td>
<td>0.34</td>
<td>-3.76 to 1.30</td>
</tr>
<tr>
<td>PLMI (events/hour)</td>
<td>3.51 ± 4.80</td>
<td>1.88 ± 3.33</td>
<td>0.02</td>
<td>0.29 to 2.96</td>
</tr>
<tr>
<td>PLMAI (events/hour)</td>
<td>1.05 ± 1.65</td>
<td>0.53 ± 1.09</td>
<td>0.02</td>
<td>0.70 to 0.72</td>
</tr>
<tr>
<td>Nadir oxygen saturation (%)</td>
<td>92.20 ± 2.06</td>
<td>92.16 ± 2.18</td>
<td>0.91</td>
<td>-0.64 to -13.17</td>
</tr>
</tbody>
</table>

a The distributions of all continuous data are normal.
b All data are presented as mean ± SD.
c p value was measured by means of independent sample t test. Statistical significance of the difference of mean between two groups was defined by p < 0.05.

Abbreviations: REM, rapid eye movement; TST, total sleep time; AHI, apnea-hypopnea index; PLMI, periodic limbs movements index; PLMAI, periodic limbs movements arousal index; SWS, slow wave sleep
<table>
<thead>
<tr>
<th>Age group</th>
<th>n</th>
<th>Alpha-Delta Sleep&lt;sup&gt;a,b&lt;/sup&gt; (% of SWS)</th>
<th>Standard Error</th>
<th>P value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MDD</td>
<td>17</td>
<td>31.56 ± 23.44</td>
<td>5.69</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>- Non-MDD</td>
<td>20</td>
<td>3.48 ± 7.53</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MDD</td>
<td>17</td>
<td>28.42 ± 30.27</td>
<td>7.341</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>- Non-MDD</td>
<td>13</td>
<td>3.40 ± 8.92</td>
<td>2.475</td>
<td></td>
</tr>
<tr>
<td>40-49 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MDD</td>
<td>18</td>
<td>22.84 ± 17.68</td>
<td>4.16</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>- Non-MDD</td>
<td>19</td>
<td>2.06 ± 7.60</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MDD</td>
<td>14</td>
<td>19.91 ± 25.78</td>
<td>6.89</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>- Non-MDD</td>
<td>14</td>
<td>1.07 ± 2.92</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MDD</td>
<td>8</td>
<td>2.73 ± 2.76</td>
<td>0.94</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>- Non-MDD</td>
<td>9</td>
<td>0.72 ± 1.20</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The distributions of all continuous data are normal.

<sup>b</sup> All data are presented as mean ± SD

<sup>c</sup> p value was measured by means of independent sample t test. Statistical significance of the difference of mean between two groups within each age group was defined by p < 0.05.

*Abbreviation: SWS, slow wave sleep; MDD, major depressive disorders*
Table 4 Post-hoc analysis: Differences in Demographics and clinical characteristics of Major Depressive Disorder Patients between those with greater than 15% of delta wave sleep with alpha intrusions (i.e. High Alpha-Delta Sleep) and those with less than 15% of delta wave sleep with alpha intrusions (i.e. Low Alpha-Delta Sleep)

<table>
<thead>
<tr>
<th>Covariates(^a)</th>
<th>MDD subjects with Low Alpha-Delta Sleep(^b)</th>
<th>MDD subjects with High Alpha-Delta Sleep(^b)</th>
<th>p value(^c)</th>
<th>95% Confidence interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Alpha-Delta in delta sleep (%)</td>
<td>8.80 ± 5.47</td>
<td>22.90 ± 10.09</td>
<td>n/a</td>
<td>-n/a</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.36 ± 15.77</td>
<td>36.92 ± 10.65</td>
<td>p = 0.001</td>
<td>4.20 to 16.69</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>36.15 ± 3.74</td>
<td>37.92 ± 10.65</td>
<td>p = 0.146</td>
<td>-2.98 to 0.45</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.15 ± 4.25</td>
<td>37.01 ± 31.10</td>
<td>p = 0.082</td>
<td>-18.88 to 1.17</td>
</tr>
<tr>
<td>ESS</td>
<td>7.92 ± 3.79</td>
<td>10.36 ± 4.09</td>
<td>p = 0.009</td>
<td>-4.25 to -0.63</td>
</tr>
</tbody>
</table>

\(^a\) The distributions of all continuous data are normal.

\(^b\) All data are presented as mean ± SD.
c p value was measured by means of independent sample t test. Statistical significance of the difference of mean between two groups was defined by p < 0.05.

