REVIEW ARTICLE

Chronic fatigue syndrom and its treatment – psychiatric view

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Abstract

Chronic fatigue syndrome (CFS) is a specific clinical condition that characterises unexplained disabling fatigue and a combination of non-specific accompanying symptoms for at least 6 months, in the absence of a medical diagnosis that would otherwise explain the clinical presentation. Consequences of CFS found include social isolation and stigmatization, physical inactivity, psychological disturbances and a reduced quality of life. Plausible mechanism for the development of CFS is based on loss of immunological tolerance to the vasoactive neuropeptides following infection, significant physical exercise or de novo. Considerable evidence points towards a prominent role for central nervous system (CNS) mechanisms in the pathogenesis of CFS. Patients with CFS are described as perfectionist, conscientious, hardworking, somewhat neurotic and introverted individuals with high personal standards, a great desire to be socially accepted and with a history of continuously pushing themselves past their limits. Fewer than 20% of persons with CFS have been diagnosed and treated. Graded exercise therapy and cognitive behaviour therapy appeared to reduce symptoms and improve function based on evidence from RCTs.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a heterogeneous disorder with unknown pathogenesis and etiology, characterized by disabling fatigue, difficulty in concentration and memory, and concomitant skeletal and muscular pain. CFS is a debilitating condition with no known cause or cure. Main characteristic is medically unexplained persistent or relapsing fatigue. It has a poor prognosis and serious personal and economic consequences. CFS is associated with a high use of health care services (Scheeres *et al* 2008).

The figures of prevalence are various. The estimated worldwide prevalence of CFS is 0.4–1% and it affects over 800,000 people in the United States and approximately 240,000 patients in the UK (Lorusso *et al* 2009). Bates *et al* (1993) wanted to determine the prevalence of unusual, debilitating fatigue and the frequency with which it was associated with CFS or other physical or psychological illness in an outpatient clinic population. The point prevalences of CFS were 0.3%, 0.4% and 1.0% using the Centers for Disease Control and Prevention, British, and Australian case definitions, respectively. Maquet *et al* (2006) in their systematic review indicated, that the prevalence of chronic fatigue syndrome has ranged from 0.2% to 0.7% in the general population.

DIAGNOSIS

Chronic fatigue syndrome (CFS) is a specific clinical condition that characterises unexplained disabling fatigue and a combination of non-specific accompanying symptoms for at least 6 months, in the absence of a medical diagnosis that would otherwise explain the clinical presentation. Syndrom is associated with phys-

ical and mental disturbances such as headache, arthralgia, myalgia, memory impairment, sore throat and tender lymph nodes (Appel *et al* 2007). Other common symptoms include post-exertional malaise; cognitive difficulties, with impaired concentration; unrefreshing sleep; and mood changes (Gur & Oktayoglu 2008). There are no laboratory tests available to underpin the diagnosis of CFS; the diagnosis is made solely on the basis of clinical criteria (Lieb *et al* 1996).

For CFS diagnosis, it is required to exclude psychiatric diseases which could cause chronic fatigue. Despite remarkably different diagnostic criteria, CFS and fibromyalgia (FM) have many demographic and clinical similarities (Buchwald 1996).

DISABILITY AND HEALTH CARE USE

Longitudinal studies suggest that some people affected by chronic fatigue syndrome improve with time but that most remain functionally impaired for several years. The Medical Outcomes Study Short-Form General Health Survey (SF-36) is an instrument that has been widely used in outpatient populations to determine functional status. Buchwald *et al* (1996) described the usefulness of the SF-36 in CFS patients and made the study to determine if subscale scores could distinguish patients with CFS from subjects with unexplained chronic fatigue (CF), major depression (MD), or acute infectious mononucleosis (AIM), and from healthy control subjects (HC). The study included 185 patients with CFS, 246 with CF, 111 with AIM, and 25 with MD. There were 99 HC subjects. A strikingly consistent pattern was found for the physical functioning, role functioning, social functioning, general health, and body pain subscales, with the lowest scores in CFS patients, intermediate scores in AIM patients, and the highest scores in the HC subjects. The CFS patients had significantly lower scores than patients with CF alone on the physical functioning, role functioning, and body pain subscales. The emotional functioning and mental health scores were worst among those with MD. The presence of fibromyalgia, being unemployed, and increasing fatigue severity all were associated with additional functional limitations across multiple functional domains, with increasing fatigue appearing to have the greatest effect. Patients with CFS and CF have marked impairment of their functional status. The severity and pattern of impairment as documented by the SF-36 distinguishes patients with CFS and CF from those with MD and AIM, and from HC, but does not discriminate between CF and CFS.

