

RUNNING HEAD: Narcolepsy

Narcolepsy: An In-Depth Investigation

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When most people I have spoken to think of the neurological disorder narcolepsy, a picture of Mr. Bean's character from the movie *Rat Race* comes to mind. Throughout the race, his character randomly falls into a deep sleep, often letting other participants pass him as a result. He falls asleep while running, while talking, and during virtually any other activity he is engaged in. The situations are extremely comedic and the viewer is left with the impression that Mr. Bean is some kind of weirdo with a goofy problem. Unfortunately, due to such depictions and a lack of knowledge about narcolepsy, the public seems to have similar inclinations when thinking of real-life narcolepsy sufferers.

As someone who has been recently diagnosed with narcolepsy, I have experienced a wide variety of reactions from other people, from laughter to disbelief. Admittedly, my knowledge of the disorder prior to my diagnosis was probably as nonexistent as that of the general public's. However, with this paper I hope to explore narcolepsy thoroughly and expand both my own knowledge and the reader's.

Narcolepsy is a chronic neurological disorder that interferes with the brain's ability to regulate normal sleep-wake cycles. The most common (and usually the first to be clinically apparent) symptom of narcolepsy is excessive daytime sleepiness (EDS), characterized by fleeting urges to sleep that can sometimes be irresistible, regardless of how much sleep the person got the night before. These sleep attacks can occur at any time, which makes narcolepsy a potentially debilitating disorder that can profoundly affect the sufferer's quality of life. The length of these sleep attacks can range from "microsleeps" of only a few seconds, during which the person might continue whatever action they were engaged in before sleep without interruption, to (in rare cases) sleep

episodes of an hour or longer. Most narcoleptics describe EDS as a constant feeling of mental cloudiness, exhaustion, or having no energy.

The other major symptoms of narcolepsy that often appear after the onset of EDS are cataplexy, sleep paralysis, and hallucinations. Cataplexy is characterized by sudden loss of muscle tone, leading to a feeling of weakness and loss of control. Episodes of cataplexy often occur with the experience of a strong emotion such as anger, fear, or excitement; laughter is the most common trigger. Sometimes an experience of cataplexy can be barely perceptible; other times, it can result in a complete physical collapse. The feature that distinguishes cataplexy from seizure disorders is that even during the most severe episodes, the sufferer remains fully conscious. Sleep paralysis is characterized by the temporary inability to speak or move while falling asleep or waking up; although it is a frightening experience (partly because a person experiencing it will remain fully conscious), people regain their full ability to move and speak once the episode passes. The interesting thing about cataplexy and sleep paralysis is that these are phenomena that non-narcoleptics experience, only they are not aware of it because they experience it while they are deep into REM sleep. Since narcolepsy interferes with the brain's sleep-wake cycles, it causes narcoleptics to experience these episodes at inappropriate times. Hallucinations are also associated with elements of REM sleep appearing at inappropriate times; these hallucinations are referred to as hypnagogic hallucinations when they occur as a person is falling asleep and hypnopompic when they occur as a person is waking up. Often these hallucinations are vivid and frightening. It is important to note that while EDS is experienced by all narcoleptics, the other symptoms do not appear in all sufferers.

The first symptoms of narcolepsy often appear during the late teenage years or early adulthood; however, 10 or 15 years often pass before a correct diagnosis is made. This is because the symptoms of narcolepsy are not exclusive to the disorder and can be mistaken for signs of other problems such as chronic fatigue syndrome, epilepsy, or depression. As a result, narcolepsy is an under-diagnosed condition that is not as rare as most people think; estimates of prevalence have been as high as 1 in 1,000 Americans. The disorder affects males and females equally.

In order to be diagnosed with narcolepsy, a polysomnogram (PSG) and a multiple sleep latency test (MSLT) are necessary. A PSG is an overnight test that measures brain activity, heart and respiratory rates, limb movements, oxygen levels, and nerve activity as a patient sleeps overnight. Patients with narcolepsy fall asleep rapidly, begin REM sleep early and have more REM episodes than non-narcoleptics, and may wake up often during the night. PSGs can be used to detect a wide variety of other sleep disorders and can help rule those out as the cause of a patient's symptoms. During the MSLT, the patient is given the opportunity to take a nap every two hours during the day while brain activity is monitored. People with narcolepsy will fall asleep rapidly and begin dreaming quickly; non-narcoleptics usually start dreaming after about 90 minutes of sleep, while a patient with narcolepsy will often enter REM sleep within a few minutes. Patients are also often asked to fill out the Epworth Sleepiness Scale (ESS), an 8-item questionnaire used to gauge the severity of daytime sleepiness by asking the patient to rate the likelihood of falling asleep during various situations on a scale of 0 to 3. The most desirable total score is 6 or below; narcoleptics' scores are significantly higher.

After the results of a PSG, an MSLT, the ESS and an examination of the patient's complete medical history results in a diagnosis of narcolepsy, there are several treatment options available. Since there is currently no cure for the disorder (and no definitive cause has been isolated), treatment focuses on alleviating the patient's symptoms. Currently, doctors most often use a two-pronged approach to treatment: stimulants to keep the patient alert during the day, and sodium oxybate (Xyrem) to improve the quality of nighttime sleep. Occasionally antidepressants are prescribed in an effort to control cataplexy. Stimulants currently used to treat narcolepsy in the United States generally fall into two classes: a new drug called modafinil (Provigil) and amphetamines (such as Adderall and Ritalin). Both classes of drugs are central nervous system stimulants. Doctors generally prescribe Provigil first; it is thought to have fewer, less serious side effects than amphetamines and does not appear to lead to tolerance. However, Provigil is not strong enough for some narcoleptics; in those cases, doctors will prescribe an amphetamine. Sodium oxybate is sometimes prescribed to patients who are still experiencing significant EDS after stimulant therapy; as the pharmaceutical form of GHB (a widely abused party and date-rape drug), its distribution is tightly regulated. However, in therapeutic doses it is highly effective in improving the quality of nighttime sleep and alleviating EDS in combination with stimulant therapy.

Because of the wide variation in the severity of narcolepsy symptoms, it can often take weeks or months to work out an optimal medication regimen. There are also behavioral strategies narcoleptics can adopt to alleviate their symptoms, including regularly scheduled naps, a consistent sleep schedule, avoiding smoking, and taking safety precautions while driving. Perhaps the most important element of treatment for

narcolepsy sufferers is seeking out appropriate support; unfortunately, many narcoleptics are improperly labeled as being lazy or unmotivated and some patients isolate themselves because of embarrassment due to their symptoms. Joining a support group, educating family and friends, and requesting accommodations at work can help narcoleptics deal with these effects. With proper treatment, people with narcolepsy can lead relatively normal lives. A wide variety of research has been done on narcolepsy, and this paper will focus primarily on the impact of the disorder on patients and on explorations of the various available treatments.

First we will examine the impact that narcolepsy can have on a person's life. A study conducted by Bruck at Victoria University in Melbourne, Australia in 2001 explored the effects of narcolepsy on patients' psychological health. The goal of the study was to assess psychosocial adjustment, disruption due to symptoms, and medication problems in narcolepsy; to determine how these variables changed with gender, age, and medication status; and to compare narcolepsy with three other illness groups (Bruck, 2001). There is a large body of literature on the psychological effects of narcolepsy, but many instruments used to measure these effects have been created specifically for narcoleptics; Bruck (2001) sought to compare narcoleptics to three other illness groups by using The Psychosocial Adjustment to Illness Scale – Self Report (PAIS-SR), a well-established questionnaire that has been used with a variety of illness groups with a high level of validity and reliability. She obtained the variables of day and night disruption and medication problems by using a second self-report questionnaire. Analysis of the results of these two questionnaires was intended to shed more light on the psychological impacts of narcolepsy, especially as they relate to role behaviors.

Subjects were obtained for the study by mail; questionnaire packages were sent out to 213 narcoleptics who had contacted the Australian Narcolepsy Support Group and expressed a willingness to participate in research. The 147 people who returned the questionnaires were carefully screened to be sure that they had been diagnosed with narcolepsy by a medical specialist and had experienced some degree of cataplexy in their history with narcolepsy; the final sample size was 129, consisting of 57 males and 72 females. The mean age of the participants was 52.8 years; ages ranged from 18 to 81 years. Those who were married, separated or divorced, never married, and widowed were all represented in the study. Each participant had some level of education, with 45 having completed college or technical school, 69 leaving school before junior year of high school, 14 having completed high school and one currently studying.

The participants completed a two-part questionnaire for this study. The first part determined the participants' medical history, medication intake, demographics, and ESS scores. It also asked a series of questions that yielded four dependent variables; the questions asked the patients to rank the occurrence of various symptoms or feelings during the past two weeks on a scale of 1 (not at all or never) to 5 (completely or always), and a score of 5 indicated more severe problems. The first variable derived from these questions was day disruption; this explored the degree to which narcolepsy hampered ability to perform daily activities. The second variable was night disruption; this concerned the degree of nocturnal sleep disturbance, sleep paralysis, and nightmares. The third variable was stimulant medication problems; this questioned the effectiveness of stimulant medication in controlling daytime sleepiness and the degree of undesirable side effects. The fourth and final variable yielded by part one of the questionnaire was

tricyclic antidepressant medication problems; this inquired about the effectiveness of tricyclic antidepressants in controlling cataplexy, sleep paralysis, and hallucinations and the degree of undesirable side effects.

