

Bipolar disorder and sleep apnea

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ABSTRACT

Good quality of sleep is essential in facilitating mood stabilization in patients with bipolar disorder, and yet very few studies have been conducted to examine the interaction between bipolar disorder and sleep apnea, which interrupts the normal sleep cycle. Bipolar disorder is characterized by fluctuating moods within manic and depressive episodes. For mood stabilization in patients with bipolar disorder, a normal sleep cycle, following regular biological circadian rhythms, is necessary. Unfortunately, sedative hypnotic medications (benzodiazepines), which are prescribed to bipolar patients to facilitate sleep, can lead to airway collapse that can precipitate apneic events during sleep. Sleep apnea is characterized by cessations of breathing lasting more than 10 seconds. This leads to decreased oxygen supply to the brain, which in turn results in disruptions of normal sleep patterns. The aim of this study was to examine the occurrence of sleep apnea in bipolar patients and to determine whether sleep apnea is more prevalent among those that use benzodiazepines. This was achieved by comparing the breathing data from a single night of sleep between a bipolar disorder group and a control group. The data indicates that sleep apnea is no more prevalent in sampled bipolar patients than in the sampled control group. Benzodiazepines were also not found to adversely affect sleep apnea incidence. However, as quality of sleep is one of the most frequent complaints among patients with bipolar disorder, it is important to continue research in this field.

Keywords: benzodiazepines; bipolar disorder; mood; quality of life; sleep; sleep apnea

You know when you're depressed? Everything just gets you down... And that's just worse when you're trying to fall asleep because then you just lie there and think about the bad things. And then not being able to sleep gets you down even more. It's horrible for me. (SK, Interview, October 28, 2008)

Bipolar disorder is a debilitating psychiatric illness that is characterized by fluctuating moods within manic and depressive episodes. For mood stabilization in patients with bipolar disorder, a normal sleep cycle, following regular biological circadian rhythms, is necessary. Sleep apnea, however, leads to disruptions to the normal sleep patterns, thereby hindering their mood stabilizing effect. The aim of this study was thus to examine the occurrence of sleep apnea in bipolar patients, as well as determine whether their medications have any impact on their quality of sleep.

DEFINITIONS OF TERMS

Bipolar disorder

This paper will refer to bipolar I disorder and bipolar II disorder under the general term of bipolar disorder (BD); that is the convention in the literature. BD is a well-known psychiatric disorder that was previously known as manic-depressive illness. A person with BD experiences dramatic shifts in mood from manic states to depressed states and vice versa. Appendix A presents a complete list of the characteristics of BD as well as the current diagnostic criteria.

BD has a prevalence of approximately 1.2 to 1.6 percent among the United States population and is as frequently diagnosed in men as in women. This disorder has the highest mortality rate of all psychiatric disorders, as it is estimated that 19 percent of individuals with BD commit suicide (Müller-Oerlinghausen, Berghofer, & Michael Bauer, 2002).

Unfortunately, no epidemiological data exists for BD in South Africa. There is, however, a study underway which is collecting these data for BD and other psychiatric disorders (Williams et al., 2004).

The neural structures associated with BD have also recently been investigated by Strakowski and colleagues (1999). They used magnetic resonance imaging to examine the neural pathways associated with mood to determine whether any structural abnormalities were present. They discovered that all of the mood-related neural pathways were structurally abnormal in BD patients compared with controls. However, the significant finding was that the prefrontal cortex, which is implicated in mood regulation and executive function, was found to be among these structures. The prefrontal cortex has also been identified as a

possible site of regulation of the switching between depressed and manic states in BD patients (Drevets, 2000). These studies and others have marked the prefrontal cortex as a potential target for interventions and pharmaceutical development. The fact that it is specifically the prefrontal cortex that is implicated is interesting because it is exactly this structure that is at risk for hypoxic damage due to sleep apnea (Beebe & Gozal, 2002).

An important consideration is that these studies investigating BD are almost always done with BD patients currently undergoing treatment by medication. Thus, a problem with studying medicated BD patients is that the findings may not be indicative of effects inherent to BD, but rather could be a result of the medication. Another consideration in the research literature is that most studies of BD are done with euthymic BD patients. Euthymia is defined as a “normal range of mood, implying absence of depressed or elevated mood” (B. J. Sadock, V. A. Sadock, & Kaplan, 2007, p. 277). Thus, it describes a state of mood when neither mania nor depression is present. When BD patients are euthymic it is indicative that their treatment is functioning correctly to alleviate their possible depressed or manic episodes.

Sleep architecture and function

Sleep is controlled by circadian rhythms, which determine the onset and amount of sleep (Vgontzas & Kales, 1999). The reported average amount of sleep per night for adults is 7.5-8.5 hours (Carskadon & Dement, 2005), although it has been hypothesized that the brain’s recuperative physiological need is satisfied after 4.5 hours of sleep (Belenky et al., 2003). This time can be divided into 4 to 6 cycles which differ in behavioural and electroencephalographic (EEG) characteristics. A single cycle can be divided into 2 distinct stages, namely non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further divided into 4 distinct stages (Carskadon & Dement, 2005). Stage 1 NREM sleep generally lasts for 1 to 7 minutes and serves as a transition from the waking state to the sleeping state. It also functions as a transition from one cycle of sleep to the next throughout the night. Stage 2 NREM sleep follows stage 1 and lasts around 10 to 25 minutes. This stage also has very distinct EEG signatures that are called sleep spindles. Stage 3 NREM sleep occurs next and appears on the EEG as increasing high-voltage slow-wave activity. It lasts for only a few minutes before the next stage begins. Stage 4 NREM sleep has the highest amount of high-voltage slow-wave activity of all the sleep stages. This stage lasts for 20 to 40 minutes before stage 3, and then stage 2 occurs again. REM sleep occurs next and lasts for 1 to 5 minutes in the first cycle of the night. After REM sleep the cycle begins again at stage 1 NREM sleep (Carskadon & Dement, 2005).

The definite reasons for sleep remain a mystery (Beebe & Gozal, 2002), but it is generally assumed that sleep provides the body and brain with time to rest and recuperate (Carskadon & Dement, 2005). Sleep deprivation and restriction studies have also shown that sleep is an integral component in the maintenance of health, safety, productivity and quality of life. Additionally, interruptions to the normal sleep pattern serve to decrease cognition and motor skills (Belenky et al., 2003). Thus, a normal night of sleep is instrumental in assuring optimal functioning during the subsequent day.

BACKGROUND

Sleep and mood

Sleep duration and quality have a pronounced effect on mood. In a survey conducted with a representative sample of the American population, the National Sleep Foundation (2002) found striking correlations between amount of time slept and mood. Respondents who reported more than 6 hours slept per night were much more likely to be optimistic and/or satisfied with life. Conversely, those respondents who reported less than 6 hours of sleep per night were much more likely to feel tired, stressed, angry, or sad.