Ross *et al* (2004) made systematic review on disability and CFS of English-language literature published between January 1, 1988, and November 15, 2001. Of 3840 studies identified, 37 reported employment status and some measure of mental or physical impairment associated with disability. Most patients with CFS in these studies were unemployed. In 22 studies, the employment status of control subjects was also available. Only depression seemed to be associated with unemployment in patients with CFS. No other measurable impairment seemed to be consistently associated with disability or work outcomes. Only cognitive behavior therapy, rehabilitation, and exercise therapy interventions were associated with restoring the ability to work.

ETIOPATHOGENESIS

The exact ethiology is still unknown. Several models were proposed to explain its etiology including chronic infection, endocrine dysfunction, autonomic imbalance, depression, decreased immunity states and an aberrant reaction to infection (Appel *et al* 2007). CFS is mostly associated with post-infection sequelae although ongoing infection is unproven (Staines 2004). Immunological aberration is likely and this may prove to be associated with an expanding group of vasoactive neuropeptides in the context of molecular mimicry and inappropriate immunological memory. Plausible mechanism for the development of CFS is based on loss of immunological tolerance to the vasoactive neuropeptides following infection, significant physical exercise or denovo. It is proposed that release of these substances is accompanied by a loss of tolerance either to them or their receptor binding sites in CFS. Such an occurrence would have predictably serious consequences resulting from compromised function of the key roles these substances perform. All documented symptoms of CFS are explained by vasoactive neuropeptide compromise, namely fatigue and nervous system dysfunction through impaired acetylcholine activity, myalgia through nitric oxide and endogenous opioid dysfunction, chemical sensitivity through peroxynitrite and adenosine dysfunction, and immunological disturbance through changes in immune modulation. Perverse immunological memory established against these substances or their receptors may be the reason for the protracted nature of this condition (Staines 2004; 2006). Immunological aberration may prove to be associated with certain vasoactive neuropeptides (VN) in the context of molecular mimicry, inappropriate immunological memory and autoimmunity. The pathophysiological mechanism of CFS is also unclear. The current concept is that CFS pathogenesis is a multifactorial condition. Several mechanisms have been suggested to play a role in CFS, such as excessive oxidative stress following exertion, immune imbalance characterized by decreased natural killer cell and macrophage activity, immunoglobulin G subclass deficiencies (IgG1, IgG3) and decreased serum concentrations of complement component. Autoantibodies were also suggested as a possible factor in the pathogenesis of CFS (Bassi *et al* 2008). Recent studies indicate that anti-serotonin, anti-microtubule-associated protein 2 and anti-muscarinic cholinergic receptor 1 may play a role in the pathogene-

sis of CFS. It has been demonstrated that impairment in vasoactive neuropeptide metabolism may explain the symptoms of CFS. Various studies have sought evidence for a disturbance in immunity in people with CFS. An alteration in cytokine profile, a decreased function of natural killer (NK) cells, a presence of autoantibodies and a reduced responses of T cells to mitogens and other specific antigens have been reported (Lorusso *et al* 2009). No convincing evidence was found to support any of the suggested pathogenic mechanisms. The current concept is that CFS pathogenesis is a multi factorial condition in which an infective agent cause an aberrant immune response characterized by a shift to Th-2 dominant response (Appel *et al* 2007). Vaccination is used in order to stimulate the immune system to induce a persistent immunity against the favorable antigens. Several syndromes that contain chronic fatigue as one of their symptoms, such as "Gulf war syndrome" and macrophagic myofasciitis were related to vaccinations.

Neuroimaging findings

An increasing amount of neuroimaging evidence supports the hypothesis that chronic fatigue syndrome patients have structural or functional abnormalities within the brain. Moreover, some neurotrophic factors, neurotransmitters and cytokines have also been evaluated in order to elucidate the mechanism of abnormal neuropsychic findings in chronic fatigue syndrome (Chen *et al* 2008).

Abnormalities of hypothalamic-pituitary-adrenal axis

Abnormalities of the biological stress response (hypothalamic-pituitary-adrenal axis and the autonomic nervous system) have been identified in chronic fatigue syndrome (CFS)(Glass *et al* 2004). Many studies of patients with long-standing chronic fatigue syndrome (CFS) have found mild hypocortisolism, heightened negative feedback and blunted responses to challenge (Tanriverdi *et al* 2007). However, recent prospective studies of high-risk cohorts suggest that there are no HPA axis changes present during the early stages of the genesis of fatiguing illnesses (Cleare 2004). Some evidence is linked to symptom production or persistence (Cleare 2003). There is evidence for heightened negative feedback and glucocorticoid receptor function and for impaired ACTH and cortisol responses to a variety of challenges. However, there is no evidence for a specific or uniform dysfunction of the HPA axis. Studies assessing GH, dehydroepiandrostenedione and its sulfate, melatonin, leptin, and neuroendocrine-monoamine interactions are also existed. There is some evidence from these studies to suggest alterations of dehydroepiandrostenedione sulfate function and abnormal serotonin function in CFS, but whether these changes are of functional importance remains unclear.