The second part of the questionnaire was the PAIS-SR, which contained 46 multiple-choice questions divided into seven categories. The first category was health care orientation; this sought to ascertain patients' feelings towards health care, including perceptions of health care professionals and quality of health care information. The second category was vocational environment; this evaluated perceived impacts on performance and satisfaction at work, at school, or in the home. The third category was domestic environment; this covered problems within the family in response to the illness, financial aspects, and the impact the illness has had on family relationships and communication. The fourth category was sexual relationships; this related to quality of sexual interest, frequency, and performance as well as level of satisfaction. The fifth category was extended family relationships, which focused on typical interactions with extended family members and any negative effects that have been observed as a result of the illness. The sixth category was social environment; this assessed interests and participation in social and leisure activities and whether or not the illness had constricted the patient. The seventh and final category was psychological distress; this asked about recent negative feelings such as depression and anxiety.

The dependent variables in this study were grouped into three categories: symptoms (day and night disruption), medication problems (stimulant and tricyclic antidepressant medication problems), and PAIS-SR variables (the seven variables described above). To examine whether these variables changed with gender, age, or

medication status, age was operationalized to form two groups: people under 40 and people over 40. Medication status was used to divide people into three groups: no medication taken, only stimulants taken, and both stimulants and tricyclic antidepressants taken.

To compare PAIS-SR scores to other illness groups and to determine the degree of psychosocial adjustment achieved by narcoleptics, the PAIS-SR scores were calculated and looked at in relation to categories psychosocial adjustment that have been well-established (a score of 0-35 indicates good adjustment, while a score of 36-51 suggests fair adjustment and a score over 52 demonstrates poor adjustment). PAIS-SR scores from the narcoleptic participants were also compared to those of three illness groups that have been published in the PAIS-SR manual: cardiac patients, mixed cancer patients, and diabetes patients. It was also questioned whether significant relationships existed between the PAIS-SR variables and the symptom and medication variables yielded by part one of the questionnaire.

In terms of gender, there was no significant difference between males and females when it came to day and night disruption and medication problems. However, males' PAIS-SR scores indicated more problems with health care orientation and sexual relationships, as well as more adjustment problems in general. In terms of age, there were no significant differences between the two groups in day and night disruption, medication problems, or PAIS-SR scores. However, younger narcoleptics indicated more vocational adjustment problems. It was unclear whether this was due to an increased symptom severity in younger narcoleptics or if older patients had created or found a work environment that accommodated their symptoms.

In terms of the three medication status groups, significant differences existed. Those participants taking stimulants only reported less day and night disruption. On the PAIS-SR, those taking stimulants only demonstrated better adjusted social environment scores, while those taking no medication were least adjusted in this category. Those taking tricyclic antidepressants experienced more day and night disruption than the other groups.

The examination of PAIS-SR scores as compared to adjustment categories (good, fair, and poor) as described earlier and other illness groups yielded interesting results. The mean PAIS-SR score among study participants was 40.9, indicating fair psychosocial adjustment. Using these categories, it was found that 31.9% of the narcoleptics fell within poor adjustment and 19.8% fell within fair adjustment; less than half (48.3%) scored within the good adjustment category (Bruck, 2001). As compared to three other illness groups as a whole, narcoleptics did not fare well: the diabetes and mixed cancer groups fell into the good category of adjustment, the cardiac group was borderline between good and fair, and narcoleptics were firmly placed into the fair category. Interestingly, narcolepsy patients had much higher negative health care orientation scores, more psychological distress and more extended family relationship problems than all the other illness groups.

As for the correlation between PAIS-SR scores and the variables yielded by part one of the questionnaire (day and night disruption and medication problems), a significant correlation was discovered. The highest correlations existed between domestic environment, extended family relationships and psychological stress scores on the PAIS-SR and disruption and medication variables. Reported levels of disruption of

day activities correlated strongly with poorer psychosocial adjustment, more psychological distress, more problems with family relationships, and more dissatisfaction with family support.

The results of this study indicate that the two-part questionnaire employed by Bruck (2001) is an effective way to gauge the psychological impacts of narcolepsy. However, she acknowledges that the self-report nature of the instruments is an obstacle to objective measuring of symptom severity and recommends that self-reports be combined with more objective tests such as the MSLT to obtain the most complete picture of narcolepsy's effects. Bruck (2001) also acknowledges that there may be problems generalizing the results of her sample to a wide population because of the facts that people who had contacted a narcolepsy support group and were willing to fill out a long questionnaire may be different than average narcoleptics, non-white ethnic groups were underrepresented, and older narcoleptics were overrepresented (only 15% were under 40 years old).

Bruck's (2001) study was the first to indicate that younger narcoleptics might have more vocational adjustment problems than older ones and there have been varying results concerning sexual relationships in narcoleptics; other than that, however, her findings in this study have been replicated in other research. These findings have indicated a big need for improvement in health care orientation and a high level of psychological distress in narcoleptics, for which more research is needed. Bruck poses the question (2001), "To what extent are factors such as patient personality, self-efficacy, locus of control and resilience factors of greater importance than objective symptom severity in determining illness impact?" (Bruck, 2001, p. 445).

A second study, conducted by United Kingdom sleep researchers Daniels, King, Smith, and Shneerson (2001), also sought to explore the impact narcolepsy has on patients' psychological well-being and quality of life. The authors acknowledged that there have been studies conducted on this topic previously, but noted that only a few of them include subjective reports of how narcoleptics perceive their own health status in terms of functional and emotional status and general well-being and most studies are more than 15 years old (Daniels, King, Smith, & Shneerson, 2001). Therefore, this particular study incorporated subjective reports from a large sample of narcolepsy patients in order to better examine their psychological health.

A sample of narcoleptics was obtained by mailing a questionnaire to 500 randomly selected members of the United Kingdom Association of Narcolepsy. A total of 313 questionnaires were returned; after careful screening, the total number of subjects included in the study was 305. Of these, 185 subjects (60.7%) were female. The subjects ranged in age from 18 to 89 years old, and the median age was 56. Participants were divided into four groups based on their medication intake: stimulants and anti-cataplexy medication (61 people), stimulants only (148 people), anti-cataplexy medication only (22 people), and neither stimulants nor anti-cataplexy medications (74 people). Statistical tests were conducted to ensure that there were no significant differences in sex distribution or age distribution among the four groups.

Each participant filled out a three-part questionnaire. The first part contained demographic questions as well as inquiries concerning the subjects' diagnosis and treatment of narcolepsy and their medical history. Participants also completed the Ullanlinna Narcolepsy Scale (UNS), a tool used to diagnose narcolepsy. The scale has 11

questions about cataplexy and sleepiness; the patient has five answers to choose from, and each possible answer carries a score ranging from 0 to 4 for a total possible score of 0 to 44. The higher the patient's score, the more severe and frequent their symptoms are and the more likely it is that they have narcolepsy. Generally, a score greater than or equal to 14 strongly suggests the presence of narcolepsy. Also during the first part of the questionnaire, subjects were asked a series of questions specifically created for this study and designed to explore the psychosocial aspects of narcolepsy; these questions centered on whether narcolepsy had caused avoidance of or problems with different areas of life such as school, work, relationships, home, or recreation (Daniels et al., 2001). Participants were also allowed to add any further comments they had regarding problems they had experienced because of narcolepsy.

The second part of the questionnaire was the UK Short Form 36 health survey questionnaire (SF-36), a widely used and validated 36-question survey that quantifies subjective reports of health in terms of functional status, emotional status, and general well-being (Daniels et al., 2001). The questions yield results concerning eight domains: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, mental health, energy/vitality, bodily pain, and general health perceptions. A lower score demonstrates poorer health status.

The third and final part of the questionnaire was the Beck Depression Inventory (BDI), a 21-question instrument that measures the existence and severity of depression. Each question has four possible answers with varying scores; the possible score range is 0 to 63, and a higher score indicates more severe depression. A score of 0-9 is normal and indicates a lack of depression, 10-15 suggests mild depression, 16-19 demonstrates mild-

moderate depression, 20-29 is indicative of moderate-severe depression, and a score greater than 29 illustrates severe depression.

On the UNS, the average score of participants was 22; 270 people had a score greater than or equal to 14, indicating the presence of narcolepsy. However, everyone in the sample had been diagnosed with narcolepsy by a health care practitioner; this fact, plus findings in other research, suggested that the UNS may not be as accurate at measuring the severity of narcolepsy as was once thought.

In regard to psychosocial aspects, narcoleptics reported a variety of problems in everyday life; over half (57.7% and 55.4% respectively) reported difficulty concentrating in class and achieving less than they were capable of. Other difficulties at school included missing days, having a hard time making friends, being bullied or teased, and being punished by teachers who thought the subjects were lazy. Upon leaving school, narcoleptics continued to have problems; 28.2% were unable to find jobs, while 36.7% lost or left a job due to narcolepsy. With respect to relationships, 27.2% of subjects felt that they had limited opportunity to meet potential partners, while 18.7% of subjects claimed that narcolepsy-related problems caused a relationship to end. Participants also reported difficulty performing home-related tasks such as cooking, ironing, bathing and supervising children. Leisure activities were also affected, with 76.7% of participants having difficulty while visiting the cinema/theater and 39.7% encountering problems while playing sports; other activities during which at least a quarter of subjects encountered difficulty included attending sports events (25.9%), taking vacations (37.4%), and visiting bars or clubs (39%). Other studies have arrived at similar findings.