Strine and Chapman (2005) conducted a similar study through telephonic administering of a health-related quality of life questionnaire to a total of 79 625 respondents across America. They saw that up to 20% of respondents who reported insufficient sleep also reported frequent depressive symptoms, and 33.7% also reported frequent anxiety.

Leibenluft et al. (1996) investigated the connection between sleep and mood in their longitudinal study of 11 BD patients. These patients were asked to complete daily sleep logs and mood ratings over the course of 18 months. This allowed the researchers to calculate the probability that the patients would experience a depressed, manic, or hypomanic mood based on amount of prior sleep obtained. The outcome of the study was that increased sleep duration was correlated with reduction in manic symptoms on the subsequent days. This result is in agreement with previous findings that sleep deprivation was shown to induce a switch into mania in approximately 60 percent of depressed BD individuals. However, the switch was merely temporary, with most individuals relapsing into a depressed mood after a single night of recovery sleep.

Mood, conversely, also has a significant effect on sleep. Hypomania and mania are associated with decreases in sleep duration, while depression is associated with hypersomnia (Leibenluft et al., 1996). Thus, a manic episode has the effect of reducing sleep, while sleep

reduction has the effect of leading to a manic episode. This self-reinforcing mechanism could lead to the rapid escalation of manic episodes (Barbini, Bertelli, Colombo, & Smeraldi, 1996). Thus, a regular sleep pattern (i.e. one that coincides with a patient's circadian rhythm) is highly recommended to aid in the stabilization of mood, especially during a manic episode (Barbini et al., 1996).

Sleep apnea

Sleep apnea, or obstructive sleep apnea syndrome, is characterized by an apnea-hypopnea index (AHI), which is the total number of incidences of apnea and hypopnea during one hour of sleep (Flemons, 2002). Apnea is a brief cessation of breathing due to complete obstruction of the upper airways that lasts at least 10 seconds. Hypopnea is a marked reduction of air-flow in the upper airways due to a partial obstruction that also lasts at least 10 seconds (Schröder & O'Hara, 2005).

These repetitive respiratory abnormalities are measurable as they cause brief arousals which can be recorded on EEG equipment. They also cause a decrease in the blood oxygen concentration, which can be directly measured in blood samples collected shortly after the apneic event. This reduction in the oxygen concentration of the blood leads to repetitive cerebral hypoxemia, which is a reduction of the oxygen supply to the brain.

Factors that affect incidence of sleep apnea are gender, age, obesity, craniofacial abnormalities, and sedative hypnotic medication. Obesity is one of the greatest risk factors for sleep apnea because it can lead to an increase in pressure on the lungs and airways, which could cause them to partially collapse if the individual is extremely overweight (Flemons, 2002). Thus, because individuals with a body-mass index (BMI) greater than 30kg/m^2 (World Health Organization, 1995) are classified as obese, they can be considered to be at risk of developing sleep apnea. Sleep apnea is more frequently diagnosed in males than in females and especially among those over age 30 (Flemons, 2002). Craniofacial abnormalities have a detrimental effect on respiration due to the abnormal development of the skull, which could result in narrowed or structurally malformed airways not conducive to optimum airflow (Young, Finn, & Kim, 1997).

The particular sleep apnea risk factor of interest here is sedative hypnotic medication, such as benzodiazepines, which are generally used to treat insomnia. Benzodiazepines are also frequently prescribed to BD patients during episodes of acute mania to decrease their states of hyper-arousal (Curtin & Schulz, 2004). This medication has a depressive effect on the CNS, which aids the BD individual in feeling calmer and also facilitates sleep onset

(Müller-Oerlinghausen et al., 2002). However, the CNS depression induced by this medication also affects muscle control and can lead to muscle relaxation. This relaxation directly impacts breathing, which is regulated by muscles in the chest and neck. A decrease in muscle tension in these areas can lead to airway collapse due to decreased pressure in the lungs. Thus, in BD patients using benzodiazepines, there is a greatly increased likelihood of sleep apnea due to airway collapse (Guilleminault, 1990). Therefore, because quality of sleep has such a large impact on mood in BD patients, it is essential that all measures be taken to ensure a good night's sleep in these patients. Sleep apnea in particular is of great importance to clinicians working with BD patients as it has a direct impact on their quality of sleep. It can also lead to hypoxic conditions in the brain, and specifically in the prefrontal region, which plays a role in the mood stabilization of patients with BD.

Decreasing the brain's oxygen supply is extremely detrimental as it has a direct impact on the efficacy of neural functioning (El-Ad & Lavie, 2005). These effects carry implications for mood as sleep is not only interrupted, but brain function is also affected. Brain function is affected due to the cerebral hypoxemia, which disrupts the oxygen-dependant functions of homeostasis in the central nervous system (CNS). One brain region that is affected in particular is the prefrontal cortex. Beebe and Gozal (2002) have showed that the prefrontal cortex is particularly vulnerable to hypoxic conditions in the brain. This carries huge implications for BD patients, as the prefrontal cortex has also been implicated in the process of mood regulation.

SUMMARY AND SPECIFIC AIMS

BD is a debilitating disorder that is characterized by fluctuating moods within manic and depressive episodes. For mood stabilization in BD patients a normal sleep cycle following regular biological circadian rhythms is necessary. Sleep apnea, however, leads to disruptions to the normal sleep patterns, which leads to hypoxic conditions in the brain. This, in turn, creates unfavourable conditions for normal brain function across the entire brain, but also specifically in the prefrontal cortex. Furthermore, the prefrontal cortex is directly implicated in the regular functioning of the brain's pathways that are responsible for mood regulation. The dysfunction of these pathways thereby hinders the occurrence of the mood stabilizing effect. This chain of events also provides a solid link between the disparate conditions of BD and sleep apnea.

There are several risk factors for sleep apnea, including age, gender, and obesity. One risk factor particularly relevant to the currently proposed study is the use of benzodiazepines, which are regularly prescribed to BD patients. This prescription is made because psychiatrists often observe sleep problems, such as insomnia, in their BD patients. Benzodiazepines, which have a sedative effect, are therefore prescribed in order to alleviate these sleep problems. Unfortunately, however, benzodiazepines lead to muscle relaxation which can, in turn, lead to airway collapse, which is the defining characteristic of obstructive sleep apnea. This interaction between bipolar disorder, sleep apnea and benzodiazepines is troubling because it forms a causative cycle that is detrimental to the patient.

The specific aim of this study is to investigate the occurrence of sleep apnea in a sample of euthymic BD patients, and to examine whether sleep apnea is characteristic of BD irrespective of specific sleep apnea risk factors (viz., age, body mass index, medication use). The possibility that benzodiazepines can increase the frequency of apneic events is also examined.

METHOD

Research design and setting

Because only one measurement was taken from each participant, the design is classified as cross-sectional. The nature of the groupings and time limitations of the study necessitated a quasi-experimental design.

Two age-, gender-, and BMI-matched participant groups were used during this investigation: a bipolar group and a control group. Breathing data was recorded during a single night of sleep for both groups. The data was collected at the participants' homes by way of a portable nasal airflow monitor.

