

Lyndonville News

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Information and Support for the ME/CFS/FM Community
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SLEEP IN CFS

Introduction:

Welcome again to the Lyndonville News, now the 2005 version. I hope that everyone had a good holiday. It goes without saying that persons with ME/CFS/FM are going to take a lot longer to recover from the holidays than healthy persons. Take your time, relax, and remember that the time and energy spent with family and friends is worth the relapse.

I have had good feedback about the definition and name of CFS suggested in the last newsletter, but many found it confusing. I would hope over the coming year that there will be mounting evidence for the concept of post-infectious dysautonomia, evidence like what we will be presenting in the February conference in Japan. I have a hunch that 2005 is going to be a very good year. Well, don't get too excited, I have said that before.

In this issue, I would like to visit the subject of sleep difficulties in CFS. Again, I look forward to your comments via e-mail, and forgive me if I do not answer them all.

Clinical Notes

Sleep Abnormalities in Chronic Fatigue Syndrome

Sleep that does not result in waking refreshed as well as disrupted or fragmented sleep, hypersomnia, and insomnia constitute a significant part of CFS symptomatology. However, despite the symptoms of disturbed sleep being well documented in CFS, important unanswered questions exist. What role does abnormal sleep, if any, play in the symptomatology of CFS, and are sleep abnormalities part of the spectrum of CNS nervous system abnormalities or do they represent a separate, exclusionary condition? In general the medical literature has struggled with these questions, and under the current

diagnostic guidelines, primary sleep disorders such as narcolepsy and sleep apnea are exclusionary conditions for the research diagnosis of chronic fatigue syndrome. Depression, anxiety, pain, immunologic abnormalities, medication use, autonomic nervous system function, along with numerous other variables affect sleep quality, and just as these factors have complicated studies on immune function and emotions, these factors need to be addressed in the research on sleep disorders in CFS.

From a clinical standpoint, the medical provider is faced with the dilemma of what symptoms to treat in an attempt to improve both daily activity and function as well as the quality of life of the patient with CFS. Because of difficulties with both definitions and objective measures, there are few controlled treatment trials in the medical literature to guide us in our decisions. And, until the many basic questions are answered, there will continue to be a dearth of treatment studies. In this brief article I would like to review the role of sleep in CFS as described in selected articles from the literature, and offer some personal observations concerning the importance of treating sleep symptoms in the overall management of CFS.

Published Studies

In 1993, Richard Morriss from the Littlemore Hospital in Oxford and his co-workers published a case control study of twelve patients with CFS who did not have major depression by research criteria. Not surprisingly, CFS patients spent more time in bed (544 min) as compared to controls (465) but slept less efficiently. They woke more frequently and spent more time awake. Seven patients with CFS were diagnosed as having a sleep disorder; four patients had trouble getting to sleep, four had trouble maintaining sleep, and one had hypersomnia. None of the controls studied were diagnosed with a sleep disorder. Those patients with CFS with sleep disorder(s) had greater functional impairment, but no change in psychiatric scores. Moreover, they noted that shortened REM latency, characteristic of major depression, was not present in this group of CFS patients, again suggesting that CFS is distinct from major depression. The authors suggest that sleep disorders may be important in the etiology of chronic fatigue syndrome.

In a 1994 study by Anthony Komaroff and Dedra Buchwald the symptoms of CFS are reviewed in patients from their clinical practices. It was based on the authors' experience with two cohorts of approximately 510 patients with chronic debilitating fatigue. In a separate paper published the same year, Dr. Buchwald performed polysomnography on 59 patients who had sleep pathology suggested from a screening questionnaire. Overall, these patients had an overlap with major depression, but when separated into those meeting, or not meeting CFS criteria, there was little difference in the frequency of sleep disorders. Eighty-two percent of those meeting CFS criteria and 81% not meeting criteria had one or more sleep disorders. Of the whole group, the type of sleep disorder defined was as follows: sleep apnea – 44%; idiopathic hypersomnia – 12%; other disorder of excessive sleepiness – 10%; restless legs – 10%; excessive daytime sleepiness – 10%; narcolepsy – 5%; and other sleep disorders – 5%.