The BDI indicated a higher prevalence of depression among the study's participants than in the general population; 56.9% of the subjects were depressed, with 15.1% demonstrating moderate or severe depression. The range of scores was 0 (no depression) to 48 (severe depression), and the median score was 11 (mild depression). The prevalence of depression in this sample is comparable to that found in other studies, including studies of samples in other countries.

Participants showed great variability in their SF-36 scores, but had significantly lower scores than the general population on all eight domains, indicating a poorer health status. The most significant domain in which the sample differed from normative data was role limitation due to physical problems; many subjects reported avoidance of situations that could be embarrassing or dangerous if they fell asleep suddenly or had an episode of cataplexy. The second most significantly affected domain on the SF-36 was the energy/vitality scale; most participants reported a feeling of excessive sleepiness rather than physical tiredness. Social functioning was the third most affected domain, followed by role limitation due to emotional problems, general health perceptions, mental health, physical functioning and bodily pain. The finding of poorer health status among narcoleptics is in agreement with findings from other studies on people with narcolepsy living in other countries.

With respect to the four medication subgroups, several differences were found. On the SF-36, those who took both stimulants and anti-cataplexy medication had significantly lower scores regarding physical and social functioning. This group also had higher BDI scores, indicating more severe depression than the rest of the sample. It is important to note that no subgroup experienced a return to normal health status,

indicating that the medications currently used in the treatment of narcolepsy are not effective enough to completely restore health status.

Daniels et al. (2001) admitted that problems may occur in generalizing the results of this study to all narcoleptics because of the fact that the sample was drawn from members of the United Kingdom Association of Narcolepsy; in addition, the 62.6% that returned the questionnaire may not be representative of the 500 people to whom it was sent. Despite these limitations, Daniels et al. (2001) points out that this study has the advantage of being based on a larger UK narcolepsy population than any other health-related quality of life study, and the results that were found have been corroborated by research conducted in other countries. The core finding of this study is that although most patients take medication for their narcolepsy symptoms, their health status is not restored to normal and their health-related quality of life remains below average.

One new medication that researchers hope can optimally alleviate the symptoms of narcolepsy, a stimulant called modafinil (Provigil), has come onto the market in the last decade. Many studies have been done on the drug, including the randomized, double-blind, placebo-controlled crossover study conducted by Broughton, Fleming, George, Hill, Kryger, Moldofsky, Montplaisir, Morehouse, Moscovitch and Murphy in 1997. Modafinil is thought to have less severe side effects and a decreased abuse liability compared to traditional central nervous system stimulants. While more than 1,000 patients had been exposed to modafinil as of 1997, very few had participated in double-blind, controlled trials; in addition, a 400-mg dose of modafinil had never been studied in this fashion. The goal of this particular study was to examine the efficacy and safety of daily 200 and 400-mg doses of modafinil in the treatment of EDS in narcolepsy patients.

Potential participants for this study underwent a complete physical exam, a careful analysis of their medical history, and a PSG; those with conditions or medication statuses that might interfere with the study's results (such as clinical depression, hyperthyroidism, severe anxiety, illicit drug use, use of antipsychotic medication, etc.) were eliminated. Seventy-five patients were enrolled in the six-week study, and 71 completed it; all met the International Classification of Sleep Disorders diagnostic criteria for narcolepsy, all suffered from moderate or severe daytime sleepiness that significantly affected their lives, and at least one MSLT had been done on all patients (their mean sleep latency was 3 minutes). Study participants were mostly middle aged (ages ranged from 16 to 43 years old), Caucasian (92%), and female (62.7%). It was confirmed that none of the female subjects were pregnant and all were using an effective method of birth control. All patients agreed to refrain from driving or engaging in any other potentially dangerous activities during the double-blind portions of the study, and all patients signed informed consent forms. In addition, the research methods of this study were approved by local ethics boards.

This study was a six-week, randomized, crossover, placebo-controlled, double-blind trial that was divided into three two-week periods. Each participant received each of the following treatments during one of the periods: placebo, 200 mg of modafinil, or 400 mg of modafinil in divided doses. To avoid carryover effects, only data from the second week of each period was used.

The primary efficacy variables were the mean sleep latency on the Maintenance of Wakefulness Test (MWT) and the mean number of sleep episodes and periods of severe sleepiness reported in a detailed patient diary (Broughton et al., 1997). The MWT

is a variation on the MSLT described in the introduction of this paper; while patients undergoing an MSLT are tested while lying down and told to try and fall asleep, patients undergoing an MWT are tested while sitting in a comfortable chair and told to try and stay awake. For this study, the MWT consisted of four sessions separated by two hours, and each session was ended after 40 minutes if sleep did not occur. Patients were also asked to write in detailed diaries that included evaluations of the previous night's sleep, records of hour of bedtime and hour of waking, the time(s) of day medication was taken, and accounts of the patient's sleepiness and sleep attacks.

At each clinic visit, the ESS was completed before an overnight PSG test. Also before the PSG test, the Profile of Mood States (POMS) was administered and used to measure the effects of modafinil on mood during the past week. The POMS examines six factors: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment; a total mood disturbance score was also determined. The POMS was also given upon waking in the morning (before the first dose of modafinil or placebo) and three hours after the morning dose to assess acute mood changes. Every two hours between MWT naps a reaction time test (FCRTT) was administered to measure daytime performance deficits. At the end of each two-week period, data from each patient was compared with the patient's pre-study condition. At the end of the entire six-week trial, physicians and patients were asked to rank the three periods in order of preference; those who had been taking stimulants before the study were also asked to compare their preferred treatment from this study to their previous stimulant therapy.

The study yielded promising results. With respect to sleep latency on the MWT, both doses of modafinil significantly increased the mean sleep latency compared with placebo; the 200-mg dose increased mean latency by 40%, and the 400-mg dose increased it by 54%. Also, more tests were ended due to no sleep on both doses of modafinil than on placebo. At all time points from 0 to 40 minutes across the test sessions, a greater percentage of patients were still awake when on 400 mg of modafinil than when taking 200 mg, and more patients remained awake on 200 mg than on placebo (Broughton et al., 1997).

The patient diaries also demonstrated the effectiveness of modafinil. Both doses significantly reduced the number of involuntary sleep attacks by 24% and the incidence of severe EDS by 26%. Interestingly, modafinil did not appear to interfere with the participants' ability to take voluntary naps. Patients were asked to choose one daily activity that was most affected by their EDS; both modafinil doses decreased the effect of EDS on these activities.

With respect to the ESS, both modafinil doses resulted in decreased scores, therefore indicating decreased EDS. The two items that were most affected were the likelihoods of falling asleep while reading and watching TV; these were also the two most commonly chosen daily activities affected by EDS in patient diaries. As for the FCRTT, no significant differences were found in the mean reaction time across the three medication groups.

Concerning the POMS, modafinil did not seem to have a significant effect on mood other than the fact that the 400-mg dose resulted in slightly increased tension-anxiety scores and vigor-activity increased after 200 mg. No acute effects of modafinil

on mood were detected. In addition, modafinil had no significant effect on overnight PSG measures of sleep characteristics or on blood pressure or heart rate.

There were reports of adverse events during the study, although none of them were major. One hundred complaints were logged from participants taking 400 mg of modafinil, 75 complaints were logged from participants taking 200 mg, and 51 complaints were logged from participants taking a placebo. The nervous and digestive systems were the most frequently affected. Headache, nausea, and nervousness were most commonly reported, although none of these symptoms lasted for more than one week. Interestingly, no significant differences were found between placebo and 200 mg of modafinil for any of the reported adverse events, while the 400-mg dose caused more nausea and more nervousness (Broughton et al., 1997).

At the end of each treatment phase, most patients experienced a decrease in EDS. Among the patients who were taking no stimulants before the study, 80% had decreased EDS while on 400 mg of modafinil, 66% while on 200 mg, and 34% while on placebo. As for the patients who had been taking stimulants prior to the study, 53% had improved EDS on 400 mg, 50% while on 200 mg, and 25% while on placebo. Interestingly, 25% of patients reported deteriorations in health status while on 200 mg of modafinil, while 33% reported deteriorations while on 400 mg.

Concerning patient preferences, 84% of patients chose one of the modafinil doses as their best phase; 50% preferred the 400-mg period while 34% preferred the 200-mg period. Of the 37 subjects who had previously been taking stimulant medication, 10 preferred their previous stimulant therapy while 26 preferred modafinil (one preferred placebo).

Taking the results of this study together, it can be seen that EDS in these narcoleptic subjects was significantly decreased by both 200-mg and 400-mg doses of modafinil with minimal side effects. However, Broughton et al. (1997) wondered why the significant improvement of MWT sleep latency was not associated with a similarly improved score on performance measures; it is suspected that this could be caused by a number of factors, including the particular performance test used. Generally, a daily dose of 200 mg of modafinil was as effective as 400 mg, although great variability occurred. Broughton et al. (1997) concluded that as little as a 200-mg daily dose of modafinil is an effective and well-tolerated treatment of EDS in patients with narcolepsy, but more research needs to be done on its long-term effectiveness.