*Abbreviation:* BMI, body mass index; ESS, Epworth sleepiness scale.
Table 5 Post-hoc analysis: Differences in the polysomnographic characteristics of Major Depressive Disorder Patients between those with greater than 15% of delta wave sleep with alpha intrusions (i.e. High Alpha-Delta Sleep) and those with less than 15% of delta wave sleep with alpha intrusions (i.e. Low Alpha-Delta Sleep)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>MDD subjects with Low Alpha-Delta Sleep&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MDD subjects with High Alpha-Delta Sleep&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p value&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95% Confidence interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Alpha-Delta in delta sleep (%)</td>
<td>8.80 ± 5.47</td>
<td>22.90 ± 10.09</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>81.61 ± 9.25</td>
<td>84.56 ± 9.90</td>
<td>p = 0.186</td>
<td>-7.36 to 1.46</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>15.94 ± 13.39</td>
<td>17.42 ± 13.23</td>
<td>p = 0.633</td>
<td>-7.61 to 4.66</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>90.36 ± 50.84</td>
<td>79.11 ± 36.36</td>
<td>p = 0.278</td>
<td>-9.24 to 31.74</td>
</tr>
<tr>
<td>N1 (% of TST)</td>
<td>9.44 ± 5.47</td>
<td>7.55 ± 5.60</td>
<td>p = 0.144</td>
<td>-0.66 to 4.44</td>
</tr>
<tr>
<td>N2 (% of TST)</td>
<td>58.56 ± 7.79</td>
<td>58.30 ± 7.13</td>
<td>p = 0.880</td>
<td>-3.18 to 3.71</td>
</tr>
<tr>
<td>N3 (% of TST)</td>
<td>8.25 ± 2.72</td>
<td>8.44 ± 3.32</td>
<td>p = 0.792</td>
<td>-1.58 to 1.21</td>
</tr>
<tr>
<td>REM (% of TST)</td>
<td>23.75 ± 6.81</td>
<td>25.71 ± 7.11</td>
<td>p = 0.225</td>
<td>-5.17 to 1.24</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>p-value</td>
<td>p-value range</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>AHI (events/hour)</strong></td>
<td>2.46 ± 1.53</td>
<td>1.62 ± 1.17</td>
<td>0.009</td>
<td>0.22 to 1.47</td>
</tr>
<tr>
<td><strong>Arousal index (events/hour)</strong></td>
<td>14.39 ± 5.96</td>
<td>12.48 ± 7.03</td>
<td>0.209</td>
<td>-1.09 to 4.89</td>
</tr>
<tr>
<td><strong>PLMAI (events/hour)</strong></td>
<td>1.21 ± 1.76</td>
<td>0.089 ± 1.52</td>
<td>0.406</td>
<td>-0.44 to 1.08</td>
</tr>
<tr>
<td><strong>Nadir oxygen saturation (%)</strong></td>
<td>91.97 ± 1.78</td>
<td>92.44 ± 2.23</td>
<td>0.327</td>
<td>-1.42 to 0.48</td>
</tr>
</tbody>
</table>

*a* The distributions of all continuous data are normal.

*b* All data are presented as mean ± SD.

*c* p value was measured by means of independent sample t test. Statistical significance of the difference of mean between two groups was defined by p < 0.05.

*Abbreviation:* REM, rapid eye movement; TST, total sleep time; AHI, apnea-hypopnea index; PLMI, periodic limbs movements index; PLMAI, periodic limbs movements arousal index; SWS, slow wave sleep
Table 6  Multivariate Model Predicting Excessive Daytime Sleepiness as Determined by Epworth Sleepiness Scale Score ≥ 10 in Subjects with Major Depressive Disorder

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted Odds Ratios(^a) (95% Confidence Interval)</th>
<th>P value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97 (0.94 to 1.01)</td>
<td>P = 0.186</td>
</tr>
<tr>
<td>BMI</td>
<td>1.02 (0.97 to 1.07)</td>
<td>P = 0.434</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>1.06 (1.00 to 1.13)</td>
<td>P = 0.054</td>
</tr>
<tr>
<td>AHI</td>
<td>1.16 (0.78 to 1.72)</td>
<td>P = 0.460</td>
</tr>
<tr>
<td>Arousal Index</td>
<td>1.05 (0.97 to 1.14)</td>
<td>P = 0.246</td>
</tr>
<tr>
<td>Alpha-Delta Sleep(^c) Category (High vs Low)</td>
<td>3.15 (1.22 to 8.14)</td>
<td>P = 0.018</td>
</tr>
</tbody>
</table>

\(^a\) Data are expressed as odds ratios with 95% confidence interval for the incident of excessive daytime sleepiness, as determined by ESS > 10, calculated by categorical multiple logistic regression analysis based on all enter algorithm.