Participants

The first group of participants (the BD group; $n = 8$) was recruited through professionals in the healthcare industry and contacts through the University of Cape Town (UCT) community. These participants were diagnosed with BD prior to recruitment. The second group (the Control group; $n = 8$) was recruited from the University of Cape Town (UCT) community. Participants in this group were unrelated to participants in the BD group and had reported no past or current psychiatric diagnoses. The control group was used to compare the prevalence of sleep apnea in BD participants with its prevalence in a normal sample of participants, representative of the general population.

Participants were selected based on the following exclusion criterion: they must not currently have a condition that complicates breathing or causes blockages in their nasal cavities. Thus, candidates were not selected if they had asthma, flu, lung cancer or similar breathing-complicating conditions.

As noted above, participants in both groups were matched on three major factors: sex, age, and BMI. This matching was done to decrease the amount that sex, age, and BMI would have covaried with AHI when comparing the BD and Control groups. These three factors are also the strongest indicators of obesity. Given that obesity is a risk factor for sleep apnea, not matching groups on these factors would likely have skewed the results in favour of the group that contained the largest amount of obese participants.

The study followed the ethical guidelines stipulated in the UCT Codes for Research. All study procedure were reviewed and approved by the Research Ethics Committee of the UCT Department of Psychology and the Research Ethics Committee of the UCT Faculty of Health Sciences prior to commencement of data collection. The participants also had incentive to participate in the study to receive a report on their quality of sleep upon the conclusion of data analysis, along with R100.00 reimbursement. The reports also included guidelines for improving quality of sleep.¹

Measures and apparatus

A basic demographic questionnaire (see Appendix B) was administered to the participants once they had agreed to take part in the study. Identifying the participant's date of birth and gender allowed me to examine whether these variables had any impact on AHI within my sample. Height and weight were needed to calculate BMI, which was also investigated as a possible indicator of AHI. It was also necessary to learn whether the participants were currently using any medication that could have an effect on AHI. Finally, current or past psychiatric diagnoses were important to take note of, especially if they occurred in conjunction with BD. It was important to have a BD sample that did not have co-occurring psychiatric illnesses as this could obscure the results.

Resmed's ApneaLinkTM device (Resmed, 2007) was used for primary data collection. This device is a portable nasal air-flow monitor that measures nasal air-flow and snoring

¹If any of the reports were indicative of a pathological breathing disorder, the relevant participants were referred to Ms. Marlene Gounder, the chief technician at Vincent Pallotti Hospital's sleep laboratory for comprehensive diagnosis of the disorder.

during sleep. This allows the device to indicate the number of apnea and hypopnea events that occur during the night. The ApneaLink™ has been shown to provide good specificity (between 87.5% and 95%) and sensitivity (between 76% and 91%) in accurately determining AHI when compared with standard polysomnography (Erman, Stewart, Einhorn, Gordon, & Casal, 2007; Wang et al., 2003). Thus, two of the reasons behind choosing the ApneaLink™ were the portability and relative accuracy it provided. The deciding factor to use the ApneaLink™, however, was because it is simple to use and non-invasive. Simplicity was important because the participant was responsible for correctly fitting and wearing the device before going to sleep.

To correctly wear the device, it is fastened around the chest of the participant with an elastic belt. A simple nasal cannula (a flexible tube) is connected to the ApneaLink™, positioned around the head, and the end shallowly inserted into the nose. Thus, nasal air-flow is measured by the ApneaLink™ and recorded on the internal memory of the device. Once data had been recorded, it was downloaded to PC via an USB-connection and rendered by Resmed's software into a report on the participant's breathing during sleep. The software automatically analyzes the airflow data and identifies apneic and hypopneic events. The standard parameter for identifying an apnea is an 80% reduction in air-flow, which lasts at least 10 seconds. A hypopnea was characterized by a 50% reduction in air-flow lasting at least 10 seconds. However, the software failed to recognize some apneic and hypopneic events, and also falsely identified some events as apneic or hypopneic. To correct for these shortcomings I manually examined the air-flow chart of each participant to add events where the software failed to identify them and remove events where the software falsely identified them.

Two participants were also chosen to partake in a semi-structured interview to give an experiential account of living with BD and the resulting sleep problems.

Procedure

Participants were contacted by the researcher and a convenient meeting place was agreed upon. At the meeting participants were given the informed consent form, demographic questionnaire and ApneaLink™ portable monitor to take home with them for the night. They were instructed on its use and questions that they had were immediately addressed. The following day the ApneaLink™, consent form, and questionnaire was collected from the participants. The informed consent form was critical to ensure the participants that their information would be kept confidential. The informed consent form also explained the method and rationale behind the study without using too much jargon that may have confused

the participants. The informed consent form also assured the participants that the study carried no risk to the participants as it was non-invasive. Following collection, the sleep-breathing data was downloaded to a PC upon which it was collated into the dataset that was used for statistical analysis.

Data analysis

The data were analysed using the Statistica 8 statistical software package (StatSoft, Inc. (2007). Descriptive statistics were used to give an overview of the data, which included the mean apnea-hypopnea index (AHI). An independent *t*-test was performed to determine whether there were statistically significant differences in AHI between the groups. A one-way analysis of variance (ANOVA) was performed to determine whether medication affected AHI. To examine the possibility that some BMI may co-vary with AHI, an analysis of covariance (ANCOVA) was also performed.

RESULTS AND DISCUSSION

It is unusual for a research report thesis to combine the “Results” and “Discussion” sections. However, due to nature of my data and its inherent limitations, I felt it important to discuss each result as it was analyzed instead of listing all the results and then discussing the findings.

Descriptive statistics

The variables used in the descriptive statistical analysis were Age, BMI, and AHI.

Table 1
Descriptive Statistics for Bipolar and Control Groups

	Valid N	Bipolar Group			Control Group		
		Mean	Minimum	Maximum	Mean	Minimum	Maximum
Age (years)	8	36.88 (13.08)	22.00	66.00	37.25 (12.56)	22.00	65.00
BMI (kg/m²)	8	25.80 (3.35)	20.93	30.09	24.94 (4.30)	20.38	33.95
AHI	8	15.00 (10.32)	2.00	30.00	9.38 (5.40)	4.00	20.00

Note: Standard Deviations are given in brackets in the Mean columns.

t-tests for independent groups

Table 2

Differences between Bipolar and Control Groups on Age, BMI, and AHI.

	Bipolar Group	Control Group	Group Difference		
	Valid N	Mean	Mean	<i>t</i> (14)	<i>p</i>
Age (years)	8	36.88 (13.08)	37.25 (12.56)	-0.058509	0.954170
BMI (kg/m ²)	8	25.80 (3.35)	24.94 (4.30)	0.445136	0.663027
AHI	8	15.00 (10.32)	9.38 (5.40)	1.365788	0.193547

Note: Standard Deviations are given in brackets in the Mean columns.