One theory about the aetiology of this hypocortisolism is that it occurs late in the course of CFS via factors such as inactivity, sleep disturbance, chronic stress and deconditioning. Roberts *et al* (2009) aimed to determine whether therapy aimed at reversing these factors – cognitive behavioural therapy – could increase cortisol output in CFS. There was a significant clinical response to CBT, and a significant rise in salivary cortisol output after CBT. Authors concuded that hypocortisolism in CFS is potentially reversible by CBT. Given previous suggestions that lowered cortisol may be a maintaining factor in CFS, CBT offers a potential way to address this.

Crofford *et al* (2004) evaluated and compared the basal circadian and pulsatile architecture of the HPA axis in groups of patients with FMS, CFS, or both syndromes with individually matched control groups. Forty patients with either FMS (n = 13), FMS and CFS (n = 12), or CFS (n = 15) were matched by age (18–65), sex, and menstrual status to healthy controls. Blood was collected from an intravenous line every 10 min over 24 h for analysis of ACTH and cortisol. There was a significant delay in the rate of decline from acrophase to nadir for cortisol levels in patients with FMS. Elevation of cortisol in the late evening quiescent period was evident in half of the FMS patients compared with their control group, while cortisol levels were numerically, but not significantly, lower in the overnight period in patients with CFS compared with their control group. Authors conclude that the pattern of differences for basal circadian architecture of HPA axis hormones differs between patients with FMS and CFS compared to their matched control groups. The abnormalities in FMS patients are consistent with loss of HPA axis resiliency.

Biogenic amines

Tryptophan is the precursor for the neurotransmiter 5-hydroxytryptamine (5-HT), which is involved in fatigue and sleep. It is present in bound and free from in the blood, where the concentration is controlled by albumin binding to tryptophan. An increase in plasma free tryptophan leads to an increased rate of entry of tryptophan into the brain. This should lead to a higher level of 5-HT which may cause central fatigue (Castell *et al* 1999). Increased plasma free tryptophan leads to an increase in the plasma concentration ratio of free tryptophan to the branched chain amino acids (BCAA) which compete with tryptophan for entry into the brain across the blood-brain barrier. The plasma concentrations of these amino acids were measured in chronic fatigue syndrome patients (CFS) before and after exercise (Castell *et al* 1998). In the CFS patients, the pre-exercise concentration of plasma free tryptophan was higher than in controls but did not change during or after exercise. This might indicate an abnormally high level of brain 5-HT in CFS patients leading to persistent fatigue. In the control group, plasma free tryptophan was increased after maximal exercise, returning towards baseline levels 60 min later. The apparent fail-

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ure of the CFS patients to change the plasma free tryptophan concentration or the free tryptophan/BCAA ratio during exercise may indicate increased sensitivity of brain 5-HT receptors, as has been demonstrated in other studies (Cleare *et al* 1995).

Postural ortostatic tachycardia

The purpose of Inbar *et al* (2001) investigation was to characterize the physiological response profiles of patients with CFS, to an incremental exercise test, performed to the limit of tolerance. Fifteen patients (12 women and three men) who fulfilled the case definition for chronic fatigue syndrome, and 15 healthy, sedentary, age- and sex-matched controls, performed an incremental progressive all-out treadmill test (cardiopulmonary exercise test). As a group, the CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group. At similar relative submaximal exercise levels (% peak VO_2), the CFS patients portrayed response patterns (trending phenomenon) characterized, in most parameters, by similar intercepts, but either lower (VCO_2, HR, O_{2pulse}), V_E, V_T, $PETCO_2$) or higher (B_f, V_E/VCO_2) trending kinetics in the CFS compared with the control group. It was found that the primary exercise-related physiological difference between the CFS and the control group was their significantly lower heart rate at any equal relative and at maximal work level. Assuming maximal effort by all (indicated by RER, $PETCO_2$, and subjective exhaustion), these results could indicate either cardiac or peripheral insufficiency embedded in the pathology of CFS patients. Authors concludes that indexes from cardiopulmonary exercise testing may be used as objective discriminatory indicators for evaluation of patients complaining of chronic fatigue syndrome.