\(^b\) p value less than 0.05 determined as statistical significance

\(^c\) Alpha-delta sleep categories as a continuous variable when used in the analysis

Abbreviation: BMI, body mass index; ESS, Epworth sleepiness scale; REM, rapid eye movement; TST, total sleep time; AHI, apnea-hypopnea index
Cleveland Clinic Sleep Center Database (07/2005 to 10/2008) (n=14519)

History of depression
n = 960
Reviewed 410 patients’ data to identify 75 patients

No history of depression
n = 13589
Reviewed 314 patients’ data to identify 75 patients

Figure 1 Overview of subjects enrolled in the study
Figure 2 Distribution of subjects in the MDD and non-MDD groups stratified by different age groups

![Bar chart showing the distribution of subjects in MDD and non-MDD groups by age group.](chart.png)

- Subjects with MDD
- Non-MDD subjects
Figure 3 The mean percentage of Alpha-Delta Sleep in MDD and non-MDD Subjects

* $F(1,148)=52.96$, $p<0.001$
Figure 4 Correlation between Gender and Percentage of Alpha-Delta Sleep in subjects with MDD and non-MDD

- Mean Percentage of Alpha-Delta Sleep (% of Slow Wave Sleep Duration)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with MDD</td>
<td>N=16</td>
<td>N=59</td>
</tr>
<tr>
<td>non-MDD subjects</td>
<td>N=41</td>
<td></td>
</tr>
</tbody>
</table>

- **p = 0.057**
- **p = 0.09**

N=16 N=59 N=41
Figure 5 Distribution of Alpha-Delta Sleep among Different Age Groups in subjects with MDD and non-MDD

- **p < 0.001**

<table>
<thead>
<tr>
<th>Age Groups (years)</th>
<th>Subjects with MDD</th>
<th>Non-MDD subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>40-49</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>&gt;60</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 6: The Association Between Prevalence of Alpha-Delta Sleep and History of Insomnia in subjects with MDD and non-MDD

- **Positive History of Insomnia**
  - Subjects with MDD: N=63
  - Mean Percentage of Alpha-Delta Sleep: 25%
  - p = 0.142

- **Negative History of Insomnia**
  - Subjects with MDD: N=13
  - Mean Percentage of Alpha-Delta Sleep: 15%

- **Positive History of Insomnia**
  - non-MDD subjects: N=57
  - Mean Percentage of Alpha-Delta Sleep: 10%
  - p = 0.118

- **Negative History of Insomnia**
  - non-MDD subjects: N=18
  - Mean Percentage of Alpha-Delta Sleep: 5%
Figure 7 The Association between the Prevalence of Alpha-Delta Sleep and other Co-morbid Psychiatric Disorders found in Major Depressive Disorder Patients

Mean Percentage of Alpha-Delta Sleep (% of Slow Wave Sleep Duration)

- None: N=52
- Bipolar disorders: N=2
- Anxiety: N=21

p = 0.776
Figure 8 Relationship of different medications on the prevalence of alpha-delta sleep in patients with MDD

* F (5,69) = 11.70 (p < 0.001)
Figure 9 The Linear Correlation between Epworth Sleepiness Scale Score and The Prevalence of Alpha-Delta Sleep in Major Depressive Disorder Patients ($r = 0.246; p = 0.034$). In the post-hoc analysis, a median split was performed (arbitrarily chosen at 15%) based on the observation that lower prevalence of alpha delta sleep was associated with a relatively lower ESS scores.
Figure 10 Post-hoc analysis: Stratification of subjects with major depressive disorder as having high and low alpha-delta sleep (≥ or < 15% of alpha-delta sleep) based on percentage of alpha-delta sleep in slow wave sleep.

Subjects with Major Depressive Disorders (n=75)

<table>
<thead>
<tr>
<th>Alpha-Delta ≥ 15% of Slow wave sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
<tr>
<td>Low Alpha-Delta Sleep (n=39)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>High Alpha-Delta Sleep (n=36)</td>
</tr>
</tbody>
</table>
Figure 11 Normal delta (or slow wave) sleep as seen on a polysomnogram.
Figure 12 Alpha-waves superimposed on delta waves (alpha-delta waves), as seen on a polysomnogram.
Bibliography


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