Participants were matched on Age and BMI, and thus we expect the means these variables for both groups to be similar. There was no significant difference in Age between the groups, $t(14) = -0.06$, $p = 0.95$. There was also no significant difference found in BMI between the groups, $t(14) = 0.45$, $p = 0.66$. No significant difference was found in AHI between the groups, $t(14) = 1.37$, $p = 0.19$. Thus, the hypothesis that sleep apnea would be more prevalent among BD participants than Control participants was disproven.

Power calculations showed that, with the given sample size, there was only a 10% chance of finding a significant difference between the groups for AHI. This means that a larger sample size would be more likely to yield significant results.

The next analysis was a one-way ANOVA to determine whether the medication taken by the participants had any effect on AHI. The variables used for the one-way ANOVA were AHI and Medication. Medication was a categorical variable which included categories for Antipsychotics, Antidepressants, Benzodiazepines, and None/Other medication types.

The first assumption tested was homogeneity of variance with Levene's test. This test was non-significant ($F(3,4) = 1.38$, $p = 0.37$), which showed that the variances between Medication's effects on AHI were heterogeneous.

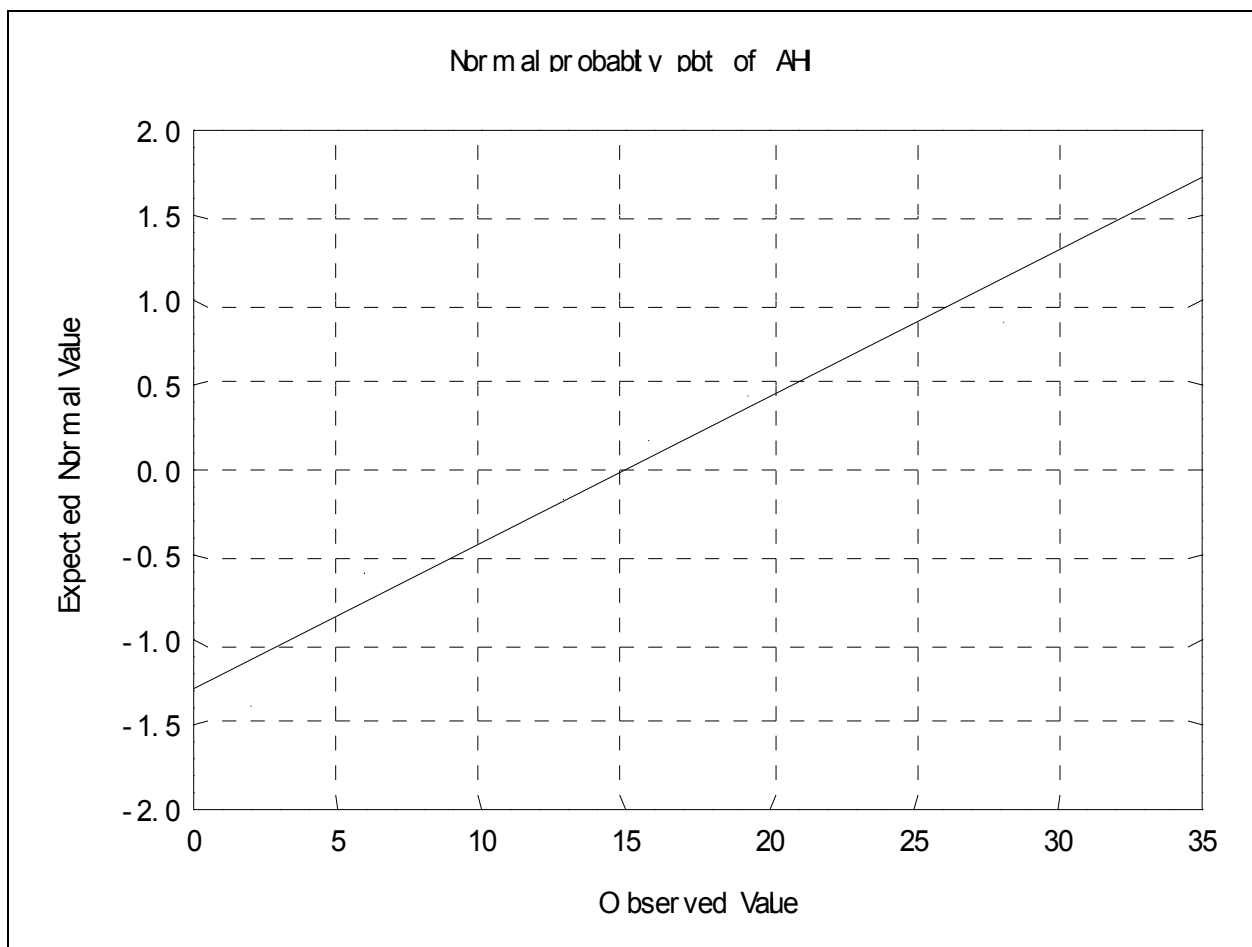


Figure 1. Normal probability plot of AHI where observed values of AHI are plotted against expected values of AHI.

Figure 1 shows the normal probability plot of AHI, which confirms that AHI is distributed relatively normally.

Table 3

Descriptive Statistics for Medication's effect on AHI

	Type of Medication	N	Mean	Std.Dev.	AHI		
					Std.Err	-95.00%	+95.00%
Total		8	15.00	10.32	3.65	6.37	23.63
Medication	Antipsychotic	3	15.67	11.24	6.49	-12.25	43.59
Medication	Benzodiazepine	2	9.00	9.90	7.00	-79.94	97.94
Medication	Antidepressant	1	30.00				
Medication	None/Other	2	12.50	9.19	6.50	-70.09	95.09