Cook *et al* (2006) investigated cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome (CFS), accounting for comorbid fibromyalgia (FM) and controlling for aerobic fitness. Twenty-nine patients with CFS only, 23 patients with CFS plus FM, and 32 controls completed an incremental bicycle test to exhaustion. Cardiorespiratory and perceptual responses were measured. Results were determined for the entire sample and for 18 subjects from each group matched for peak oxygen consumption. In the overall sample, there were no significant differences in cardiorespiratory parameters between the CFS only group and the controls. However, the CFS plus FM group exhibited lower ventilation, lower end-tidal CO_2, and higher ventilatory equivalent of carbon dioxide compared with controls, and slower increases in heart rate compared with both patients with CFS only and controls. Peak oxygen consumption, ventilation, and workload were lower in the CFS plus FM group. Subjects in both the CFS only group and the CFS plus FM group rated exercise as more effortful than did controls. Patients with CFS plus FM rated exercise as significantly more painful than did patients with CFS only or controls. In the subgroups matched for aerobic fitness, there were no significant differences among the groups for any measured cardiorespiratory response, but perceptual differences in the CFS plus FM group remained. With matching for aerobic fitness, cardiorespiratory responses to exercise in patients with CFS only and CFS plus FM are not different from those in sedentary healthy subjects. While CFS patients with comorbid FM perceive exercise as more effortful and painful than do controls, those with CFS alone do not. These results suggest that aerobic fitness and a concurrent diagnosis of FM are likely explanations for currently conflicting data and challenge ideas implicating metabolic disease in the pathogenesis of CFS.

Immunology and genetics

Several aspects of cellular immunity in patients with clinically defined chronic fatigue syndrome (CFS) were evaluated and compared with those in healthy individuals. Baker *et al* (1994) describes that flow cytometric analyses revealed normal expression of total T (CD3+), B (CD19+), and NK (natural killer) (CD16+, CD56+) markers on the surface of peripheral blood mononuclear cells (PMC) from patients with CFS. However, compared with those of healthy individuals, patients' CD8+ T cells expressed reduced levels of CD11b and expressed the activation markers CD38 and HLA-DR at elevated levels. In many of the individuals in whom expression of CD11b was reduced the expression of CD28 was increased. These findings indicate expansion of a population of activated CD8+ cytotoxic T lymphocytes. A marked decrease in NK cell activity was found in almost all patients with CFS, as compared with that in healthy individuals. No substantial abnormalities in monocyte activity or T cell proliferation were observed. The results of this study suggest that immune cell phenotype changes and NK cell dysfunction are common manifestations of CFS.

The observed high level of pro-inflammatory cytokines may explain some of the manifestations such as fatigue and flu-like symptoms and influence NK activity (Lorusso *et al* 2009). Abnormal activation of the T lymphocyte subsets and a decrease in antibody-dependent cell-mediated cytotoxicity have been described. An increased number of CD8+ cytotoxic T lymphocytes and CD38 and HLA-DR activation markers have been reported, and a decrease in CD11b expression associated with an increased expression of CD28+ T subsets has been observed. This review discusses the immunological aspects of CFS and offers an immunological hypothesis for the disease processes.

Maes *et al* (2006) study examined serum zinc concentrations in patients with chronic fatigue syndrome (CFS) versus normal volunteers. They found that serum zinc was significantly lower in the CFS patients than in the normal controls. There was a trend toward a signifi-

cant negative correlation between serum zinc and the severity of CFS and there was a significant and negative correlation between serum zinc and the subjective experience of infection. The study found that serum zinc was significantly and negatively correlated to the increase in the alpha2 protein fraction and positively correlated to decreases in the expression of mitogen-induced CD69+ (a T cell activation marker) on CD3+ as well as CD3+CD8+ T cells. These results show that CFS is accompanied by a low serum zinc status and that the latter is related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong anti-oxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress.

Imaging

According Mathew *et al* (2008) compared lateral ventricular volumes derived from tissue-segmented T_1-weighted volumetric MRI data and cerebrospinal fluid (CSF) lactate concentrations measured by proton MRS imaging ($_1$H MRSI) in 16 subjects with CFS with those in 14 patients with generalized anxiety disorder (GAD) and in 15 healthy volunteers. Mean lateral ventricular lactate concentrations measured by $_1$H MRSI in CFS were increased by 297% compared with those in GAD and by 348% compared with those in healthy volunteers, even after controlling for ventricular volume, which did not differ significantly between the groups. Regression analysis revealed that diagnosis accounted for 43% of the variance in ventricular lactate. CFS is associated with significantly raised concentrations of ventricular lactate, potentially consistent with recent evidence of decreased cortical blood flow, secondary mitochondrial dysfunction, and/or oxidative stress abnormalities in the disorder.