A 1996 study by Besset, Chetrit, Carlander and Billiard attempted to do just that. The researchers noted the fact that modafinil had demonstrated impressive efficiency in other studies, but pointed out that most of these studies used a small number of subjects and a short-term follow-up. Therefore, these researchers sought to explore the long-term effects of modafinil in a large narcoleptic population.

Potential study participants underwent a clinical examination, an overnight PSG, and an MSLT to determine the existence of narcolepsy; 140 patients were eventually included in the study. These patients ranged in age from 8 to 79 years old, with a mean age of 42. The majority of the patients (104) were male; 36 were female. Each patient was given 200 to 400 mg of modafinil daily from 1984 onwards, with follow-up assessments occurring annually.

The main variables noted during annual follow-ups were treatment duration, EDS reduction, and side effects. The clinical efficacy of modafinil on EDS was evaluated on a

four point scale: 0 indicated no effect, 1 indicated a fair effect, 2 indicated a good effect, and 3 indicated an excellent effect. At the end of the study, patients were divided into two groups according to continued or interrupted treatment; Group A contained 87 patients (63 male and 24 female) still taking modafinil, while Group B consisted of 53 patients (41 male and 12 female) who had discontinued their modafinil treatment. The age distribution was similar in both groups.

With respect to the efficacy of modafinil, 64.1% of all patients showed a good or excellent improvement in EDS. In Group A, 74.3% of patients demonstrated good or excellent improvement; the figure in Group B was 49.1%. Signs of dependency were never observed. However, more than 50% of the subjects in Group B had discontinued their use of modafinil after two years of treatment.

The main reason given for discontinuation of modafinil treatment was loss of efficacy; 81.1% of patients who discontinued the drug complained of a loss of efficacy, and for 62.3% of subjects this was the only reason for discontinuance. The loss of efficacy usually occurred during the last few months before discontinuing treatment, but it is unknown whether the experienced decreasing effect was progressive or abrupt. Interestingly, this loss of efficacy was not solved by increasing the patients' dosage up to 400 mg, and those patients who did not experience a loss of efficacy after two or three years generally experienced consistent efficacy for up to nine years. Clinical aspects of narcolepsy did not appear to be responsible for the loss of efficacy experienced by some patients. The second most common reason for modafinil discontinuation was adverse effects, mentioned by 22.8% of the subjects. Although the reported adverse effects were not serious, they were severe enough to prompt 11.3% of subjects to discontinue their use

of modafinil due to adverse effects alone. The most common adverse effects were nausea, inner tension, headache, poor sleep, and sweating.

Despite the statistics of Group B, modafinil appeared to be an efficacious treatment on the whole. The majority of patients (64.1%) experienced good or excellent improvement in EDS and 62.2% of participants remained on modafinil after two years, while only 4.28% of subjects discontinued treatment due to adverse effects and only 2.6% experienced poor sleep due to modafinil. Generally, modafinil can be administered on a long-term basis without serious side effects or risks of dependency. Therefore, modafinil appears to be an important alternative to stimulant medication in the alleviation of EDS associated with narcolepsy.

As we have seen, modafinil appears to be impressively effective in many narcoleptic individuals; however, there are still a large number of sufferers that do not find relief with this medication. In some cases, treatment with amphetamines is more efficacious for these individuals. One of the most common amphetamines prescribed today is Adderall, a central nervous system stimulant that is a mixture of dextroamphetamine and levoamphetamine salts. In the 70s, there was debate about the efficacy of these amphetamine isomers; since evidence had indicated that dextroamphetamine was twice as potent as the mixture of dextro- and levoamphetamine together, it was thought that levoamphetamine itself was inactive. To complicate this evidence, it had also been found that levoamphetamine had been successfully used in narcolepsy patients who were unresponsive to dextroamphetamine. Because of this apparent controversy and as the two amphetamine isomers have different biochemical

and behavioral effects, Parkes and Fenton reinvestigated the use of dextro- and levoamphetamine in treating patients with narcolepsy (Parkes & Fenton, 1973).

The sample in this study was five male and seven female narcoleptic patients, for a total of 12 participants. Their ages ranged from 18 to 59, with a mean of 40 years. All but one of the subjects was Caucasian; there was one African-American male involved in the study. All participants had either been untreated for narcolepsy or could tolerate the withdrawal of their previous medication; of the participants who had been previously medicated, all experienced an increased number of narcoleptic attacks during the one-week withdrawal period. The untreated patients had an average of seven narcoleptic attacks each day, ranging from two to 11 per day; each of these episodes lasted from 5 to 60 minutes, with a mean of 19 minutes. Eight patients experienced cataplexy, while five (four of whom had cataplexy) also experienced hypnagogic hallucinations and eight had experienced sleep paralysis. Each participant underwent a complete examination to be sure that they did not have any condition that would affect the study's outcome.

The variables used in this study to determine the efficacy of both isomers included patient assessments, EEG recordings and urine tests. Patients were asked to record the onset and duration of day and night sleep on clock-face diagrams every Tuesday and Thursday. They also noted episodes of cataplexy, sleep paralysis, hypnagogic hallucinations and side effects of their treatment. Finally, the participants stated their preferred treatment. In addition, blood pressure, pulse rate, and temperature were recorded weekly during this study.

Several objective tests were used to assess the efficacy of both levo- and dextroamphetamine in this study. EEG recordings were used to perform MSLTs during

the study; onset and duration of sleep was recorded during the first 40 minutes. Urine tests were used to determine levo- and dextroamphetamine content in the body, thereby ensuring that participants were taking the isomers at the appropriate times.

This study was divided into three phases. Phase I aimed to compare levoamphetamine to a placebo during a three-week period. Every participant took a placebo during the first week; during the second week, either a 40-mg divided dose of levoamphetamine or a placebo was given in a double-blind fashion. In the third week, the order of administration was reversed. The EEG recordings were important during this phase; each patient was tested during placebo and levoamphetamine treatment. Phase II of this study sought to compare the potencies of levoamphetamine and dextroamphetamine given in 20-mg divided doses. Each participant took each drug for one week; this phase of the study was also double-blind. At the end of this phase, patients were asked about their preferences. Phase III of this study followed the participants for six months to assess the long-term effects of their chosen medication. Optimum dosages were 20-60 mg/day for levoamphetamine and 10-45 mg/day for dextroamphetamine.

Phase I showed that while the frequency and duration of narcoleptic attacks in untreated participants and those taking a placebo were similar, levoamphetamine doses of 40 mg per day reduced the frequency of attacks. Nine patients experienced no narcoleptic attacks during levoamphetamine treatment, and the other three patients experienced a decrease in the frequency and duration of their attacks. Cataplexy and hypnagogic hallucinations occurred in similar frequencies during both placebo and levoamphetamine treatment. During MSLT tests, every patient fell asleep during both

placebo and levoamphetamine treatment, but there were no significant differences in sleep characteristics. Urine tests of the participants showed that all were taking levoamphetamine during the appropriate period; traces of dextroamphetamine or other confounding medications were not found. When patients were asked about their preferences, 11 preferred the levoamphetamine period over the placebo and one patient had no preference. With respect to side effects, five patients complained of insomnia; nervousness, sweating, and palpitations occurred during both treatments. In terms of blood pressure, pulse rate, and temperature, there was no significant change during levoamphetamine treatment.

Phase II indicated that dextroamphetamine was more effective than levoamphetamine, but the differences were very slight and not statistically significant. The average number of daily narcoleptic attacks was 2.1 while taking levoamphetamine and 1.4 while taking dextroamphetamine. Three patients had narcoleptic attacks on both amphetamines, a further three patients had no attacks while taking dextroamphetamine, and six reported no narcoleptic attacks with either isomer (Parkes & Fenton, 1975). Cataplexy and hallucinations were not affected by either isomer. In terms of patient preference, seven preferred dextroamphetamine while five preferred levoamphetamine.

Phase III did not show significant change in the efficacy of the subjects' preferred treatment; the daily number of narcoleptic attacks after six months was similar to the numbers recorded during phase II. Only one patient required dosage adjustment, increasing their levoamphetamine intake from 40 to 50 mg/day after three months.

Taken together, the results of this study indicate that levoamphetamine is not inactive and that both levo- and dextroamphetamine can be effective in the treatment of

EDS in narcoleptic patients. In addition, neither isomer has an effect on the other hallmarks of narcolepsy: cataplexy and hallucinations. Parkes and Fenton (1975) recommended that levoamphetamine be tried in narcoleptics for whom dextroamphetamine proves undesirable. They also settled the debate on the activity of levoamphetamine; today, levo- and dextroamphetamines are combined in one of the most widely prescribed medications used to combat narcolepsy: Adderall.

In the study outlined above, the effects of amphetamines were investigated by comparing two different types of amphetamines to each other; the following 1985 study conducted by Shindler, Schachter, Brincat and Parkes in England took a different approach to investigating amphetamines in narcolepsy treatment by comparing an amphetamine preparation with two other central nervous system stimulants that have similar properties.