In a paper reviewing immune function in CFS, the relationship between immune activation and abnormal sleep was discussed by Dr. J. M. Mulligan and co-workers at the Beth Israel Deaconess Medical Center in Boston. Immune stimulation is known to affect CNS mediated behaviors such as sleep, and they note that cytokine elevation is found in sleep deprivation. Given the complex relationship between CFS and cytokine abnormalities, a relationship may exist between immune state and degree of sleep abnormalities.

The pediatric literature also notes significant sleep disturbance as a prominent symptom. In one paper comparing children with chronic fatigue syndrome who either met, or did not meet, criteria for primary juvenile fibromyalgia syndrome, one of the few differences between groups was that those children meeting criteria for both CFS and fibromyalgia had more severe sleep symptoms than those children meeting criteria for CFS alone. In a paper studying forty one adolescents, Akemi Tomoda and coworkers looked at the relationship between sleep and circadian rhythm disturbances. On the basis of a daily log of sleep time, all adolescent CFS patients in this study had one or more of the following sleep abnormalities: delayed sleep phase syndrome, non-24 hour sleep-wake syndrome, irregular sleep, or long sleeper. In a study from the Netherlands, Lidewij Knook and co-workers noted that, despite the symptom of unrefreshing sleep, melatonin levels were elevated in adolescents with CFS compared to controls.

Teruhyisa Miike from the department of child development at the Kumamoto Graduate School in Kumamoto Japan with co-workers have been evaluating CFS in children with school refusal. They note that 80% of these children have sleep abnormalities including day/night reversal, decreased NREM and delayed latency of REM sleep, suggesting “deteriorated quality of night sleep.”

In a 2000 study attempting to answer the question of how significant primary sleep disorders are in CFS, Dr. Le Bon and coworkers emphasized that sleepiness and fatigue are not the same and attempted to address the issue with 53 patients from their fatigue clinic in Brussels. They showed a high incidence of primary sleep disorders, 46% in this patient group, and sleepiness was present in only one third of cases.

In a recent study which came as an outgrowth of the Centers for Disease Control population-based study of CFS, Elizabeth Unger and co-workers looked at subjective sleep in 339 patients with CFS. As a population based study, the patients with CFS were identified through telephone screening in Wichita, Kansas, rather than from self report. 81.4 % of patients had an abnormality in at least one sleep factor on the questionnaires utilized. From their data, the authors suggest that CFS patients are fatigued but not sleepy.

In a series of recent papers, Dedra Buchwald’s group at the University of Washington has been examining monozygotic twins discordant for chronic fatigue syndrome, and these studies may change the views that have been built up over the past fifteen years. The sleep studies were conducted for monozygotic twin pairs, one twin healthy, and the other

ill with CFS. The polysomnograms were conducted on the same night, and attention was paid to medications and other possible variables. The great strength of these studies is that the healthy twin is able to serve as a perfectly matched control for age, sex, genetic predisposition and many environmental influences.

In an evaluation of sleepiness using the Epworth Sleepiness and Stanford Sleepiness Scales along with a sleep diary, ill twins were quite different from their healthy siblings with subjectively poor sleep as would be expected. Objectively, polysomnograms were followed the next day with a four-nap multiple sleep latency test. The twenty twin pairs did not differ in either the presence of objective sleep disorders or the multiple sleep latency tests. Thus, CFS twins experience more subjective sleepiness without objective changes suggesting a sleep disorder. The authors offer the suggestion that there may exist an altered circadian rhythm with subjective sleepiness. Alternatively, CFS patients may experience a “heightened perception of sleepiness or may be unable to distinguish fatigue and sleepiness.”

In another paper comparing the subjective and objective measures of sleep the authors note that CFS twins reported that they had slept less hours and were less well rested despite similar objective measures. The authors suggest that CFS twins “suffer from an element of sleep-state misperception.”

In a study examining objective measures of sleep, also in the co-twin group, objective measures by polysomnography were examined for sleep latency, REM latency, sleep efficiency, awakenings, percentages of sleep stages 1 thru 4, percentage of REM sleep, periodic limb movements, leg arousal index, snoring, apnea-hypopnea index, upper airway resistance, and overall arousal. Only one CFS patient had a sleep disorder, sleep apnea. While there were two minor differences, the results of objective measures were remarkably similar for the healthy and CFS twin. “These results do not provide strong evidence for a major role for abnormalities in sleep architecture in CFS.”