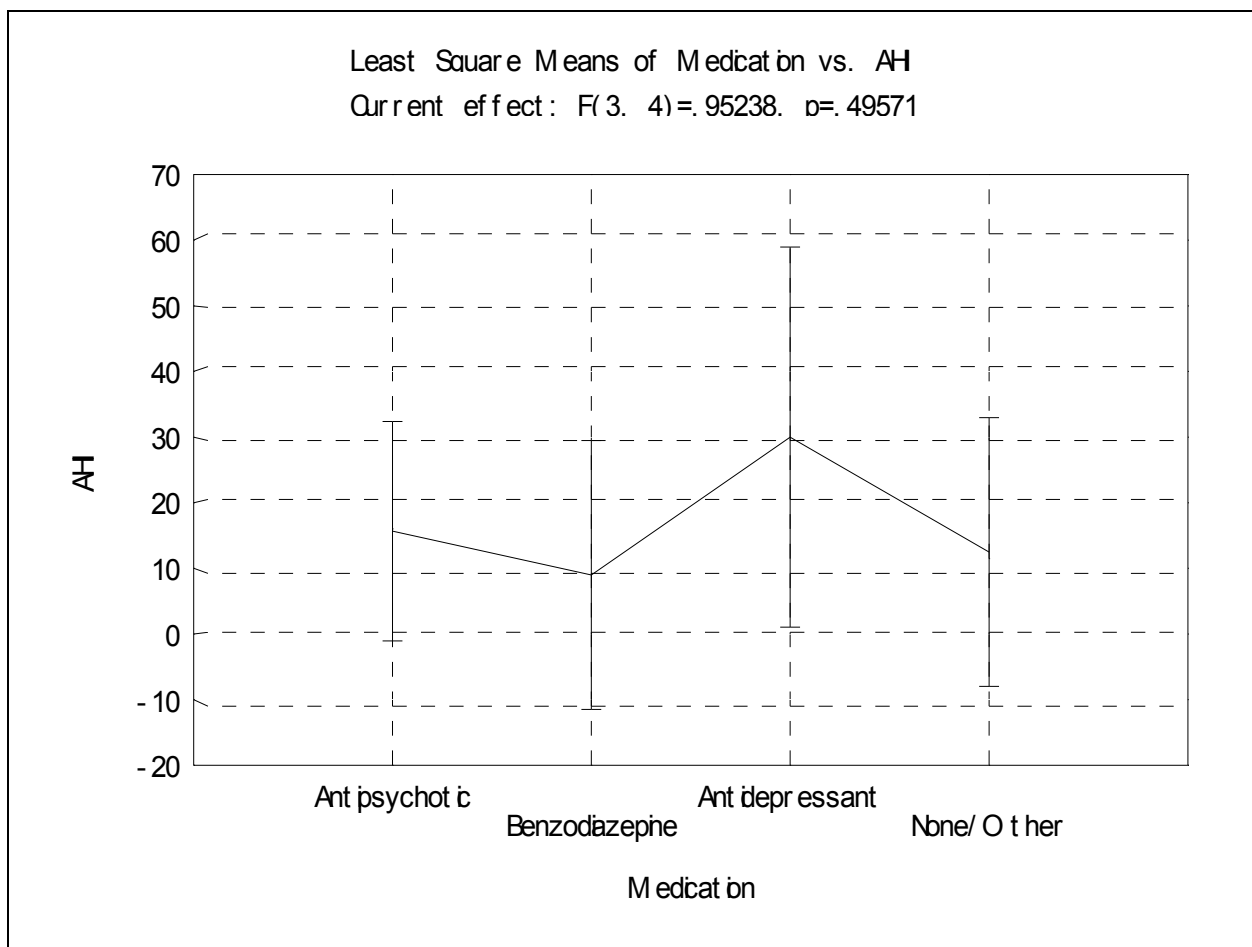


Figure 2. The least square means of Medication plotted against AHI.

The result of the ANOVA was non-significant, $F(3,4)=0.95$, $p=0.50$. Even though Figure 2 shows that the Antidepressant category of Medication had the greatest effect on AHI, the effect was not great enough to stand out significantly from the other categories.

Table 4

Effect size and observed power of ANOVA

	SS	df	MS	F	p	Partial η^2	Non-centrality	Observed power ($\alpha=0.05$)
Medication	310.833	3	103.611	0.95238	0.495705	0.416667	2.85714	0.133722
Error	435.167	4	108.792					

The ANOVA had a medium effect size with partial $\eta^2 = 0.42$, but the power was small. This indicated that there was only 13.4% of finding a significant difference between the categories of Medication. This is due to the small sample size of the study. To increase power and effect size would require many more participants than the 8 in the current study.

The small sample size would suggest that an analysis of covariance (ANCOVA) would also have a non-significant result, but it was performed regardless to ensure that varying BMI didn't interfere with the effect between Medication and AHI.

Levene's test found that the variance in BMI was significant ($F(3,4) = 222.11, p = 0.000067$). This means that the assumption of homogeneity of variance has been violated and in a study with a larger sample size would indicate that ANCOVA cannot be performed. However, due to the small sample size of this study we can ignore this violation and continue performing ANCOVA.

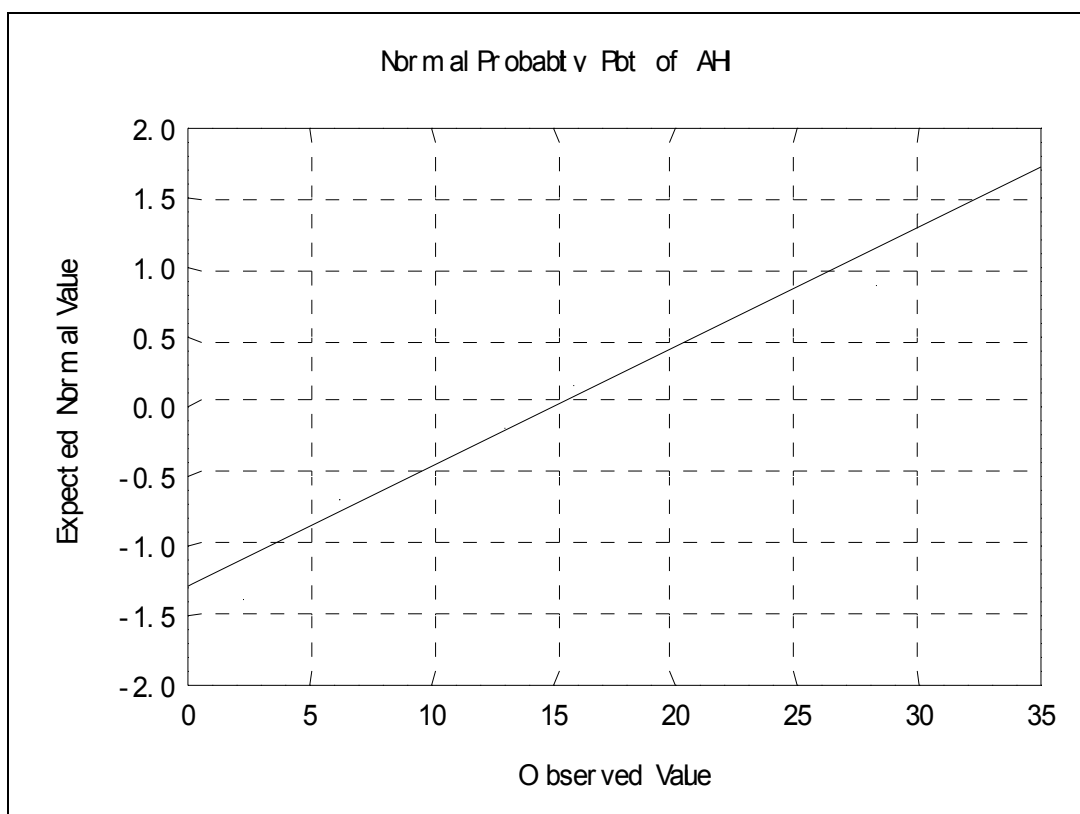


Figure 3. The normal probability plot of AHI shows that it is normally distributed when the observed AHI is plotted against the expected AHI.