Recent studies have detected a decrease in cortical grey matter volume in patients with CFS, but it is unclear whether this cerebral atrophy constitutes a cause or a consequence of the disease. De Lange *et al* (2008) tested the hypothesis that cerebral atrophy may be a reversible state that can ameliorate with successful CBT. They have quantified cerebral structural changes in 22 CFS patients that underwent CBT and 22 healthy control participants. At baseline, CFS patients had significantly lower grey matter volume than healthy control participants. CBT intervention led to a significant improvement in health status, physical activity and cognitive performance. Crucially, CFS patients showed a significant increase in grey matter volume, localized in the lateral prefrontal cortex. This change in cerebral volume was related to improvements in cognitive speed in the CFS patients. These findings indicate that the cerebral atrophy associated with CFS is partially reversed after effective CBT. This result provides an example of macroscopic cortical plasticity in the adult human brain, demonstrating a surprisingly dynamic relation between behavioural state and cerebral anatomy.

Central sensitization

The pain complaints show the greatest overlap between CFS and fibromyalgia (FM). Although the literature provides evidence for central sensitization as cause for the musculoskeletal pain in FM, in CFS this evidence is currently lacking, despite the observed similarities in both diseases. The knowledge concerning the physiological mechanism of central sensitization, the pathophysiology and the pain processing in FM, and the knowledge on the pathophysiology of CFS lead to the hypothesis that central sensitization is also responsible for the sustaining pain complaints in CFS (Meeus & Nijs 2006). This hypothesis is based on the hyperalgesia and allodynia reported in CFS, on the elevated concentrations of nitric oxide presented in the blood of CFS patients, on the typical personality styles seen in CFS and on the brain abnormalities shown on brain images. To examine the present hypothesis more research is required.

COMORBIDITY

Patients with CFS frequently complain of psychological symptoms including depression, anxiety, and neuropsychological impairment. In addition, patients with CFS have been reported to be more likely to have psychiatric diseases such as major depressive disorder, panic disorder, generalized anxiety disorder, and personality disorder (Yoshiuchi 2007) somatization or anxiety disorders (Youssefi & Linkowski 2002). Antidepressants can be useful particularly in the case of comorbid affective disorders. The current research determined the prevalence and correlates of depression among individuals with CFS in a community sample (Fuller-Thompson & Nimigon 2008). The nationally representative Canadian Community Health Survey, conducted in 2000/2001, included an unweighted sample size of 1045 individuals who reported a diagnosis of CFS and had complete data on depression. Respondents with CFS who were depressed (n = 369) were compared to those who were not depressed (n = 676). Thirty-six per cent of individuals with CFS were depressed. Among individuals with CFS, depression was associated with lower levels of mastery and self-esteem. In the logistic regression analyses, the odds of depression among individuals with CFS were higher for females, younger respondents, those with lower incomes and food insecurity and those whose activities were limited by pain. Two in five depressed individuals had not consulted with any mental health professional in the preceding year. Twenty-two per cent of depressed respondents had seriously considered suicide in the past year. Individuals with CFS who were depressed were particularly heavy users of family physicians, with an average of 11.1 visits annually.

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PERSONALITY

Among clinical psychologists, consulting physicians, scientific researchers and society in general an image has emerged of patients with CFS as perfectionist, conscientious, hardworking, somewhat neurotic and introverted individuals with high personal standards, a great desire to be socially accepted and with a history of continuously pushing themselves past their limits (van Geelen *et al* 2007). Johnson *et al* (1996) investigated the relative rates of personality disturbance in CFS. Individuals who met criteria for CFS were compared to two other fatiguing illness groups, mild multiple sclerosis and depression, as well as sedentary healthy controls. Subjects were administered a structured psychiatric interview to determine Axis I psychiatric disorders and two self-report instruments to assess Axis II personality disorders and the personality trait of neuroticism. The depressed group had significantly more personality disorders and elevated neuroticism scores compared with the other three groups. The CFS and MS subjects had intermediary personality scores which were significantly higher than healthy controls. The CFS group with concurrent depressive disorder (34% of the CFS group) was found to account for most of the personality pathology in the CFS sample.

Christodoulou *et al* (1999) Examinated the Cloninger's basic dimensions of personality in chronic fatigue syndrome and multiple sclerosis. The personality profiles of 38 CFS subjects were compared with 40 healthy controls and 40 subjects with multiple sclerosis (MS), a chronic illness that shares many symptoms with CFS (e.g., fatigue), but has a known neurological substrate. Subjects were examined within Cloninger's biosocial theory of personality, which delineates basic dimensions of temperament. Both illness groups displayed similarly elevated levels of Harm Avoidance, and lower levels of Reward Dependence as compared with healthy controls. The MS group showed a lower level of Persistence than controls and CFS subjects.

On the other side, an individual's spirituality and/or religion is be one of the factors that can influence the experience of chronic pain or fatigue (Baetz & Bowen 2008). The Canadian Community Health Survey (2002) obtained data from 37,000 individuals 15 years of age or older. From these data, four conditions with chronic pain and fatigue were analyzed together – fibromyalgia, back pain, migraine headaches and chronic fatigue syndrome. Additional data from the survey were used to determine how religion and spirituality affect psychological well-being, as well as the use of various coping methods. Religious persons were less likely to have chronic pain and fatigue, while those who were spiritual but not affiliated with regular worship attendance were more likely to have those conditions. Individuals with chronic pain and fatigue were more likely to use prayer and seek spiritual support as a coping method than the general population. Furthermore, chronic pain and fatigue sufferers who were both religious and spiritual were more likely to have better psychological well-being and use positive coping strategies.

SOCIAL SUPPORT

Several studies suggested that the surroundings of CFS patients are of importance in the persistence of complaints. Contrary to what was expected, participation in support groups has not led to clinical improvement. The purpose of Prins *et al* (2004) study was to describe social support in CFS patients as compared with other fatigued and non-fatigued groups. Further, changes in social support and the influence of social support on the course of CFS over a period of more than 1 year were studied in patients with and without treatment. Baseline data were assessed in 270 CFS patients, 150 disease-free breast cancer patients, 151 fatigued employees on sick-leave and 108 healthy subjects using the Social Support List and Significant Others Scale. CFS patients were followed in cognitive behaviour therapy (CBT), guided support groups and natural course at 8 and 14 months. CFS patients and fatigued employees reported more negative interactions and insufficiency of supporting interactions than cancer patients and healthy controls. No differences in frequency of supporting interactions were found. Negative interactions decreased significantly after treatment with CBT, but did not change in support groups or natural course. In the natural course, higher fatigue severity at 8 months was predicted by more negative interactions at baseline. In CFS patients and fatigued employees, social support is worse than in disease-free cancer patients and healthy controls. Lack of social support was identified as a new factor in the model of perpetuating factors of fatigue severity and functional impairment in CFS.

COGNITIVE FUNCTION

Michiels and Clyudts (2001) reviewed critically the current status of neurocognitive studies in patients with chronic fatigue syndrome. The current research shows that slowed processing speed, impaired working memory and poor learning of information are the most prominent features of cognitive dysfunctioning in patients with CFS. Furthermore, to this date no specific pattern of cerebral abnormalities has been found that uniquely characterizes CFS patients. There is no overwhelming evidence that fatigue is related to cognitive performance in CFS, and researchers agree that their performance on neuropsychological tasks is unlikely to be accounted solely by the severity of the depression and anxiety.

Busichio *et al* (2004) examined the degree of neuropsychological dysfunction across multiple domains in individuals suffering from chronic fatigue syndrome. In this descriptive study, a similar series of neuropsy-

chological tests was administered to a group of CFS patients and healthy participants. More specifically, CFS patients (n = 141) were compared to 76 healthy control participants on tests of memory, attention (concentration), speed of information processing, motor speed, and executive functioning. On the 18 measures administered, CFS patients scored 1 standard deviation below the healthy mean on nine measures and scored 2 standard deviations below the healthy mean on four of the measures. Moreover, results indicated that CFS patients were more likely than healthy controls to fail at least one test in each of the following domains: attention, speed of information processing, and motor speed, but not on measures of memory and executive functioning.

TREATMENT

CFS is a complicated illness for providers and patients. Fewer than 20% of persons with CFS have been diagnosed and treated (Brimmer *et al* 2008). For providers, compounding the issue are the challenges in making a diagnosis due to the lack of a biomedical marker. Improvement may occur with medical care and additional therapies of pacing, cognitive behavioural therapy and graded exercise therapy (Maquet *et al* 2006). The latter two therapies have been found to be efficacious in small trials, but patient organisations surveys have reported adverse effects. Although pacing has been advocated by patient organisations, it lacks empirical support. Specialist medical care is commonly provided but its efficacy when given alone is not established. Evidence for the effectiveness of any treatment for CFS/ME in primary care, where most patients are seen, is sparse. Development of good therapeutic doctor-patient alliance with empathic care is central to the effective management of CFS (Youssefi & Linkowski 2002). Treatment strategies for CFS include psychological, physical and pharmacological interventions. Understanding psychological and psychosocial contributing and coping factors, and working with patients to modify them, is one goal of management (Baetz & Bowen 2008). An integrated medical and psychological approach should be adopted, with the aim of preventing significant secondary negative results of the illness, such as interpersonal conflicts or chronic disability (Lieb *et al* 1996).

Whiting *et al* (2001) assessed the effectiveness of all interventions that have been evaluated for use in the treatment or management of CFS in adults or children. Nineteen specialist databases were searched from inception to either January or July 2000 for published or unpublished studies in any language. The search was updated through October 2000 using PubMed. Controlled trials (randomized or nonrandomized) that evaluated interventions in patients diagnosed as having CFS according to any criteria were included. Study inclusion was assessed independently by 2 reviewers. Of 350 studies initially identified, 44 met inclusion criteria, including 36 randomized controlled trials and 8 controlled trials. The number of participants included in each trial ranged from 12 to 326, with a total of 2801 participants included in the 44 trials combined. Across the studies, 38 different outcomes were evaluated using about 130 different scales or types of measurement. Studies were grouped into 6 different categories. In the behavioral category, graded exercise therapy and cognitive behavioral therapy showed positive results and also scored highly on the validity assessment. In the immunological category, both immunoglobulin and hydrocortisone showed some limited effects but, overall, the evidence was inconclusive. There was insufficient evidence about effectiveness in the other 4 categories (pharmacological, supplements, complementary/alternative, and other interventions). Overall, the interventions demonstrated mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with the methodological inadequacies of the studies. Interventions which have shown promising results include cognitive behavioral therapy and graded exercise therapy.

PHARMACOTHERAPY

Because of the similarities between both fibromyalgia and chronic fatigue syndrom it was suggested that they share a common pathophysiological mechanisms, namely, central nervous system (CNS) dysfunction. Current hypotheses center on atypical sensory processing in the CNS and dysfunction of skeletal muscle nociception and the hypothalamic-pituitary-adrenal (HPA) axis. Although fibromyalgia is common and associated with substantial morbidity and disability, there are no US Food and Drug Administration (FDA)-approved treatments except pregabalin. Recent pharmacological treatment studies about fibromyalgia have focused on selective serotonin and norepinephrine (NE) reuptake inhibitors, which enhance serotonin and NE neurotransmission in the descending pain pathways and lack many of the adverse side effects associated with tricyclic medications. To date, no pharmacological agent has been reliably shown to be effective treatment for CFS. Management strategies are therefore primarily directed at relief of symptoms and minimising impediments to recovery.

PSYCHOEDUCATION AND EXERCISE THERAPY

To assess the efficacy of an educational intervention explaining symptoms to encourage graded exercise in patients with chronic fatigue syndrome Powell *et al* (2001) made randomised controlled trial in CFS. 148 consecutively referred patients were randomised to

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the control group received standardised medical care. Patients randomised to intervention received two individual treatment sessions and two telephone follow up calls, supported by a comprehensive educational pack, describing the role of disrupted physiological regulation in fatigue symptoms and encouraging home based graded exercise. The minimum intervention group had no further treatment, but the telephone intervention group received an additional seven follow up calls and the maximum intervention group an additional seven face to face sessions over four months. Intention to treat analysis showed 79 (69%) of patients in the intervention groups achieved a satisfactory outcome in physical functioning compared with two (6%) of controls, who received standardised medical care. Similar improvements were observed in fatigue, sleep, disability, and mood. No significant differences were found between the three intervention groups. Treatment incorporating evidence based physiological explanations for symptoms was effective in encouraging self managed graded exercise. This resulted in substantial improvement compared with standardised medical care.

Powell *et al* (2004) determined 2-year outcomes for the same treated patients from the study above and the response to treatment of patients formerly in the control condition. Patients in the treatment groups (n=114) were followed up at 2 years; 32 patients from the control group were offered the intervention after 1 year and were assessed 1 year later. Assessments were the self-rated measures used in the original trial. At 2 years 63 of the treated patients (55%) no longer fulfilled trial criteria for CFS compared with 64 patients (56%) at 1 year. Fourteen of 30 crossover patients (47%) achieved a good outcome at 1 year and seven (23%) no longer fulfilled criteria for CFS. Benefits of the intervention were maintained at 2 years. Delaying treatment is associated with reduced efficacy and required more intensive therapy.

COGNITIVE BEHAVIORAL THERAPY

Cognitive behavioural therapy (CBT) is an effective behavioural intervention for CFS, which combines a rehabilitative approach of a graded increase in physical activity with a psychological approach that addresses thoughts and beliefs about CFS which may impair recovery (de Lange *et al* 2008). In the CBT for CFS, it is important to quit seeking physical causes, to accept the pathological state as it is, to monitor daily activity and recognize the cognitive and behavioral patterns which might prolong fatigue, to maintain a constant activity level and to make planned increases in activity. There is controversy about the nature of the change following treatment; some suggest that patients improve by learning to adapt to a chronic condition, others think that recovery is possible (Knoop *et al* 2007b).

Price and Couper (2000) systematically reviewed all randomised controlled trials fo cognitive behaviour therapy (CBT) for adults with chronic fatigue syndrome (CFS) and tested the hypothesis that CBT is more effective than orthodox medical management or other interventions in adults with CFS. These trials demonstrated that CBT significantly benefits physical functioning in adult out-patients with CFS when compared to orthodox medical management or relaxation. CBT appeared highly acceptable to the patients in these trials. Prins *et al* (2001) compared CBT with guided support groups and the natural course in a randomised trial at three centres. Of 476 patients diagnosed with CFS, 278 were eligible and willing to take part. 93 were randomly assigned CBT (administered by 13 therapists recently trained in this technique for CFS), 94 were assigned the support-group approach, and 91 the control natural course. Multidimensional assessments were done at baseline, 8 months, and 14 months. The primary outcome variables were fatigue severity (on the checklist individual strength) and functional impairment (on the sickness impact profile) at 8 and 14 months. Data were analysed by intention to treat. 241 patients had complete data (83 CBT, 80 support groups, 78 natural course) at 8 months. At 14 months CBT was significantly more effective than both control conditions for fatigue severity and for functional impairment. Support groups were not more effective for CFS patients than the natural course. Among the CBT group, clinically significant improvement was seen in fatigue severity for 20 of 58 (35%), in Karnofsky performance status for 28 of 57 (49%), and self-rated improvement for 29 of 58 (50%). CBT was more effective than guided support groups and the natural course in a multicentre trial with many therapists, but this study showed a lower proportion of patients with improvement than CBT trials with a few highly skilled therapists.

O'Dowd *et al* (2006) tested the hypothesis that group cognitive behavioural therapy (CBT) will produce an effective and cost-effective management strategy for patients in primary care with CFS. A double-blind, randomised controlled trial was adopted with three arms. Outcomes were assessed at baseline and 6 and 12 months after first assessment and results were analysed on an intention-to-treat basis. The three interventions were group CBT incorporating graded activity scheduling, education and support group (EAS) and standard medical care (SMC). A total of 153 patients were recruited to the trial and 52 were randomised to receive CBT, 50 to EAS and 51 to SMC. Group CBT was effective in treating symptoms of fatigue, mood and physical fitness in CFS. It was found to be as effective as trials using individual therapy in these domains. However, it did not bring about improvement in cognitive function or quality of life. There was also evidence of improvement in the EAS group, which indicates that there is limited value in the non-specific effects of therapy.

Quarmby *et al* (2007) evaluated the results of a successful RCT against those of the same treatment given in the same setting as part of routine practice. Fatigue and

social adjustment scores were compared for patients who received CBT for CFS as part of a RCT (N=30) and patients who received CBT as part of everyday clinical practice (N=384). The results in the RCT were superior to those in routine clinical practice. Between pre-treatment and 6-month follow-up, the RCT showed a larger reduction in fatigue and greater improvement in social adjustment than those in routine treatment. The changes in fatigue scores were similar for both groups during treatment but were greater in the RCT between post-treatment and follow-up. Potential reasons for the superior results of the RCT include patient selection, therapist factors and the use of a manualised treatment protocol. Practitioners need to pay particular attention to relapse prevention and ensuring adequate follow-up in addition to encouraging patients to continue with cognitive-behavioural strategies once treatment has ended.

Knoop *et al* (2007a) wanted to find out whether recovery from CFS is possible after CBT. The outcome of a cohort of 96 patients treated for CFS with CBT was studied. Data from healthy population norms were used in calculating conservative thresholds for recovery. After treatment, 69% of the patients no longer met the CDC criteria for CFS. The percentage of recovered patients depended on the criteria used for recovery. Using the most comprehensive definition of recovery, 23% of the patients fully recovered. Fewer patients with a co-morbid medical condition recovered. Authors concluded that significant improvement following CBT is probable and a full recovery is possible.

Knoop *et al* (2008) were tested a minimal intervention, based on cognitive-behavioural therapy for chronic fatigue syndrome and consisting of self-instructions combined with email contact, in a randomised controlled trial. A total of 171 patients participated in the trial: 85 were allocated to the intervention condition and 86 to the waiting-list condition. All patients met the Centers for Disease Control and Prevention criteria for chronic fatigue syndrome. An intention-to-treat analysis showed a significant decrease in fatigue and disability after self-instruction. The level of disability was negatively correlated with treatment outcome.

Malouff *et al* (2008) conducted a meta-analysis of the efficacy of CBT in CFS. Across analyses, which included a total of 1371 participants, there was a significant difference, d=0.48, in post-treatment fatigue between participants receiving CBT and those in control conditions. Results indicate that CBT for chronic fatigue syndrome tends to be moderately efficacious. Dropout rates in CBT varied from 0–42%, with a mean of 16%. In the five studies that reported the number of CBT clients who were no longer in the clinical range with regard to fatigue at the latest follow-up, the percentage varied from 33% to 73% of those assigned to CBT, with a mean of 50%.

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