Primary or secondary?

The question remains: are the symptoms of CFS due to sleep abnormalities, or are the sleep abnormalities part of the global central nervous system symptomatology of CFS? As can be seen from the studies cited, clarity in this area is still lacking. However, as progress creeps along we can now say a number of things about the relationship between sleep and CFS. First, it is clearly established that the subjective symptoms of unrefreshing and fragmented sleep are clearly an important part of CFS symptomatology. Yet objective measures of sleep pathology are of uncertain significance. With the current diagnostic guidelines, primary sleep disorders are exclusionary conditions for the diagnosis for chronic fatigue syndrome. Yet with some studies showing high frequencies of sleep disorders diagnosed over time, the question remains, are these sleep disorders primary or secondary? Does the presence of excessive daytime sleepiness or sleep apnea on testing that does not respond to CPAP treatment mean that a person cannot be diagnosed with CFS?

While it will take more experience for the academic community to come to a consensus on these issues, I would like to suggest that for the medical provider, the diagnosis of CFS remain clinical. That is, CFS can be diagnosed in patients with the pattern of exhaustion, pain and other symptoms as previously. If during the evaluation, a sleep disorder such as narcolepsy or sleep apnea is found and treatment for that sleep disorder removes the debilitating fatigue, the diagnosis of CFS is no longer valid. But if that treatment does little to improve the overall pattern of symptoms, the clinical diagnosis of CFS remains. In this latter case, the presence of a sleep disorder would be similar to the presence of treated hypothyroidism in that it does not serve to explain the clinical condition. As such, it should not be considered an exclusion in general clinical practice.

Clinical Experience

In general, it has been my experience that aggressive treatment of sleep disorders in patients with CFS has been disappointing. Yet, I also feel that it is one of the most important symptoms to aggressively pursue. The approach is one of common sense. If a patient with CFS identifies insomnia or unrefreshing sleep as one of the most disturbing symptoms present, I would treat this symptom aggressively.

Perhaps the first and most important aspect of treatment is sleep hygiene. Avoidance of stimulants, relaxing with “wind-down” time in the evening, and avoidance of television or computer use before bedtime should be emphasized. The CFS patient should not use the sleeping bed as a place for daytime resting, reading, watching TV or talking on the telephone. As with migraine, attempting to establish a consistent, but not rigid, schedule is also important.

Medications have a role, and most medical providers are very familiar with them in the patient with severe insomnia or fragmented sleep. These medications include tricyclics, trazedone, sedating muscle relaxants, and even benzodiazepines, all of which can help establish sleep to improve the symptom. Yet it has been my experience that while the patient may experience much improved sleep quality, the degree of their activity limitation rarely changes.

Clinically, the patient with CFS is very sensitive to medications which have a role in sleep symptomatology. With doxepin or other tricyclics, for example, the patient will frequently feel drugged in the morning and experience a hangover. I would not consider this a limiting side effect as reduction in the dosage often results in good sleep quality. Sometimes the liquid preparations are useful in that they permit very low doses.

It is important to differentiate those patients who have light, fractured sleep from those who have hypersomnia, as the former usually have more severe activity limitations and are more difficult to treat. Those patients with daytime somnolence and hypersomnia may respond to medications with stimulant properties, and the increased activity during the day may lead to a better quality of sleep at night. However, I no longer even try stimulant

medications in those patients with insomnia. A good rule of thumb to separate these two groups of patients is their ability to tolerate coffee.

It is my feeling that patients with CFS have one or more central nervous system disturbances that causes the sleep symptomatology. Changing the diagnosis from 'CFS' to 'sleep disturbance' because the patient has a disturbance found on a questionnaire or even polysomnography will artificially lower the number of patients who carry the diagnosis of CFS but not result in improved quality of care. For example, in a recent paper on the clinical course of patients with CFS, at two and three years of follow-up, only 21% of the subjects were classified as having CFS. If this were entirely due to improvement of the degree of fatigue and other symptoms, this would be wonderful news. However, in this study, sleep apnea is listed as one of the more common causes of re-classification, yet we have no indication of whether the sleep apnea responded to appropriate treatment. For some clinicians reading this paper it appears that the original diagnosis of CFS was made in error, and that CFS is a benign condition - neither of which may be true. Most clinicians forget that the diagnostic criteria are for research purposes only.