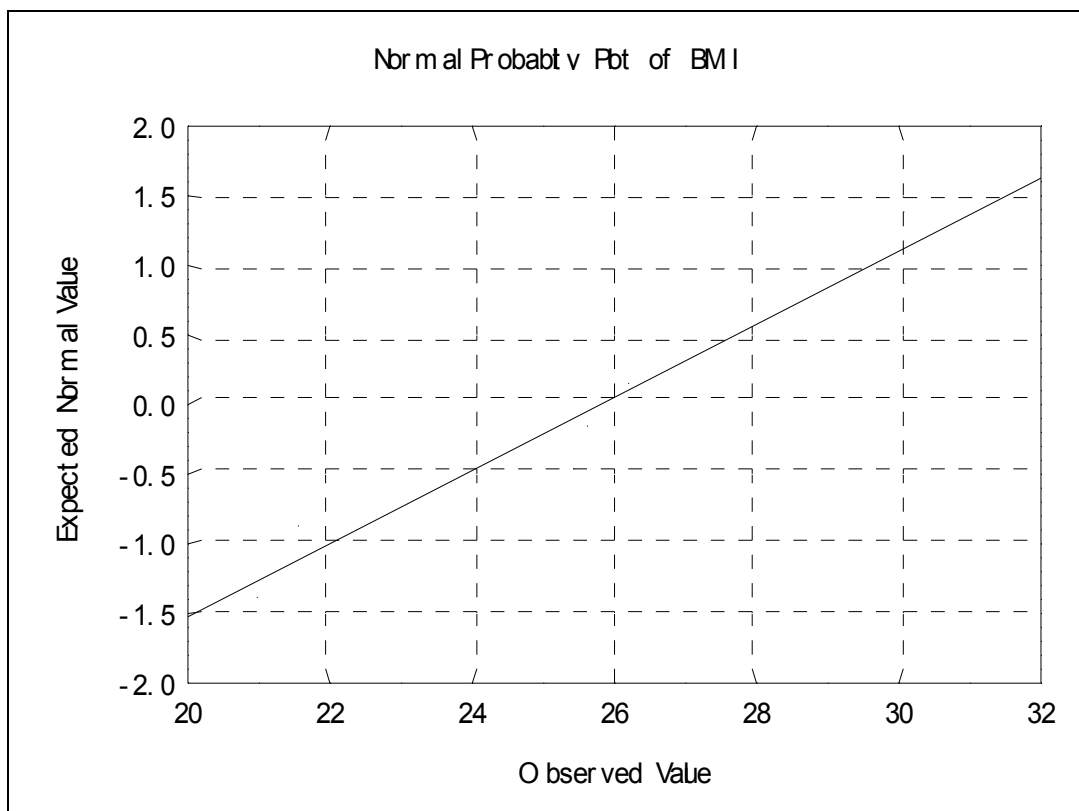


Figure 4. The normal probability plot of BMI shows that it is normally distributed when the observed BMI is plotted against the expected BMI.

Figures 3 and 4 show that both AHI and BMI were distributed relatively normally.

Descriptive statistics for Medication's effect on AHI is exactly the same in the ANCOVA as in the ANOVA, thus refer to Table 3.

Table 5

Descriptive statistics for the covariate BMI

		BMI (kg/m ²)					
	Type of Medication	N	Mean	Std.Dev.	Std.Err	-95.00%	+95.00%
Total		8	25.80	3.35	1.18	23.00	28.60
Medication	Antipsychotic	3	26.02	0.61	0.35	24.51	27.54
Medication	Benzodiazepine	2	23.64	2.83	2.00	-1.80	49.07
Medication	Antidepressant	1	30.09				
Medication	None/Other	2	25.49	6.44	4.55	-32.37	83.34

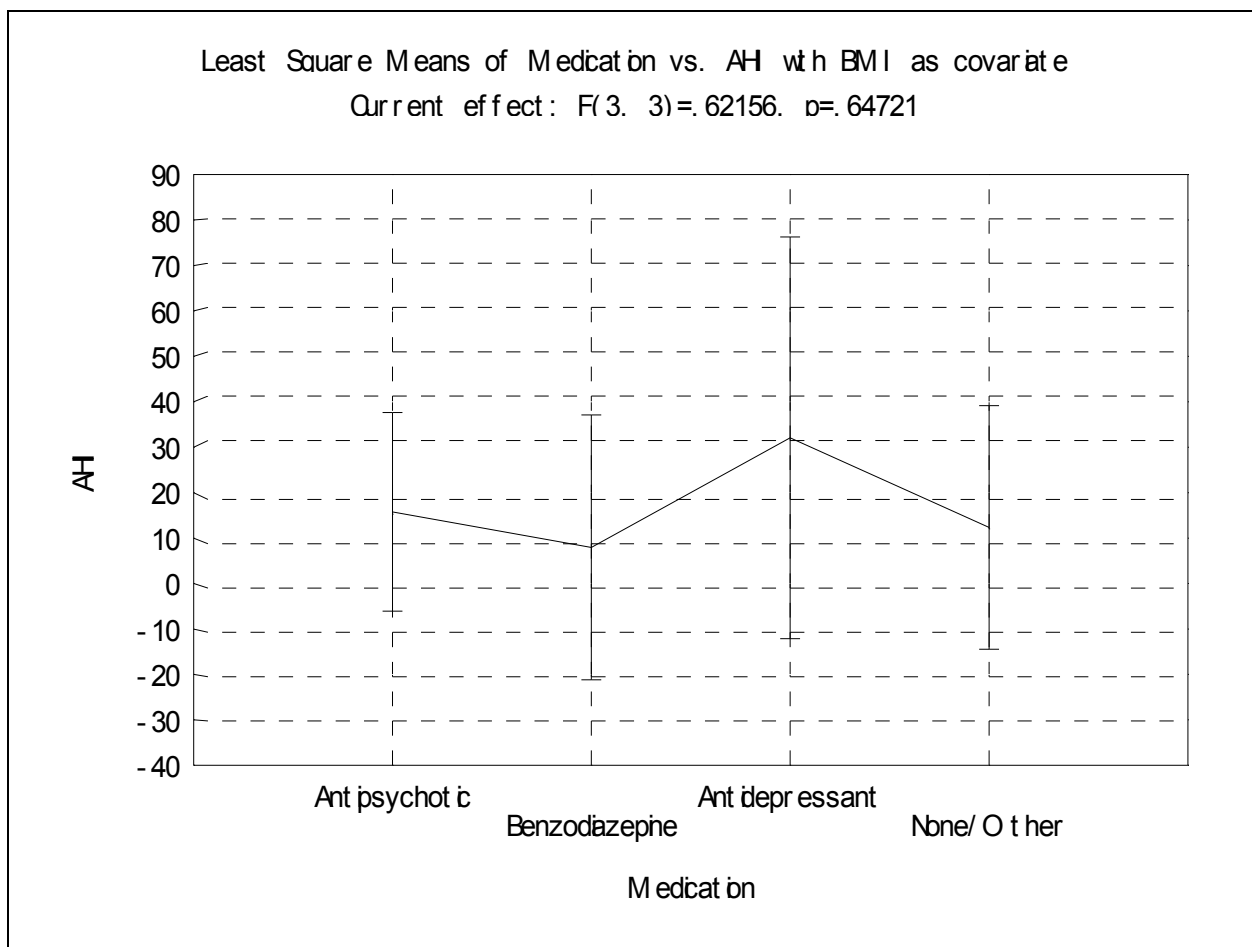


Figure 5. The least square means of Medication plotted against AHI with BMI as covariate.

