In this lesson, we review Chronic Fatigue Syndrome & Fibromyalgia. These are important diseases, and we are often asked to disseminate information about them. Our goal is to provide the most current data. This lesson provides 2.00 hours (0.2 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-02-011-H01.
Pharmacists completing this lesson by November 30, 2005 may receive full credit. (November 30, 2004 for California.)

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

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The objectives of this lesson are such that upon completion the participant will be able to:

1. List the factors that may contribute to CFS.
2. Describe the symptoms of CFS.
3. State the various approaches recommended in the management of CFS.
4. Define FM, & describe the American College of Rheumatology criteria for classification.
5. List the clinical overlap as well as the differences between CFS & FM.

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For over a century, observant physicians have encountered an illness characterized by severe disability, physical and mental fatigue, pain that worsens with activity, unexplained by usual biomedical diagnosis, and often associated with stress and psychological factors. In the past, different diagnostic labels such as neurasthenia, hyperventilation syndrome, myalgic encephalomyelitis, chronic mononucleosis and post-viral fatigue syndrome were coined to describe these symptoms. Chronic fatigue syndrome (CFS) is a relatively new diagnostic term that is used to describe this illness. The literature is replete with unexplained clinical conditions such as CFS, fibromyalgia, multiple chemical sensitivity, myofacial pain, temporomandibular disorders and Gulf War illness. All share some demographic, clinical and psychological features. In the scope of this lesson emphasis will be placed on CFS and fibromyalgia. Additionally, the overlap among these clinical conditions will be discussed.

CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome is a common debilitating disorder characterized by physical and mental fatigue, neuropsychological complaints and inconsistent demonstration of laboratory abnormalities. The 1998 definition by the Center for Disease Control and Prevention indicates that the disorder is present when a clinically evaluated, unexplained, persistent or relapsing fatigue of new onset occurs as a result of exertion. The fatigue is not relieved by rest, and four or more of the following symptoms persist or recur for a minimum duration of six consecutive months. Those symptoms are: impairment of short-term memory or concentration, sore throat, tender cervical or axillary nodes, muscle pain, multi-joint pain without redness or swelling, headache, sleep disorders and post-exertion malaise lasting for approximately 24 hours.

Symptoms

The symptoms are elusive, baffling, and can be associated with many existing diseases. The fact that the patient’s main complaints are fatigue and pain, coupled with lack of distinct laboratory results, gives few diagnostic clues. The symptoms usually occur suddenly in a previously active individual. The patient usually complains of persistent intense fatigue, inadequate concentration, and muscle and joint pain. These are aggravated by minor physical or mental stress. Abandonment of social activities and work is not uncommon. The symptoms may occur following febrile episode or flu-like illness, viral infection or some other acute stress. These factors are believed to be the triggering event. Once these incidences subside, the patient experiences unbearable fatigue.

Within several weeks, other features emerge. The patient may experience episodes of depression, sleep disturbances, tender lymph nodes, feverishness, and lassitude. CFS may be predisposed by lifestyle, work stress, personality, viral infections, and life events. It may be perpetuated by cerebral dysfunction, sleep disorders and depression. One hundred percent of patients with CFS reported fatigue; 90% difficult concentration; 90% headache; 85% sore throat; 80% tender lymph nodes; 80% muscle aches; 75% joint aches; 75% feverishness; 70% difficultly sleeping; 65% psychiatric problems; 55% allergies; 40% abdominal cramps, 20% weight loss; and, 10% rash. Other reported symptoms such as rapid pulse, weight gain, chest pain, and night sweats ranged from 5% - 10%.
Chronic fatigue symptoms are twice as common among women than men, and occur primarily in individuals 25–45 years of age. However, CFS seems to affect patients at any age. Even though causes occur sporadically, during the last seventy years, a number of outbreaks have taken place in the U.S., Iceland and the U.K. Some clinicians attributed these to environmental or infectious factors, none of which has been confirmed. The difficulty in determining the prevalence of CFS is due to lack of consistent diagnostic laboratory results, lack of precise definition of the disorder and lack of compelling evidence of abnormal neuromuscular fatigability. Most of the prevalence studies were examined by general practitioners or family physicians. In a recent study, it was estimated that the prevalence as recognized by general practitioners is 112 cases per 100,000; whereas, if the original case definition by the CDS is followed, the prevalence of the disorder is estimated to be 2 to 7 individuals per 100,000 people. In another study conducted on 28,673 adults who reside in Chicago, it was found that CFS occurred in approximately 0.42% of the sample. In a study conducted on Gulf Registry Veterans, the findings were that 15.75% of veterans have met the definition of CFS as stated by the CDC in 1994. About 17% of Dutch military personnel who served as peace keepers in 1992 and 1993 reported forgetfulness, difficulty concentrating and fatigue. Those symptoms were also reported by Gulf War veterans.