Sleep symptoms should be pursued aggressively, and only if there is a good clinical response should the diagnosis be changed. Too often the patient with CFS hears the medical provider say, "Aha, we have finally found the cause of your symptoms," only to be disappointed when treatment has little or no effect. This treatment failure then encourages alienation of the patient from the medical provider and increases both the frustration and confusion of the patient which, by itself, leads to greater distress.

Agents for the Sleep Disorder Associated with Chronic Fatigue Syndrome

One of the reasons for writing the following information on medications used to treat sleep disorders has been the concern raised about the chronic usage of some medications. Certainly if a person does not have symptoms, they should not take medication. On the other hand, if there are significant or severe symptoms, then taking medications may be a possible recourse. It should be noted that every medicine has side effects and this sheet is not meant to be comprehensive in terms of the side effects with the different medications. This sheet is meant to be informal, to be used by the patients that I see or to be discussed by patients with their physicians. Many physicians would disagree with the statements which I will be making in this information sheet, and this represents merely my impression of how to approach sleep disorders.

The first and central aspect of treating sleep disorders is good sleep hygiene. What this means is having available a comfortable, relaxing place to sleep which should be used only at the time of going to sleep. For example, if a person is tired but is not planning to sleep, they should lie down in a place other than where they go to sleep. This is so that behavioral associations will be connected between going to sleep and the place to sleep. Secondly, the lighting should be appropriate to encourage sleep. Most importantly,

people should avoid stimuli for up to two hours before attempting sleep. This would include medications that are energizing such as coffee and some types of tea, television shows, computer games and other activities which tend to make sleep onset more difficult. For the young persons in my practice with chronic fatigue syndrome, I would suggest that they get very bored for about an hour prior to going to sleep.

For myself, I find that reading a good medical journal frequently will put me to sleep quite nicely. It is unreasonable to think that medications can take the place of good sleep hygiene. Moreover, it is particularly important to establish a regular schedule for sleep, and this is more important for people with chronic fatigue syndrome and fibromyalgia than for the general public. Particularly if there is a sleep phase reversal, people need to force themselves to get up at around 8 o'clock in the morning even if they have to rest thereafter. Exposure to bright light in the category of 2,500 to 3,000 lux for up to 30 minutes in the morning is also sometimes effective to help with the sleep disorder. The consistency of maintaining a standard time to get up and a standard time to go to bed will sometimes help in the achieving of good sleep. The following medications are possible adjuncts to sleep hygiene:

1. Melatonin 3 mg. Melatonin does not require a prescription and is a hormone which may encourage sleep. Taking it 30 minutes prior to attempting sleep is perhaps the best.

2. Diphenhydramine (Benadryl®) 50 mg. This medication is an antihistamine used for allergies and has sedation as a side effect. It tends to be most effective approximately half an hour to 45 minutes after taking it and frequently will initiate sleep without difficulty. Unfortunately, the soporific effect of this medication tends to wear off if used on a chronic basis. This medicine also tends to be helpful if there is congestion, allergies or stuffy nose which interfere with sleep.

3. Cyclobenzaprine (Flexeril®) 10 mg. This medication, which is related to the tricyclic antidepressants is used primarily as a muscle relaxant, and has no antidepressant activity. Again, there is a sedative effect which is noted about 45 minutes after taking it and for some people there will be an excellent degree of both muscle relaxation and sedation, and it can be very useful as a sleep aid.

4. Carisoprodol (Soma®) 350 mg. This medication is also a muscle relaxant but is chemically distinct from cyclobenzaprine mentioned previously. This should not be used in the children under the age of 12. Like all the medications used to initiate sleep, there are persons who will have idiosyncratic reactions and the medication may not be effective.

5. Amitriptyline (Elavil®) 10-75 mg. This medication, as well as doxepin, are tricyclic antidepressants which have a prominent sedative effect. They tend to be useful in helping with sleep and can also have some effect in reducing pain. The pain effect is more pronounced with nortriptyline, however. Should these medications be used, they need to be used in the smallest doses possible, as people tend to experience a hangover. Should

this occur, the dose should be reduced. If people cannot get to sleep and still get the hangover, these medicines will be not useful.

6. Trazodone (Desyrel®) 50-150 mg. Trazodone is one of my most favorite medications for sleep. Again, some will have a hangover and the dose needs to be as low as possible. In general, I would start with a very low dose such as 25 mg and increase it to the point where it is effective. It should taken approximately one-half hour to two hours prior to attempting sleep in order for its usage to be maximized. Some people will get congestion with this medicine which limits its use.

7. Clonazepam (Klonopin®) 0.5 mg. This medication is a benzodiazepine and as such is a controlled substance. Like other benzodiazepines, it enhances GABA activity which is an inhibitory neurotransmitter, so it tends to be effective in treating both seizure disorders and panic disorders. Virtually all people who have chronic fatigue syndrome will have many of the symptoms of panic disorder and that diagnosis can be implied with persons with CFS. In general, I do not like most benzodiazepines for the treatment of sleep. However, Klonopin is very mild and I feel that it can be used even up to long-term if necessary for the treatment of the sleep disorder associated with CFS/fibromyalgia. Other benzodiazepines such as Xanax® and Valium®, I try to avoid. All drugs of this class have the potential to be habit forming, so clonazepam needs to be used cautiously and intermittent use is best.

8. Triazolam (Halcion®) This medication is a very powerful hypnotic and has been associated with inappropriate behaviors. In general, I never use this medication or other short acting benzodiazepines.

9. Zolpidem (Ambien®) 10 mg. This medication is a non-benzodiazepine which is indicated "for short-term use" of sleep disorders, primarily because it has never been studied in long term studies. It is probably safe but should be used with caution. One drawback is that patients wake at three in the morning with it and are unable to get back to sleep, so combining it with a long acting agent is useful.

10. Zaleplon (Sonata®) 10 mg. This is very similar to Ambien. It is in the pyrazolopyrimidine class of medications if that makes anybody feel more reassured. Consider it a clone of zolpidem.

11. Topiramate (Topamax®) 25-100 mg. This medication is an anti-epileptic drug which has prominent sedative effects. Because of the sedation it can be effective for initiating sleep. It has as a side effect the tendency toward weight loss which is a side effect that most people are not particularly annoyed about. However, many patients with CFS have difficulty with this drug as it causes cognitive disturbances. It is finding increased use in the prevention of migraine. In general, it is not a medication that has proven very useful for initiating sleep in CFS and it is rarely used for this purpose.

12. Olanzapine (Zyprexa®) 2.5 mg. This medication is indicated for psychosis. It is also one of the few medications that has been shown to increase stage 3 and stage 4 sleep. As

a result, it tends to be an excellent medication to initiate sleep in CFS. It is effective as an antidepressant as well and may reduce pain, although there are no formal indications. Weight gain is a serious problem. I rarely use it in CFS.

A final note about sleep difficulties. It may be good not to worry about insomnia. You may not need as many hours of sleep as you think you need. One patient told me that they were very disturbed about waking at three AM and not being able to get back to sleep. He finally decided to not worry about it and enjoy the time. He used the hours from three to five am for rest, prayer, meditation, and listening to music. No one ever bothered him during these times, and he came to view these hours not as the nuisance of insomnia, but as constructive time forced upon him by his illness.

Lyndonville Research Group Report

The Lyndonville research group is back in business with two new studies. One is collecting and analyzing data from a follow-up questionnaire on persons who had the onset of CFS twenty years ago when they were either children or adolescents. As nearly everyone with CFS knows, this is not a benign or trivial illness. Fortunately, however, there are a number of persons who recovered completely and we are happy for them. The lingering question is why some recover and some do not.

A second study will be presented as a poster in the conference February 8th in Karawazua, Japan, and it is entitled Muscarinic Acetylcholine Receptor IgA Antibodies in patients with chronic fatigue syndrome. The study compared 25 patients with CFS with 25 healthy persons and the laboratory analyses were performed by Dr. Vojdani at Immunoscience Laboratories for no charge. The results indicate that it is possible to separate patients and controls by the presence of an autoantibody to an acetylcholine receptor. More on this to come, maybe lots more.

Another project is the school nurse education project under the capable leadership of Emily Saxton. So far we have two school nurse lectures lined up. Our thought is that if we can educate school nurses about CFS, it will make the life, and education, of children with CFS much easier.

We are always looking for help in the Lyndonville research group.

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