As expected, the results of the ANCOVA was non-significant, $F(3,3)=0.62$, $p=(0.65)$. Once again the Antidepressant category seems to have the greatest effect on AHI, but it still is not different enough from the other Medication categories to be significant.

Table 6

Effect sizes and observed power of ANCOVA

	SS	df	MS	F	p	Partial η^2	Non-centrality	Observed power ($\alpha=0.05$)
BMI (kg/m²)	11.6876	1	11.6876	0.082797	0.792275	0.026858	0.082797	0.055060
Medication	263.2194	3	87.7398	0.621564	0.647213	0.383311	1.864692	0.092536
Error	423.4790	3	141.1597					

Table 6 shows that the effect size of Medication is slightly lower, partial $\eta^2=0.38$, when BMI covaries with Medication than when it does not. The power of the effect is still small, which indicates that there was only a 9.2% chance of finding a significant effect size when BMI covaries with Medication.

The reason behind both the ANOVA and the ANCOVA being non-significant is the small sample size. The problem lies in the fact that it is almost impossible to obtain a sample that is representative of the population with only 8 participants per group. This is the main limitation of the study and is the first issue that should be addressed in future studies in the field. Ideally both the bipolar and control groups should contain at least 100 participants each to increase the statistical power of the resultant analyses.

Another limitation is illustrated in the literature by Fenn et al. (2005). They examined the comorbidity of bipolar disorder with various other health problems and illnesses. In their sample only 3.4% of bipolar patients had a concurrent diagnosis of sleep apnea. This indicates an extremely small effect size and would also necessitate a large number of participants if the interactions between bipolar disorder and sleep apnea are to be thoroughly investigated.

Future studies should also critically examine whether to use a portable air-flow monitor or a full polysomnograph to monitor apneic events in participants. The advantages of the portable monitor are that it is non-invasive and relatively simple to operate by the participants. However, because the participants sleep in their own homes there are a number of possibilities of data contamination. The recording may be interrupted when the participant has to wake up in the middle of the night to care for their child, or when the participant's partner shifts their weight and accidentally pulls the nasal cannula out of the participant's nose. The only way to control for these factors would be to perform the study in a sleep lab. This would put the researcher in control of the environment, which would eliminate unforeseen events such as family interference. A sleep lab would also use a polysomnograph to record not only nasal air-flow, but EEG characteristics, oxygen levels in the blood, eye movement, and body movement as well. This should provide a more complete picture of the characteristics of apneic events when they occur in the bipolar patient.

Case studies are among the best methods to illustrate the problems that bipolar patients experience related to mood and sleep. Therefore I conducted brief (30 minutes) interviews with 2 of the bipolar patients in my study to identify their thoughts on sleep and mood in bipolar disorder. The case studies will refer to these participants by initials only in order to preserve their anonymity.

Case 1:

AH is an artist with architectural and construction training. He spends his days doing freelance drawings for architect firms.

He was diagnosed with BD in 1996, although he believes that he may have been suffering from BD since he was born. As a child he experienced irrational fears that would not only paralyze him with anxiety, but also seemed to occur without any discernable cause. Now his anxiety is controlled by medication. The medication allows him to function adequately for most of the time, but he still experiences instances of severe depressed mood which have the same effect on him as his childhood fears. Interestingly, he says that these moods also occur seemingly at random, just like his childhood fears. He has taken to self-medicating with alcohol to alleviate the depressed moods. This led to several years of struggling with alcoholism, which he described as the worst years of his life. His manic periods are characterized by outbursts of anger which can be easily triggered by other people causing him frustration.

AH usually has no trouble going to sleep at night. In the event of trouble falling asleep he would take only a mild sleeping tablet to help him drift off. He does, however, complain of daytime tiredness. Even though he may have 9 hours of sleep in a night, he will still feel as if he's just run a marathon when he wakes up. He tries to overcome the tiredness by taking caffeine pills to give him a "jumpstart". One problem with caffeine though, is that it tends to make him irritable. This in turn forces him to take Valium, which is an anti-anxiety medication with CNS-depressant effects, to calm down again.

It is evident that he takes large amounts of medication; not only from the interview, but from the demographic questionnaire as well. This seems to be the norm for bipolar patients as they find it difficult to stay in a stable mood, even when not in a depressed or manic mood. His complaints of daytime tiredness and difficulty with mood stabilization are typical symptoms of sleep apnea.

Case 2:

SK comes from a family that is familiar with psychiatric disorders. Her sister was diagnosed with BD when she was very young and SK herself was diagnosed with BD in 2004. She has accepted her diagnosis and is learning how to live with BD. However, just because she has accepted it, doesn't mean she likes it. She said that she would trade her leg or arm if it meant she could be cured.

She is very much at the mercy of her mood and has had to start working from home to ensure she is in a safe place if her mood unexpectedly switches from manic to depressed or vice versa. She believes that she doesn't get frustrated very easily, but also said that if someone aggravated her enough that she would have verbal outbursts of anger.

She also complains about sleep difficulties. When she is in a manic mood state her mind races, which makes it impossible to relax enough to drift off to sleep. Interestingly, she had a similar complaint when she was in a depressed mood state. Although her mind doesn't race, it also won't settle on one idea. She says that everything gets her down because she can't fall asleep. She tries to think happy thoughts to counter the depressed mood, but sometimes spends hours just lying in bed. SK is part of a support group for BD patients where one of the most frequent and most important issues they discuss is the problems they have with sleep. Many members of the group admit to self-medicating with alcohol and/or sleeping pills just so they can fall asleep at night. One group member also developed severe sleep apnea after an overdose of sleeping pills caused muscles in his airway to become paralyzed and collapse.

These case studies illustrate that BD patients struggle not only to fall asleep, but to achieve good quality sleep. These sleep difficulties not only lead to daytime tiredness, but have negative implications for their already dysfunctional mood regulatory mechanisms.

CONCLUSION

Mood regulation in bipolar disorder is dependant on the normal functioning of the prefrontal cortex. It is exactly this neural structure that is most affected by sleep apnea-induced hypoxia. The co-occurrence of sleep apnea and bipolar disorder should therefore be noted as having severely negative mood-related effects for the bipolar patient. Thus, the aim of this study was to determine whether sleep apnea is more prevalent in patients with bipolar disorder in comparison with the general population.

I found no significant difference between the occurrence of sleep apnea in bipolar patients when compared with the general population. However, the sample size was very small and was found not be an accurate representation of the bipolar population. The effect size was also very small and made it nearly impossible to find a statistically significant difference between the groups. Both of these limitations could be solved by increasing the sample size from 8 to at least 250. With that amount of participants a researcher would be much more likely to find a significant difference between the groups, if one indeed exists.