Pathogenesis

The etiology of CFS is unknown. There are many conditions that cause fatigue that is experienced by normal individuals. However, some individuals will have this fatigue for a longer duration or at a great intensity than others. It has been postulated that the contributing factors for CFS include: infection, chemical intolerance, psychiatric disorders and irregularity in the hypothalamic-pituitary-adrenal relationship and immunologic disturbances. Infection: Some investigators have postulated that CFS occurs as post-infections, especially those caused by viruses such as lymphotropic herpes viruses, retroviruses, and enteroviruses. Following the acute phase of herpes virus in children, the infection becomes latent. It has been reported that there is an increased level of herpes virus antibody in patients suffering from CFS. Additionally, a decrease in cellular immune responses was observed in such patients. It was concluded that reactivation of the virus may contribute to the pathogenesis of CFS. Titers of antibody to measles virus, rubella virus, and coxsackievirus B may act as a precipitating factor to CFS. However, there is no evidence that these viruses play a role in the long-term characteristics.

The spirochete, *Borrelia burgdorfei*, that was identified as the Lyme disease microorganism, may play a role in precipitating CFS. It was reported that persons who tested positively for the presence of *Borrelia* antibody and who had never suffered from Lyme disease or neuroborreliosis, manifested significantly more CFS symptoms and weakness than individuals who showed seronegative results.

The Epstein-Barr (EB) virus is a herpes virus that in some parts of the world is acquired in early childhood. The vast majority of children in these regions who are over four years of age have acquired antibodies against EB. The infection in early childhood is asymptomatic. However, if the infection appears in early adulthood, which often takes place in the U.S., the individual will develop infectious mononucleosis. Incidence of this condition usually occurs between the ages of 15 to 25 years. The symptoms are sore throat, fever, swollen lymph nodes in the neck and fatigue. These symptoms subside within a few weeks, after which the patient acquires immunity. The EB virus is speculated as a cause of CFS. It has been found that persons who suffered from CFS have a high antibody level of EB virus.

Chemical Sensitivity: It has been estimated that 10 – 20% of the population are affected by chemical intolerance that may occur as an isolated symptom causing little or no disability. However, chemical intolerance may co-exist with other chronic symptoms such as pain, weakness, and stress, and may result in severe functional disability. It often is referred to as multiple chemical sensitivity (MCS). This syndrome is frequently placed in a group of chronic diseases along with CFS, fibromyalgia, and Gulf War illness. It is not known whether MCS has a physiological or psychological etiology. However, it has been shown that there is clinical overlap between it and CFS and fibromyalgia. In 1990-91, the U.S., along with many countries, deployed over 700,000 troops in the Persian Gulf region. Following
the end of the war, approximately 45% of these veterans, and 15% of the non-deployed veterans, experienced symptoms such as muscle and joint pain, fatigue, headache, memory loss and gastrointestinal disturbances. These symptoms became known as the Gulf War illness. It was experienced by veterans from both the U.S. and the U.K. After extensive medical testing, it was concluded that these complaints were not a result of a single disorder, but rather a cluster of symptoms and syndromes similar to CFS and fibromyalgia. While many studies showed that there is no connection between environmental exposure and the occurrence of these symptoms, one study has identified a single environment that could have triggered this illness. That study has identified a review of vaccinations administered to the U.K. troops as a possible triggering mechanism.

**Depression:** Psychiatric disorders, such as depression, appear to play a role in CFS. It is estimated that 20 – 40% of persons with CFS have mood disorders such as depression, or anxiety disorders. Some investigators contend that psychiatric coexistence with CFS is similar to other chronic conditions. Others believe that a relationship exists between depression and CFS, and that prevalence of depression in CFS is higher than that seen in other chronic illnesses. However, it is known that psychological factors play an important role in the transition from acute pain to chronic pain, and even disability. Aggravating factors such as job loss, financial difficulties and social problems can cause increased stress, and can intensify pain, probably by interrelated physiologic and psychological mechanism. Some clinicians have postulated that CFS is essentially a psychiatric disorder. However, the majority of individuals with CFS are of the opinion that their condition is the result of an organic disease process and disagree with those who suggest that it is psychological in origin or psychiatric in nature. Patients often state that a psychiatric designation to their symptoms gives the impression that their condition is unreal and that they are responsible for developing it.

**Endocrine System Irregularities:** It has been speculated that a reduction in the production of corticotropin-releasing hormones in the hypothalamus may contribute to CFS. Patients with CFS have shown lower mean serum cortisol concentrations than controls, and levels of adrenocorticotropic hormone (ACTH) were higher in the presence of CFS. It was concluded that these neuroendocrine irregularities may contribute to fatigue, weakness and mood changes.

**Immunologic Disturbances:** Immune disturbances may play a role in causing CFS. These patients have shown an increased number of activated T lymphocytes, including cytotoxic T cells. Additionally, the level of proinflammatory cytokines has been found to be higher than normal. The immune cell function of CFS patients is inadequate, since the natural killer cell cytotoxicity (NKCC) is low, immunoglobulin, in particular IgG1 and IgG3, are deficient, and lymphocyte response to mitogens in vitro is weak. The immune disturbances in CFS can be associated with irregularities in physiological and psychological function, as well as with activation of latent viruses or other pathogens. Furthermore, they can result in perpetuation of CFS with remission and flare-up cycles. Some patients with Gulf War illness have demonstrated a T-helper type-2 predominance. These immune characteristics do not appear in all patients, and none are specific for CFS. Therefore, they are not considered diagnostic.

**Diagnosis**

Physical examination and laboratory tests must be conducted in order to rule out other conditions that may cause similar symptoms. There are no laboratory tests that can confirm CFS or determine its severity. The fact that CFS is a constellation of symptoms, with no distinctive pathogenomic characteristics, makes diagnosis by exclusion the only way to suspect or confirm its presence. Abnormal physical symptoms such as swollen or tender lymph nodes along with headache, and fatigue, should not be a definite indication of the presence of CFS. Lymphadenopathy requires investigation of the course of such symptoms. Likewise, the sensation of feverishness should be investigated to determine its etiology. Many of the symptoms that accompany CFS may be associated with chronic ill health. Laboratory tests that are recommended include: full blood count, erythrocyte sedimentation rate, urea and electrolytes, thyroid function tests, urinalysis for protein and tests for blood sugar. Other tests that can be helpful are Epstein-Barr serology, chest X-ray film, rheumatoid factor, and serological testing for toxoplasmosis or HIV.
There is no single treatment for CFS, and there is no definite evidence as to the effectiveness of drug therapy, because the exact cause has not been identified. A thorough history is essential in addressing the cause and management. Emphasis should be placed on the following elements: somatic, psychological and social problems; nature of symptoms, especially fatigue; changes in life, activity and sleep, and associated distress; onset of symptoms and their course. A complete physical examination should follow. And, finally, while assessing the case, differential diagnosis should be considered.

It is important to obtain a detailed description of the complaint of fatigue, duration and effect on activity. The fatigue associated with CFS usually consists of a deep feeling of lack of energy that is aggravated by exertion. Differentiation should be made between sleepiness and lack of energy. Aggravation of fatigue appears to be due to central causes rather than muscular ones. According to the current definition, the fatigue must be more than six months in duration, and must impair activity. Somatic symptoms such as muscle pain, sore throat, and tender lymph nodes may be associated with CFS. However, a long list of somatic complaints may indicate the likelihood of psychiatric disorders. A detailed sleep history is important, because sleep disturbances may lead to the development of symptoms. If present, sleep disturbances should be treated. On the other hand, excessive time in bed, which is often indicated by patients with CFS, can create similar consequences like sleepiness. It is believed that persistent rest as a method of managing symptoms can lead to more problems than it solves. As a target for treatment interventions, a balance should exist between rest, activity, sleep and exercise.

Cognitive disturbances such as impaired concentration and memory are frequently stated as a major complaint by patients. However, neuropsychological testing reveals no memory disorders.

Family history of depression and anxiety disorders, evidence of early trauma, including physical and sexual abuse, may give a clue in the diagnosis and treatment.

Once other illnesses are excluded, it is essential that a long-term strategy be established to assist in the management of CFS. First, the patient should be assured that the complaints are taken seriously. Most patients with CFS are convinced that their symptoms are caused by an organic disease process and resent the notion that the symptoms are due to psychological or psychiatric causes. The patient should never be told that the symptoms are imaginary or unreal. Statements such as, “there is nothing wrong with you,” “CFS is not a real illness,” or, “it is all in your head,” are not helpful in treating the patient. Instead, the patient should be educated about CFS and the factors that are believed to trigger the disease, its potential effect on the patient’s physical, psychological and social well being, and its prognosis. Second, regular assessment is helpful in keeping abreast of any changes that may take place. Family involvement in the patient’s rehabilitation is helpful. Third, lifestyle modification may be necessary to prevent relapse and provide symptomatic relief. For example, consumption of caffeine may interfere with sleep. Total rest and frequent lying in bed and sleeping for long periods can compound the symptoms, and can create the self-image of being physically impaired and worthless. A regular sleeping pattern and limiting the time spent in bed should be adopted. Simple exercise programs should be encouraged, and strenuous ones should be avoided to prevent exacerbation of exhaustion. It is important that the patient be warned that resumption of activity may cause some initial discomfort. Fourth, many of the symptoms of CFS may be relieved by using medications. The use of nonsteroidal anti-inflammatory medications alleviate headaches, muscular and joint pain and feverishness. Decongestants may provide relief from rhinitis and sinusitis. Antidepressants, particularly the non-sedating ones, are frequently recommended in order to improve the mood and disturbed sleep, thereby alleviating fatigue. A change in mood no matter how slight, may improve the patient’s self-sufficiency and appreciation of his or her surroundings. Some clinicians advocate the use of antidepressants only for patients who are clearly depressed. Throughout the years, many treatments have been attempted, but very few have been properly evaluated. Numerous therapies are spread widely among persons, some of which are traditional and, others are non-traditional. Patients should be discouraged from attempting unproven treatments that may be expensive or even harmful, and could
distract the patient from formal treatment. The use of the antiviral drug Acyclovir, antifungals, intramuscular liver extract-folic cyanocobalamin, magnesium injections, immunoglobulin infusions, and fish oil, have all been shown to be of no value.

**FIBROMYALGIA**

Fibromyalgia (FM) is a common, nonarticular, rheumatic disorder that is characterized by pain, paresthesias, and stiffness in muscle and soft tissue surrounding joints. Additionally, physical fatigue and widely distributed tender point sites may be involved. Even though the terms fibromyalgia and fibromyositis are sometimes used interchangeably, they possess similarities as well as differences. Fibromyalgia indicates the presence of pain in the fibrous connective tissue of the muscle, tendons, and ligaments; whereas, the term fibromyositis denotes the presence of inflammation in the muscular tissue. In some cases, these two disorders may coexist and form what is known as muscular rheumatism. To fulfill the criteria for FM, which was established in 1990 by the American College of Rheumatology, a person must have a widespread chronic pain in the left side of the body, in the right side of the body, above the waist, below the waist and in the axial skeleton. In addition, the person should experience pain on digital palpitation in several of the following tender sites:

1. Occiput: bilateral, at the suboccipital muscle insertion
2. Low cervical: bilateral, at the anterior aspect of the intertransverse spaces at C5-7
3. Trapezius: bilateral, at the midpoint of the upper border
4. Supraspinatus: bilateral, at the origin, above the scapular spine near the medial border
5. Second rib: bilateral, at the second costochondral junction, just lateral to the junction on the upper surface
6. Lateral epicondyle: bilateral, 2 cm distal to the epicondyle
7. Gluteal: bilateral, in the upper outer quadrant of the buttock in the anterior fold of muscle
8. Great trochanter: bilateral, posterior to the trochanteric prominence

A tender point is defined as an anatomic site where an individual feels pain upon digital palpitation, with an approximate pressure of 4 kilograms.

**Epidemiology**

Fibromyalgia affects both men and women at any age, even children. It has been estimated that 3.4% of women and 0.5% of men in the United States have FM. Prevalence among women increases to 7.4% between the ages of 70 to 79 years. Some rheumatology clinics have reported that FM was diagnosed in 20% of patients.

**Etiology**

Although the precise cause of FM has not been determined, several causative mechanisms have been postulated. Poor sleep, which results in waking up tired, has been implicated as a factor. Patients with FM experience nonrestive sleep, probably due to disruption of normal stage 4 sleep (non-rapid eye movement sleep (NREM)). It has been found that patients with FM may be deficient in serotonin, a neurotransmitter that plays a role in pain and NREM sleep. Even though pain is experienced in the musculotendinous area, structural and physiological studies revealed no abnormalities. Some reports indicated that the level of somatomedin C, a major mediator of the anabolic function of growth hormone and essential for muscle repairs, is lower in FM patients than normal persons. This low level of somatomedin may impair the muscular healing process and contribute to pain following excretion. Psychological disorders may play a role in precipitating FM. Mental stress, trauma, hypothyroidism, and viral or bacterial infection have also been implicated.
Symptoms and Signs

Symptoms begin gradually, and the patient complains of generalized, diffused pain in the trunk, hip and shoulder. In addition, some patients may experience muscle weakness and pain, especially after very mild exertion. If the pain is limited to local sites, the symptoms are usually abrupt and acute. Tenderness may be localized to certain anatomic sites. Inflammation is usually absent in FM, but if present, it may indicate the existence of an underlying condition. Patients with FM may complain of back pain that radiates to the buttock, while others may experience stiffness in the neck and shoulders. Some degree of pain is ever present, and is usually described as burning or stiffness, soreness or aching. Stiffness is noticed on arising in the morning or after considerable inactivity, but pain diminishes later on in the day. The most common complaint beside pain is fatigue. Stress, anxiety or exposure to damp or cold weather may exacerbate the symptoms. Conversely, warm weather and a relaxing vacation may improve the symptoms.

Diagnosis

Fibromyalgia is usually diagnosed by the exclusion of other systemic diseases that may have similar symptoms such as rheumatoid arthritis, polymyositis, polymyalgia rheumatica, and connective tissue diseases. Fulfillment of the American College of Rheumatology criteria is useful in the diagnosis of FM. Fibromyalgia may coexist with other muscular and connective tissue diseases, and its symptoms may clinically overlap with those of CFS. Since joint and muscle examination are normal in FM, the presence of any muscle or joint abnormality should be a clue to co-existence of another disorder.

Treatment

Fibromyalgia may disappear spontaneously by overcoming the illness-perpetuating factors. Left untreated, FM may become a chronic or recurring condition. A good clinician-patient relationship is an important initial step for obtaining symptomatic relief. It is essential that the patient become cognizant of the nature of the disease, as well as the factors that may have predisposed them to develop the disorder. The patient should be reassured that it can be managed. Lifestyle change is important. Stretching exercises, improved sleep, stress management and relaxation are recommended. Local measures such as the application of heat, counterirritant creams, or injection of corticosteroids or local anesthetic at the tender point site will provide temporary relief. The intake of 650 mg of aspirin 3 to 4 times daily (if tolerated) or NSAIDs may provide relief. Opiate analgesics are not recommended. The use of glucocorticoids has been shown to be of no value. To help achieve a restorative sleep, medications such as doxepin (10-25 mg), amitriptyline (10-25 mg) or a pharmacologically similar drug may be used. Depression and/or anxiety may be treated with appropriate drugs, appropriate counseling, or support groups.

OVERLAP AMONG RELATED CONDITIONS

The previous discussion clearly revealed that CFS and FM share many unexplained features such as fatigue, pain, inconsistent demonstration of laboratory abnormalities and association with stress and psychosocial factors. There are other clinically unexplained conditions that possess certain symptoms that overlap with CFS and FM. These include: temporomandibular disorder, multiple chemical sensitivity, irritable bowel syndrome (IBS) and tension headache. These shall be reserved for discussion in future lessons.

It has been reported that up to 70% of patients with FM meet the criteria for CFS, and, conversely, that 35% to 70% of patients with CFS have FM. Additionally, 32% to 80% of patients with FM, 58% to 92% of patients with CFS and 64% of patients with temporomandibular disorder also have IBS. Furthermore, 32% to 65% of those with IBS meet the criteria for FM.
Conclusion

Chronic fatigue syndrome and FM are disorders that share features, including fatigue, pain, disability, and stress. It is important for pharmacy practitioners to be aware of these conditions. They are actual diseases, and awareness leads to better treatment and monitoring.

References

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1. Relevance of topic to practice. 1 2 3 4 5 6 7
2. Author’s ability to communicate. 1 2 3 4 5 6 7
3. Author’s knowledge of topic. 1 2 3 4 5 6 7
4. Appropriateness of topic. 1 2 3 4 5 6 7

5. Do you have any further comments about this lesson? ______________________________________________________________________
_________________________________________________________________________________________________________________________

Please Select the Most Correct Answer

1. Which is not a symptom of CFS?
   A. Sore throat
   B. Impairment of short-term memory or concentration
   C. Hypotension
   D. Muscle pain

2. CFS:
   A. Is most common in women
   B. Is precisely diagnosed by laboratory examination
   C. Affects patients older than 65 only
   D. Is an imaginary disorder

3. Which of these is not considered a contributing factor to CFS?
   A. Infection
   B. Psychological disorders
   C. Immunologic disturbances
   D. Heredity

4. Which statement is incorrect regarding treatment of CFS?
   A. Drug therapy is the only treatment of choice for CFS
   B. Patients should never be told “there is nothing wrong with you”
   C. A regular sleep pattern & limiting time spent in bed should be adopted
   D. Therapies like magnesium injection, fish oil, immunoglobulin infusion & acyclovir are of no value

5. Which of the following is NOT a postulated mechanism for causing FM?
   A. Non-rsive sleep
   B. Excessive amounts of the neurotransmitter serotonin
   C. The level of somatomedin C is lower in FM than in normal persons
   D. Mental stress & trauma

6. Fibromyalgia:
   A. Is an inflammatory condition that affects the muscles
   B. Is characterized by pain in the fibrous connective tissue of the muscle, tendon & ligaments
   C. Is confirmed if the patient experiences pain in 5 tender point sites or less
   D. Never affects children

7. Which of the following is an incorrect statement regarding FM?
   A. Inflammation of the muscles is present in FM
   B. Stiffness is usually noticed upon arising in the morning
   C. Exposure to damp & cold weather may exacerbate the condition
   D. Symptoms usually begin gradually & the patient complains of generalized pain

8. Diagnosis of FM may be achieved via:
   A. X-ray film
   B. Serological examination
   C. Exclusion of other systemic diseases having similar symptoms
   D. None of these

9. Which treatment has been shown to be of no value in relieving FM symptoms?
   A. NSAIDs
   B. Local application of heat
   C. Doxepin
   D. Glucocorticoids

10. Which disorder has symptoms that may not clinically overlap with CFS?
    A. IBS
    B. FM
    C. Anemia
    D. Temporomandibular disorder
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