The amphetamine used in this study was dextroamphetamine in the form of Dexedrine (both standard and time-released variations were used). These variations of Dexedrine were compared to mazindol and fencamfamin; both drugs are legal in the U.S., but not FDA-approved for the treatment of narcolepsy. Both drugs were originally developed to be used as appetite suppressants or psychostimulants but have shown to have an effect on sleep and alertness. Mazindol has been shown to prevent REM sleep much like amphetamines do, while fencamfamin is from the same drug family as amphetamines (phenylethylamines) and has been shown to prevent fatigue.

The sample in this study consisted of 20 narcolepsy patients at the King's College Hospital Sleep Disorders Clinic in Britain. The age range of the sample was 28-65 years old, with a mean of 49 years; 11 participants were female. Twelve patients had cataplexy

and eight had experienced sleep paralysis, and no patients had other medical conditions that might interfere with the study's results. The study was approved by the hospital's ethics committee, and informed consent was obtained from all 20 patients.

The severity of narcolepsy and the effect of treatment were evaluated by self-rating scales for sleep, alertness, mood and appetite developed by the MRC Applied Psychology Unit in Cambridge; score systems devised to evaluate drugs in narcolepsy were also used. The scales were completed every two weeks on the same day during each phase of the study. In addition, patients completed a questionnaire about the adverse reactions they experienced. Pulse, blood pressure and weight were also measured regularly throughout the study.

The trial began with a two-week drug free period. At the end of the two weeks, baseline assessments for the frequency of narcoleptic attacks and episodes of cataplexy were determined as were scores for sleep, alertness, mood and appetite.

Next, Phase I of the trial began. This was a 12-week period of low-dose treatments of Dexedrine (standard and time-released) and mazindol. The 12 weeks were divided into three sequential four-week periods; during each period, patients took a medication regimen consisting of two placebo preparations and one active preparation. In one period, patients took 10 mg of time-released Dexedrine at 8 AM; they also took matched placebos at 8 AM and noon, which were for 5 mg of standard-release Dexedrine and 2 mg of mazindol. In a second period, patients took 5 mg of standard-release Dexedrine at 8 AM and noon; they also took matched placebos for 10 mg of time-released Dexedrine at 8 AM and for 2 mg of mazindol at 8 AM and noon. In the third and final period of Phase I, patients took 2 mg of mazindol at 8 AM and noon; they also

took matched placebos for 10 mg of time-released Dexedrine at 8 AM and for 5 mg of standard-release Dexedrine at 8 AM and noon.

Phase II of the study was an eight-week period of high-dose treatments of standard-release Dexedrine and fencamfamin. The eight weeks were divided into two sequential four-week periods. During one period, patients took 10 mg of standard-release Dexedrine at 8 AM, noon, and 2 PM; they also took a matched placebo for 20 mg of fencamfamin at the same times of day. During the other period, patients took 20 mg of fencamfamin at 8 AM, noon, and 2 PM; they also took a matched placebo for 20 mg of standard-released Dexedrine at the same times of day.

It is important to note that during both phases of this study, the order of taking the active drug was random and the trial was double-blind. In addition, five patients kept inadequate records during phase one, so their data is only included in the analysis of adverse events during that phase of the study. At the end of the trial, the results from periods of active medication were compared to patients' baseline scores. Remember, the variables being examined were scales for sleep, alertness, mood and appetite; adverse events experienced; and physiological measurements of pulse, blood pressure and heart rate.

The results of Phase I demonstrated that both mazindol and standard-release and time-released Dexedrine all roughly halved the number of sleep attacks experienced by patients. No treatment affected the characteristics of nighttime sleep or episodes of cataplexy, and each drug reduced the frequency of sleep paralysis. The four subjective rating scales that were affected included alertness (drowsy-alert, dreamy-attentive), motor coordination (clumsy-well coordinated), energy (lethargic-energetic), and mood (sad-

happy); all were improved on each drug. No significant affects were shown on appetite. Adverse effects reported during this phase included sweating, palpitations, and a feeling of edginess; however, these complaints occurred less frequently during active treatment than during placebo periods and the two-week drug-free period. As for patient preferences at the end of the first phase, four patients preferred standard-release Dexedrine, two preferred time-released Dexedrine, six preferred mazindol and three had no preference.

Phase II indicated that 30 mg of standard-release Dexedrine and 60 mg of fencamfamin were equally effective in reducing sleep attacks. In addition, it was found that the 30-mg Dexedrine dose was only slightly more efficacious than the 10-mg standard-release dose used in phase one in terms of reducing the number of daily sleep attacks. After the first 48 hours of active treatment, neither drug preparation used during phase two affected characteristics of patients' nighttime sleep. Interestingly, the number of episodes of cataplexy and sleep paralysis was slightly greater during fencamfamin treatment; however, measures of mood and appetite were similar during both active treatments and comparable to patients' baseline assessments. As in phase one, the adverse events experienced during phase two (sweating, palpitations, and edginess) were less in number than the same effects experienced during periods of no treatment. In addition, two participants required a dose reduction during the Dexedrine portion of this phase because of anxiety and headache in one participant and continued insomnia in the other. No significant changes in pulse, blood pressure, weight or appetite were observed. With respect to patient preferences, seven preferred Dexedrine, nine preferred fencamfamin and four had no preference.

An important point Shindler, Schachter, Brincat and Parkes (1985) made is that it is critical to examine the effects of narcolepsy medication through subjective evaluations from narcoleptic patients using the medication in everyday life. As we can see from the fact that none of these drugs affected appetite or weight when taken by the narcoleptic subjects, even though these effects are observed in normal volunteers and obese subjects, medications affect narcoleptics differently than others. Additionally, pharmacokinetic properties of different stimulants seem to be unimportant in narcoleptic patients; for example, the stimulant effect of a single dose of any of the drugs used in this study lasts about four to six hours (even though their half-lives in the body are supposed to range from six to 30 hours). To complicate matters further, narcoleptics themselves vary widely in their treatment preferences and experiences. Under real life circumstances no single stimulant drug can be determined as a “best” treatment, and there are pronounced individual differences in preference (Shindler et al., 1985).

The important commonalities of the three drugs in this study were that all decreased the frequency of narcoleptic attacks, raised mood and reduced REM sleep. Also, low-dose treatment was shown to be almost as effective as high-dose treatment. There was no decisive evidence of superiority among the three drugs studied; because of this, the researchers in this study recommend that all three drugs should be options in the treatment of narcolepsy. Again, the most important factors in finding an efficacious narcolepsy treatment are the experiences and preferences of each individual patient.

As we have seen from the above studies, narcoleptics have a wide range of variability in their experiences with medication. While modafinil and amphetamines have proven to be effective in alleviating EDS in many narcoleptics, some still

experience an undesirable level of drowsiness. In these patients, sodium oxybate (Xyrem) is sometimes prescribed as a nighttime sleep aid meant to work in conjunction with daytime stimulant medication. The primary problem with narcolepsy is the brain's disorganized sleep/wake patterns; because of this, narcoleptics feel incredibly sleepy at inappropriate times and elements of REM sleep often intrude into wakefulness. What Xyrem attempts to do is "glue together" narcoleptics' disorganized sleep; it is thought to restore normal patterns of sleep at night, thereby making sleep more restful. With Xyrem promoting restorative sleep during the night and stimulants promoting wakefulness during the day, the hope is that narcolepsy symptoms can be optimally alleviated.

A double-blind, crossover study by Scrima, Hartman, Johnson, Thomas, and Hiller published in 1990 examined the effects of Xyrem (also known as GHB or sodium oxybate) on the sleep of narcolepsy patients. The researchers used objective assessments of nighttime and daytime sleepiness to assess sodium oxybate's effectiveness, and their study used these assessments to describe the results of sodium oxybate on the sleep characteristics of narcolepsy patients.

The sample of this study was 20 narcolepsy patients diagnosed with narcolepsy at the accredited Sleep Disorders Center of the University of Arkansas for Medical Sciences. Ten patients were male and ten were female; the mean age of the male patients was 46 (with a range from 16 to 64), while the mean age of the female patients was 49 (with a range from 21 to 64). All patients were off whatever antidepressants or stimulants they had been taking for at least 15 days prior to the study; however, they were permitted to take up to 30 mg of methylphenidate, a stimulant also known as Ritalin, during the trial. All patients were interviewed by an accredited sleep doctor, underwent a

physical exam, and took an overnight PSG and an MSLT to obtain baseline measures.

To be included in this study, all patients had to meet the following criteria: a history of EDS and cataplexy, REM sleep during at least two naps and a sleep latency of less than five minutes during their MSLT, experience of at least ten attacks of cataplexy in the past two weeks, and be between 16 and 65 years old. Patients were excluded from the study if they had other major health problems, other sleep disorders, were fertile females not using birth control, were nursing mothers or had taken sodium oxybate before. Informed consent was obtained from all patients included in the study.

This study was divided into six phases: baseline (14 days), first treatment (29 days), first washout (6 days), second treatment (29 days), and second washout (6 days). Half of the females and half of the males received sodium oxybate during the first treatment period and a placebo in the second, and the other half of patients received a placebo during the first treatment period and sodium oxybate in the second. During the sodium oxybate treatment period, each patient took 25 mg of sodium oxybate at bedtime and another 25 mg three hours later; the same timing was used with the placebo. An overnight PSG test followed by an MSLT was performed on the last night of patients' baseline period and the first and last night of both treatment periods. Participants did not take methylphenidate on the day of the PSG tests or on the next day until after the MSLT had been done. Researchers measured sleep latency, sleep efficiency, and the amount of time spent in each stage of sleep.

For the purposes of this study, it is important that the reader understands the various stages of sleep. In this particular study, wakefulness was considered to be stage 0. Stage 1 sleep is extreme drowsiness during which the body prepares for sleep. Stage 2

is light sleep, with intermittent periods of muscle tension and relaxation. Stages 3 and 4 are the deep stages of sleep known as slow-wave or delta sleep. Together, stages 1-4 are considered non-REM (NREM) sleep; the entire period of NREM sleep lasts from about 90 to 120 minutes, with each stage lasting from 5 to 15 minutes. The final sleep stage is REM sleep, during which dreaming occurs as the eyes move rapidly back and forth. In each sleep cycle, stages 2 and 3 are repeated backwards before REM sleep occurs; therefore, a normal sleep cycle looks like this: 0, 1, 2, 3, 4, 3, 2, REM. As mentioned earlier, REM sleep in normal individuals usually occurs after 90 minutes; however, narcoleptics often experience SOREM, or sleep-onset REM, which occurs when a person goes into REM sleep within a few minutes of falling asleep. Knowledge of these sleep stages will help the reader understand the results of this study.

Several significant results came from the overnight PSG tests the patients took. First, it is important to note that methylphenidate usage did not vary significantly during the entire study. During sodium oxybate treatment, patients experienced the following significant changes: less stage 1 sleep, more stage 3 and 4 sleep, longer sleep latency, fewer sleep stage shifts, and fewer awakenings. Interestingly, there were much more awakenings and much less sleep efficiency during the last two hours of the night; researchers discovered that because of sodium oxybate's short half-life, patients' last two hours of sleep were unaffected by the drug. With respect to day interaction, there were no significant results except for the fact that stage 3 sleep was significantly increased on the 29th day of sodium oxybate treatment but not on day one. Concerning gender, several differences were found: females taking sodium oxybate experienced a slightly larger increase in stage 4 sleep than males, and REM latency was significantly shorter in males

taking sodium oxybate but not in females. When looking at day interaction and gender together, it was found that females experienced much less stage 1 sleep on the 29th day of sodium oxybate treatment but not on day one (this effect was not seen in males); in addition, females' latency to sleep was longer on the 29th day of sodium oxybate treatment but not on day one, while males' latency to sleep was slightly longer on the first day of sodium oxybate treatment but not on the 29th day. The order of treatment did not appear to have any significant effects. Lastly, two significant placebo effects were found with respect to the overnight PSG: time spent in stage 2 sleep as well as sleep efficiency was greater on day one of placebo treatment than baseline.

The MSLT tests also yielded significant results. The first deal with stage 0, or wakefulness: sleep latency was slightly longer during sodium oxybate treatment, and this stage was modestly increased overall. However, 80% of narcolepsy patients still had a pathological sleep latency mean (less than five minutes) on the 29th day of sodium oxybate treatment, compared to 90% with a pathological sleep latency mean on the 29th day of placebo treatment (Scrima, Hartman, Johnson, Thomas & Hiller, 1990, pg. 485). With respect to REM sleep and gender, females had significantly fewer REM naps on the 29th day of sodium oxybate treatment but not on day one; males did not show this difference. Concerning REM sleep and day, total REM sleep did not show significant differences on sodium oxybate day 29 or day one. With respect to NREM sleep, there were no differences in stages 1 and 2 sleep, but males had much less stage 3 and 4 sleep while taking sodium oxybate; females did not show this effect. Interestingly, the MSLT measures showed no placebo effects.

The results of this study taken together indicate that sodium oxybate improves sleep depth and continuity (Scrima et al., 1990). Overall, stage 3 and 4 sleep significantly increased while stage 1 sleep, awakenings, and sleep stage shifts were decreased. These results agree with the findings of several other studies. The researchers acknowledge that the results of the PSG portion of this study may have been affected by the fact that patients were required to spend eight hours in bed, even if they were ready to get up earlier; this might account for the increased stage 0 sleep found in comparison to other studies. As explained previously, the last two hours of the PSG sleep period were unaffected by sodium oxybate (the drug is only detectable in the blood for 2.5 to 3 hours after ingestion), therefore resulting in increased awakenings and decreased sleep efficiency. The increase in sleep latency found in this study might be explained by the theory that sodium oxybate sometimes induces a state of agitation; as the drug's levels rose in the body during the first few minutes after ingestion, patients may not have been able to fall asleep because of sodium oxybate-induced agitation. However, once patients fell asleep they experienced more normal sleep patterns and less awakenings; the researchers theorize that sodium oxybate might raise the arousal threshold (the stimulus intensity necessary to disrupt sleep). Interestingly, although sodium oxybate promoted a decrease in objective EDS, patients did not report a decrease in subjective EDS; the researchers posit that higher doses of sodium oxybate or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients (Scrima et al., 1990).

The results seem to support the theory that sodium oxybate decreases the pressure for REM sleep and its related characteristics in narcolepsy patients by improving their

nighttime sleep (Scrima et al., 1990, pg. 488). It is important to note that this study did not find any significant side effects or evidence of tolerance. Sodium oxybate is also thought to decrease incidents of cataplexy, but patients still need stimulants to control EDS. Generally, sodium oxybate fosters normal sleep in narcolepsy patients who otherwise have very disturbed and disorganized sleep, thereby giving patients and doctors another tool to decrease narcolepsy's symptoms and restore patients' health status.

Another study that sought to explore the effectiveness of sodium oxybate (Xyrem) in the treatment of narcolepsy was conducted by Black and Houghton and published this year. The researchers noted that until recently, treatment for narcolepsy has primarily consisted of stimulant therapy and that modafinil (Provigil) has been established as a standard of care in this area, although it does have the disadvantage of decreased potency when compared to amphetamines. This particular study sought to explore the treatment of narcolepsy with both Provigil and Xyrem. The following double-blind, placebo-controlled trial represents the first trial that attempted to characterize the efficacy of sodium oxybate as a single agent, or in combination with modafinil, for the treatment of EDS in a large population of patients with narcolepsy (Black & Houghton, 2006, p. 940).

The sample for this study was carefully selected. Patients were considered for inclusion in the study if they were at least 18 years old and met the following criteria: met the International Classification of Sleep Disorders criteria for the diagnosis of narcolepsy, had been taking stimulants to treat their EDS for at least three months before the trial and were taking stable doses of modafinil at least six weeks before the trial began, were willing to sacrifice operating motor vehicles or heavy machinery if asked, and were willing to complete the study and give informed consent. Patients were excluded from

the trial if they had been using sodium oxybate within 30 days before the trial, had any other sleep disorder, used drugs that may affect the study's outcome, had a history of substance abuse, had abnormal blood test results, heart problems, seizure disorder or head trauma, or an occupation with shift work or night shifts.

A total of 278 patients were enrolled in the study; 231 were assigned to one of the four treatment groups, and 222 patients completed the study. The sample consisted of 107 men and 115 women with a mean age of 38 years. Several ethnic groups were represented in the sample: 195 were white, 21 were black, one was Asian, and five patients were classified as "other". The study was conducted at 44 sites worldwide; patients represented the United States, Canada, the Czech Republic, France, Germany, Netherlands, Switzerland and the United Kingdom. Each center's review or ethics board approved this trial, and informed consent was obtained from all patients.

The medications used in this trial included Xyrem and a matched placebo as well as Provigil tablets and a matched placebo. Both placebos had previously been shown to be indistinguishable from the actual medication. Patients were allowed to keep taking antidepressant medications, if applicable.

Patients were evaluated for possible trial inclusion at Visit 1. During this visit a complete medical history was taken, a physical exam was done, vital signs were measured and samples for clinical laboratory testing were obtained. Patients were also evaluated against the inclusion criteria described above. If deemed acceptable for inclusion, patients signed an informed consent and were trained on how to keep an adequate daily diary to be used for data in the study.

Clinic Visit 2 happened one to two weeks later; during this visit, an overnight PSG was conducted, followed by a MWT test. During this time, patients remained on established doses of modafinil to make baseline assessments about its effectiveness in treating EDS. Patients then entered the two-week single-blind baseline period; they took modafinil at their usual daily dose (between 200 and 600 mg per day) in addition to a placebo sodium oxybate solution every night, once at bedtime and again 2.5 to 4 hours later.

Visit 3 involved obtaining baseline PSG and MWT recordings and entering the treatment phase. Patients were divided into four randomly assigned treatment groups: Group 1 (placebo group) took placebo sodium oxybate + placebo modafinil, Group 2 (sodium-oxybate group) took sodium oxybate + placebo modafinil, Group 3 (modafinil group) took placebo sodium oxybate + modafinil, and Group 4 (sodium-oxybate/modafinil group) took sodium oxybate + modafinil. Those patients taking modafinil continued to take their established dose; patients taking a modafinil placebo took tablets that matched their established dose. Patients taking sodium oxybate took 6 g nightly; patients taking a sodium oxybate placebo took the same amount.

Four weeks later, Clinic Visit 4 occurred. PSG and MWT measures were taken again, and medication continued at the previous doses with the exception of the sodium oxybate dosage being increased from 6 to 9 nightly grams. Safety assessments were also performed during Visit 4. Four weeks later, final efficacy and safety assessments were made during Clinic Visit 5.

The primary instrument used to measure the efficacy of the various medications was the MWT test. The ESS, the Clinical Global Impression of Severity (CGI-s), the

Clinical Global Impression of Change (CGI-c), and daily patient diaries were also used to obtain data. In addition, any adverse events experienced were thoroughly reviewed at each clinic visit; all adverse events reported were followed until resolution of the event, and all patients who discontinued their participation in the trial due to an adverse event were followed until a satisfactory resolution occurred. Physical examinations and measurements of vital signs were also performed at each clinic visit.

The MWT results showed several significant differences between groups. Generally, all groups besides the placebo group experienced longer average daytime sleep latency after eight weeks of treatment; the most significant change occurred during the first four weeks of the trial. The placebo group, on the other hand, experienced a decrease in average daytime sleep latency. There were no significant differences between the sodium-oxybate and modafinil treatment groups, but the sodium-oxybate/modafinil group increased their average sleep latency by 2.68 minutes. This indicates an improvement of EDS by the addition of sodium oxybate over the response produced by modafinil alone.

With respect to the ESS scores, the sodium-oxybate and sodium-oxybate/modafinil groups had significant reductions in their scores. Scores for the modafinil group did not show any significant changes and were not different from the scores of the placebo group.

Weekly sleep attacks as indicated in patient diaries significantly decreased in the sodium-oxybate and sodium-oxybate/modafinil groups. The sodium-oxybate patients experienced 7.10 weekly sleep attacks as compared to 10.05 per week at baseline; the sodium-oxybate/modafinil patients experienced 5.55 weekly sleep attacks as compared to

11.82 per week at baseline. There were no significant changes in the placebo or the modafinil groups, and no significant differences existed between these two groups.

The CGI-s and CGI-c scores of participants at baseline showed that despite modafinil treatment, all participants were still considered to be markedly ill. However, members of the sodium-oxybate group and the sodium-oxybate/modafinil group showed overall improvement in their clinical condition and demonstrated a successful treatment response; 48% of members in the sodium-oxybate group and 46.3% of members in the sodium-oxybate/modafinil group were deemed to be much improved or very much improved. In contrast, the modafinil and placebo groups ultimately demonstrated no significant change in disease severity.

Adverse events were carefully recorded during this study; at least one adverse event was experienced in 151 out of 231 treated patients, a percentage rate of 65.4%. The sodium-oxybate/modafinil group reported slightly more adverse events. The most common events reported among all patients were headache, nausea, dizziness, common cold, vomiting and drowsiness. However, only nausea, vomiting, and dizziness were statistically significant among groups, with nausea and vomiting occurring more in the sodium-oxybate group and dizziness occurring more in the sodium-oxybate/modafinil group. Six patients in the sodium-oxybate/modafinil group withdrew from the study due to adverse events, compared with four patients in the sodium-oxybate group, two in the modafinil group and one in the placebo group. Four patients reported serious adverse events, which included pregnancy, abdominal pain, palpitations and a psychotic disorder due to a general medical condition (narcissistic personality disorder); of these, only the psychotic disorder was determined to be drug-related, and it occurred in the sodium-

oxybate/modafinil group. In terms of changes in vital signs, four patients in the sodium-oxybate/modafinil group experienced the following potentially treatment-related changes: hypertension, hypotension, hyperventilation and low-grade fever. Each event was mild or moderate in severity and occurred in one patient. All reported adverse events were consistent with known profiles of each drug.

Taken together, the results of this study indicate that the coadministration of sodium oxybate and modafinil reaps more benefits to narcolepsy patients than the administration of either medication on its own. Sodium oxybate's ability to consolidate narcoleptics' fragmented sleep resulted in increased sleep latencies on the MWT, improved ESS scores, and CGI-s and CGI-c results that indicated improvements in the narcolepsy disease state. All of these assessments were further improved with the addition of modafinil. The researchers point out that one limitation to this trial was the fact that the participants had already been taking modafinil prior to the trial; therefore, adverse events due to modafinil use were probably underrepresented since all study participants had demonstrated an ability to tolerate the medication. Generally though, sodium oxybate and modafinil each demonstrated effectiveness in alleviating EDS in narcoleptic subjects; in addition, sodium oxybate is the only medication currently known to treat cataplexy, sleep fragmentation, and EDS. The results of this study indicated that these drugs are more efficacious when used together than when administered alone, and each drug should be a strong consideration in the treatment of narcolepsy.

What we have learned from the previous eight articles is that although narcolepsy is a chronic and incurable disorder that often has negative psychological effects, there are several treatment options available to optimally alleviate the potentially debilitating

symptoms of the disease. Stimulant therapy, most often with modafinil or amphetamines, has shown promise in its ability to relieve EDS in narcolepsy sufferers; the addition of sodium oxybate to patients' treatment plans has shown even more significant improvements in EDS as well as a reduction of cataplexy and fragmented sleep. In terms of the psychological effects of narcolepsy, the most important factor seems to be support and understanding; family members, teachers, employers and loved ones should educate themselves on the realities of narcolepsy in order to avoid false attributions of laziness or disinterest and best prepare themselves to provide adequate support.

After an in-depth introduction to narcolepsy and a careful analysis of the previous eight articles concerning the psychological effects of the disorder and its most common treatments, the reader should be left with a deeper knowledge of this chronic neurological disease. Mr. Bean's character from *Rat Race*, while amusing, should no longer come to mind when narcolepsy is mentioned; the realities of the disorder are far from Hollywood depictions and the general public's perceptions. While narcolepsy sufferers may never restore a completely normal health status, they can come close; the right medication regimen, adequate social support, and general understanding are the first steps in the right direction.

My personal journey with narcolepsy has been a long one. Like many people who begin to experience symptoms, I dismissed mine as being the result of everyday tiredness; as a college student, feeling tired is not unusual or unexpected. However, my excessive daytime sleepiness (EDS) soon began to affect my grades because I was having problems staying awake in class and was unable to study for tests without falling asleep. I also began to feel frustrated at my inability to perform normal daily activities; I exercise

regularly and enjoy having an active lifestyle, and before long my sleepiness was interfering with that. My relationship with my boyfriend was affected negatively as well; he did not know what to make of my sleepiness and often took it personally if I fell asleep while hanging out with him. As my sleepiness interfered more and more with my daily life, I became more and more frustrated. After several months of feeling this way, I mentioned my symptoms to my general care physician during a routine physical.

As is the case with many people exhibiting narcolepsy symptoms, my general care doctor did not immediately diagnose my condition. She performed a blood test and discovered that my iron levels were slightly low; they were not low enough to cause symptoms in most people, but she prescribed me an iron supplement anyway. After six weeks of taking the supplements, my condition still had not improved; another blood test was done, and the results indicated the presence of thalassemia-trait minor, a genetic blood disorder that can result in low blood counts but often does not produce symptoms. My iron supplements were withdrawn due to the fact that such supplements can exacerbate thalassemia-trait, and my primary care doctor referred me to a hematologist who expressed extreme doubt that the disorder was the cause of my tiredness.

After undergoing several blood tests with no definitive results, I visited a gastroenterologist and an allergist; my mother is gluten-intolerant, and it was suspected that I may have inherited the allergy, which can cause tiredness. All the allergy tests I underwent yielded negative results, and the gastroenterologist could not pinpoint a cause for my symptoms. My psychological state began to deteriorate as I continued to experience symptoms with no known cause; my family and friends began suggesting that

the problem was “all in my head” and that I was exaggerating my symptoms. With no diagnosis from the various specialists I had seen, I began to wonder if they were right.

As a last-ditch effort, my general care physician suggested that I see a neurologist and undergo a sleep study. She expressed doubts that the study would yield anything since I was so young, exhibited virtually no symptoms other than EDS, and was otherwise healthy. On July 13th, six months after my first trip to the doctor, I made my first visit to the Baptist Sleep Institute in Knoxville. I filled out a checklist detailing my symptoms and answered questions about my usual sleep schedule in addition to providing an extensive medical history of myself and my family as well as a lifestyle profile detailing my living, work, school, and activity situations. It was during this visit that I filled out my first Epworth Sleepiness Scale (ESS)—I scored a 12, double the “normal” score of six or below. After reviewing this information, the neurologist determined the need for an overnight polysomnogram (PSG) and a multiple sleep latency test (MSLT).

Almost two weeks later, on July 25th, I returned to the center for my sleep study. I arrived about two hours before my bedtime of 10:30 PM to be attached to the recording devices and to become accustomed to the new environment. Having multiple electrodes attached to my scalp, face, chest, and legs was distracting, and I expressed concerns about being able to sleep like I normally would. The technician assured me that I would be surprised how easy it was to sleep normally and that my test results would be compared to controlled statistics of people who also slept at the center. For the most part, she was right; I fell asleep in 4.5 minutes. However, I also woke up 33 times throughout the night; while this is consistent with many narcoleptics’ disorganized sleep patterns, I did not feel that it was characteristic of my own usual sleep patterns since I normally sleep

through the night when sleeping in my own bed, free of attachments to various machines. Nonetheless, this was not the only symptom of narcolepsy I exhibited during the PSG; I entered REM sleep after one hour, 30 minutes earlier than normal. My disorganized sleep patterns were also indicative of narcolepsy; I experienced five REM episodes, one more than the high end of normal. In addition, I spent only 14.4% of my sleep time in restorative Stage 3 sleep and no time in Stage 4 sleep. I spent the majority of my time (55.9%) in light Stage 2 sleep; 19.6% of my sleep time was spent dreaming, and I was in Stage 1 sleep 10.1% of the time. Taken together, these results indicated that I was not getting restorative sleep at night; the short sleep latency demonstrated the existence of extreme sleepiness consistent with narcolepsy.

The MSLT the following day made my diagnosis of narcolepsy all but inevitable. Generally, patients are given five opportunities to take naps throughout the day. To be diagnosed with narcolepsy, patients must have a sleep latency of five minutes or less and demonstrate REM sleep in two of these five naps. Remember, non-narcoleptics typically take about 15 minutes to fall asleep and do not begin dreaming until about 90 minutes has passed; therefore, non-narcoleptics should not usually dream during short naps. My first nap occurred at 9:09 AM, two and a half hours after my waking time. The first nap lasted 24 minutes; I fell asleep in four minutes and entered REM sleep after seven minutes. The second nap was at 10:59 AM and lasted 24 minutes as well; this time, I fell asleep in five minutes and entered REM sleep one minute later, at six minutes. Since I demonstrated compelling narcolepsy symptoms during my first two naps, the MSLT was ended and I was not required to attempt three additional naps. My mean sleep latency for the MSLT was 4.5 minutes; my mean REM latency was 6.5 minutes.

Two weeks later I returned to Baptist Sleep Institute to hear the results of my sleep study and my diagnosis. My neurologist confidently diagnosed me with narcolepsy; instead of being upset or afraid of the fact that I had just been diagnosed with a lifelong chronic disorder, I felt relieved that my symptoms finally had a name. Everything had not been “all in my head” after all; I was encouraged by the fact that my problem had been defined and that if it had a name, it must also have a treatment plan. I was excited about the possibility of finally relieving my symptoms and being able to return to my old activity level; my neurologist promptly prescribed me Provigil, with the instructions to take a 200-mg daily dose.

I was slightly discouraged to find out that a month’s supply of Provigil would cost me \$85, even with the help of my insurance, but I was willing to pay any price to relieve my sleepiness. During the first week of my treatment, I began to feel much better; I stayed awake in class and concentrated more easily. However, I felt that Provigil’s efficacy began to decline after several weeks, which has been demonstrated in clinical trials; Besset, Chetrit, Carlander and Billiard (1996) found that loss of efficacy was the number one reason for participants’ discontinuance of Provigil treatment. While I still felt more alert than before, distressing symptoms of EDS persisted; before long, the main effect of Provigil I experienced was constant insatiable thirst. I began to feel that all Provigil did for me was make me incredibly thirsty and \$85 poorer, so I went back to my neurologist on September 11th to discuss a change in treatment.

It was during this office visit that my negative health care orientation began to skyrocket; this corroborates the results of Bruck’s 2001 study discussed previously. My ESS score during that visit was an 11, only a one-point improvement over my baseline

measure and still much higher than the desirable score of six or below; however, my neurologist insisted that I remain on Provigil. She mentioned that she had spoken nationally on behalf of the medication, and I became suspicious of her intentions; I wondered if she enjoyed some kind of professional or financial gain by prescribing Provigil to her patients. She recommended that I stay on the Provigil and instead take behavioral steps to decrease my sleepiness, among them going to sleep at 11 PM and waking up at 8 AM every day. She informed me that if I failed to stick to this schedule even once, I would be unable to return to baseline for two weeks. When I expressed extreme doubt at being able to follow such a schedule considering the fact that I am a college student, she told me that being a narcoleptic and refusing to stick to such a schedule was “like being a diabetic who wants to eat cake”. She implied that a regimented sleep schedule was possible with a little discipline, effort, and concern for my physical health. This was when I began to doubt her ability to provide the best care for me; I began to notice that every patient in her waiting room was easily three times as old as me, and I doubted that she could provide realistic treatment to an active college student. Nonetheless, I agreed to double my dose of Provigil to 400 mg and see what developed.

After that office visit, I began to do my own research on Provigil and its use in the treatment of narcolepsy. That was how I discovered that Provigil can decrease the effects of hormonal birth control (Provigil, 2006); I had been taking birth control pills for years, a fact of which my neurologist was well aware. I was furious that she had not mentioned this side effect to me and immediately scheduled another office visit. During this time I began to experience breakthrough bleeding, an indication that my birth control pills were

not working as they should. In response to repeated calls to her office about this, my neurologist brushed off my concerns and told me that the chances of my birth control failing were really quite small; although I have been in a monogamous relationship for almost five years, to me there is no such thing as a “small” chance of pregnancy that is not a big deal. I also experienced no improvement in my narcolepsy symptoms as a result of my doubled dose of Provigil; Besset, Chetrit, Carlander and Billiard (1996) found that in patients who experienced loss of efficacy with the drug, an increase in dosage had no effect. My neurologist’s unbending attitude toward my treatment had frustrated me, and this oversight escalated my frustration into fury; I made the decision to honor my office visit with her simply to obtain a prescription for another drug, after which I would stop seeing her and replace her with a more empathetic neurologist.

On September 19th, I went to the Baptist Sleep Institute for the last time. My ESS score that day was a 12, the same as it had been before I had gotten any treatment at all. I refused my neurologist’s suggestion to switch birth controls and remain on Provigil; I demanded a prescription for a different drug that would not interfere with any medications I was currently taking. She tried to convince me to try Xyrem in addition to Provigil, but by that point my trust in her had deteriorated to the point where I was not comfortable taking prescription GHB under her care. After warning me about the horrible side effects of amphetamines and their potential for addiction, she wrote me a prescription for 5 mg tablets of standard-release Adderall and gave me vague instructions to begin taking one in the morning and one in the afternoon, gradually escalating the dosage until I discovered what was best for me.

I filled my Adderall prescription the next day and was delighted to find out that a month's supply would cost me only \$30, quite a decrease from the \$85 I paid for Provigil. I then made an appointment with a prominent Nashville neurologist for several weeks later. During those weeks, I tinkered with my Adderall dosage but did not know quite how much to take or what would be safe; my old neurologist's instructions had been vague, and judging from her previous oversights in my treatment, I was not confident in how to take my new medication. I hoped that a change in physicians would provide me with a more confident direction for fighting my disorder.

My visit to the Nashville neurologist on October 5th marked an upswing in both my treatment and my psychological state. My ESS score at that meeting was a 10, the lowest it had ever been but still much higher than the target score of six or below. This doctor immediately recommended that I move to a more stable dose of Adderall and switch to the time-released variety; he wrote me a prescription for 30-mg Adderall XR. He told me that in narcoleptics, addiction really has not been a problem with the drug and that drug holidays would not be necessary; this goes along with Shindler, Schachter, Brincat and Parkes' (1985) and Parkes & Fenton's (1973) research that found no evidence of addiction or tolerance to amphetamines. He also told me that in terms of my sleep schedule, it was not necessary to go to sleep at 11 PM and awake at 8 AM every day; the more important thing is to maintain a consistent bedtime and waking time, regardless of exactly what those times are. I left his office feeling encouraged and hopeful about my new treatment plan.

Since that office visit two months ago, I have been taking 30 mg of Adderall XR daily and doing my best to maintain a consistent sleep schedule, even if it does entail

going to bed at 2 AM and getting up at 10 AM. Since beginning this new stimulant therapy, my symptoms have improved markedly; my current ESS score stands at an all-time low of 8, which is as close to the target score of six or below as I have ever been. My sleep attacks have been largely eliminated; while before I fell asleep in class at least four times a week, now the figure is closer to one weekly sleep attack (if any) during class, although I do still sometimes fall asleep while studying for tests. My side effects have been largely nonexistent; I have experienced some anxiety, but usually it is at a productive level. As I have been able to return to my normal activity level, I have lost almost ten pounds and feel more energetic and happier than ever.

I know that my level of functioning, while markedly improved, is still not completely restored to normal; this is consistent with all the studies cited in the first part of this report, and it is expected. While I have elected not to explore it thus far, the use of Xyrem in addition to my stimulant therapy remains an option and I may decide to try it sometime in the future. For now though, I am happy with how things are going; I never realized how much sleepiness had become a part of my life until I began living largely without it. Now I only grapple with sleepiness while studying for long periods of time or during long car trips; I have coped with these situations by changing my behaviors, like studying in blocks on separate nights instead of last-minute cramming and taking turns driving during road trips. While I am not at completely normal levels of functioning, my stimulant therapy in combination with behavioral changes has resulted in a dramatic improvement in my psychological state and health status.

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