However, complaints about quality of sleep from bipolar patients persist. This is a field that needs to be further investigated to determine the extent of the interaction between sleep and bipolar disorder. Finding significant correlations or links should be a priority as these may indicate treatments that could lead to increased sleep quality and better quality of life for bipolar patients.

REFERENCES

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.; Text Revision). Washington, D.C.: Author.
- Barbini, B., Bertelli, S., Colombo, C., & Smeraldi, E. (1996). Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Research*, *65*, 121-125.
- Beebe, D. W., & Gozal, D. (2002). Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *Journal of Sleep Research*, *11*, 1-16.
- Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., et al. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *Journal of Sleep Research*, *12*, 1-12.
- Carskadon, M. A., & Dement, W. C. (2005). Normal human sleep: an overview. In M. H. Kryger, T. Roth, W. C. Dement, & T. Roehrs (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 13-23). Philadelphia: Elsevier Saunders.
- Curtin, F., & Schulz, P. (2004). Clonazepam and lorazepam in acute mania: a Bayesian meta-analysis. *Journal of Affective Disorders*, *78*, 201-208.
- Drevets, W. C. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry*, *48*, 813-829.
- El-Ad, B., & Lavie, P. (2005). Effect of sleep apnea on cognition and mood. *International Review of Psychiatry*, *17*, 277-282.
- Erman, M. K., Stewart, D., Einhorn, D., Gordon, N., & Casal, E. (2007). Validation of the ApneaLink™ for the Screening of Sleep Apnea: a Novel and Simple Single-Channel Recording Device. *Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *3*, 387-392.
- Fenn, H. H., Bauer, M. S., Alshuler, L., Evans, D. R., Williford, W. O., Kilbourne, A. M., et al. (2005). Medical comorbidity and health-related quality of life in bipolar disorder across the adult age span. *Journal of Affective Disorders*, *86*, 47-60.
- Flemons, W. W. (2002). Obstructive sleep apnea. *New England Journal of Medicine*, *347*, 498-504.
- Guilleminault, C. (1990). Benzodiazepines, breathing, and sleep. *The American Journal of Medicine*, *88*, 25S-28S.
- Leibenluft, E., Albert, P. S., Rosenthal, N. E., & Wehr, T. A. (1996). Relationship between sleep and mood in patients with rapid-cycling bipolar disorder. *Psychiatry Research*, *63*, 161-168.

- Müller-Oerlinghausen, B., Berghofer, A., & Bauer, M. (2002). Bipolar disorder. *The Lancet*, 359, 241-247.
- National Sleep Foundation. (2002). 2002 Sleep in America Poll. .
- Resmed. (2007). ResMed - ApneaLink™. *ResMed*.
- Rivas-Vazquez, R. A., Johnson, S. L., Rey, G. J., Blais, M. A., & Rivas-Vazquez, A. (2002). Current treatments for bipolar disorder: A review and update for psychologists. *Professional Psychology: Research and Practice*, 33, 212-223.
- Sadock, B. J., Sadock, V. A., & Kaplan, H. I. (2007). *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (10th ed.). Lippincott Williams & Wilkins.
- Schröder, C., & O'Hara, R. (2005). Depression and obstructive sleep apnea (OSA). *Annals of General Psychiatry*, 4, 13.
- StatSoft, Inc. (2007). *STATISTICA (data analysis software system), version 8.0*.
<http://www.statsoft.com>.
- Strakowski, S. M., DelBello, M. P., Sax, K. W., Zimmerman, M. E., Shear, P. K., Hawkins, J. M., et al. (1999). Brain Magnetic Resonance Imaging of Structural Abnormalities in Bipolar Disorder. *Archives of General Psychiatry*, 56, 254-260.
- Strine, T. W., & Chapman, D. P. (2005). Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. *Sleep Medicine*, 6(1), 23-27.
- Vgontzas, A. N., & Kales, A. (1999). Sleep and its disorders. *Annual Review of Medicine*, 50, 387-400.
- Wang, Y., Teschler, T., Weinreich, G., Hess, S., Wessendorf, T. E., & Teschler, H. (2003). Validation of microMESAM as screening device for sleep disordered breathing. *Pneumologie*, 57, 734-40.
- Williams, D. R., Herman, A., Kessler, R. C., Sonnega, J., Seedat, S., Stein, D. J., et al. (2004). The South Africa stress and health study: Rationale and design. *Metabolic Brain Disease*, 19, 135-147.
- World Health Organization. (1995). WHO :: Global Database on Body Mass Index. .
- Young, T., Finn, L., & Kim, H. (1997). Nasal obstruction as a risk factor for sleep-disordered breathing. *Journal of Allergy and Clinical Immunology*, 99, S757-S762.

APPENDIX A

Clinical Definition of Bipolar Disorder

Bipolar disorder is characterized by the text revised version of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) by the occurrence of a combination of manic, hypomanic, mixed, or major depressive episodes. A manic episode is a distinct period of hyper-arousal in which mood is persistently elevated, expansive, or irritable and lasts for at least 1 week. Hypomanic episodes share most of the manic episode features, with the exception of the length of incidence, which is shortened to 4 days. A major depressive episode is exactly the converse, as mood is depressed and a loss of pleasure or interest is experienced. A major depressive episode also differs from a manic episode in duration, as it lasts for at least 2 weeks. A mixed episode is a combination of manic and major depressive episodes over the course of 1 week. In order to make a clinical diagnosis these episodes must all be debilitating enough to cause impairment in occupational functioning, relationships or social activities. An exception of this requirement is the hypomanic episode, in which functioning is affected but not impaired (American Psychiatric Association, 2000).

Different types of bipolar disorder are described by the DSM-IV-TR and are classified according to severity. Bipolar I disorder is the combination of at least one manic, or mixed episode, and at least one major depressive episode. Importantly, however, according to Dubovsky and Buzan (as cited in R. A. Rivas-Vazquez, Johnson, Rey, Blais, & A. Rivas-Vazquez, 2002), bipolar I disorder may be diagnosed if only manic or mixed episodes have presented, with the assumption that a major depressive episode will occur in the future. Bipolar II disorder is the combination, or history of, at least one hypomanic episode and at least one major depressive episode. Further distinctions in the bipolar spectrum disorders are cyclothymic disorder and bipolar disorder not otherwise specified. Bipolar disorder can further be classified as 'rapid cycling' if 4 or more alternations between episodes occur over a 12 month period (American Psychiatric Association, 2000).

APPENDIX B**Basic Demographics Questionnaire**

(Answers to these questions will be used for statistical purposes only)

1. Age: _____

2. Sex (circle one)

Male Female

3. What is your ethnicity? (circle one)

Black/African Coloured Indian White Other

4. Height: _____m - please indicate if using other units, i.e. centimetres(cm)

5. Weight: _____kg

6. Please list any prescription and/or “over-the-counter” medications that you are currently using: _____

7. Please indicate any past or current psychiatric and/or neurological diagnoses:
