REVIEW

A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS

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Abstract

Benign Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS) is a debilitating disease which, despite numerous biological abnormalities has remained highly controversial.

Notwithstanding the medical pathogenesis of ME/CFS, the (bio)psychosocial model is adopted by many governmental organizations and medical professionals to legitimize the combination of Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) for ME/CFS. Justified by this model CBT and GET aim at eliminating presumed psychogenic and socially induced maintaining factors and reversing deconditioning, respectively.

In this review we invalidate the (bio)psychosocial model for ME/CFS and demonstrate that the success claim for CBT/GET to treat ME/CFS is unjust. CBT/GET is not only hardly more effective than non-interventions or standard medical care, but many patients report that the therapy had affected them adversely, the majority of them even reporting substantial deterioration.

Moreover, this review shows that exertion and thus GET most likely have a negative impact on many ME/CFS patients.

Exertion induces post-exertional malaise with a decreased physical performance/aerobic capacity, increased muscoskeletal pain, neurocognitive impairment, "fatigue", and weakness, and a long lasting "recovery" time.

This can be explained by findings that exertion may amplify pre-existing pathophysiological abnormalities underpinning ME/CFS, such as inflammation, immune dysfunction, oxidative and nitrosative stress, channelopathy, defective stress response mechanisms and a hypoactive hypothalamic-pituitary-adrenal axis.

We conclude that it is unethical to treat patients with ME/CFS with ineffective, non-evidence-based and potentially harmful "rehabilitation therapies", such as CBT/GET.

INTRODUCTION

Benign Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS) is a highly incapacitating illness classified by the WHO as a neurological disease (G93.3) since 1969 (WHO ICD-8, 1967).

The CFS Fukuda case definition (Fukuda *et al.* 1994), which has been has been criticized by several researchers, states that a CFS patient needs to experience chronic fatigue of new or definite onset, that is not substantially alleviated by rest, is not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities. The Fukuda case definition also requires the concurrent occurrence of at least four to eight other CFS symptoms, i.e. impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multiple joint pain, new headaches, unrefreshing sleep, and post-exertional malaise.

ME/CFS is considered to be a rather harmless condition by most physicians, but patients with ME/CFS are often more functionally impaired than those suffering from type 2 diabetes, congestive heart failure, multiple sclerosis, and end-stage renal disease (Anderson & Ferrans, 1997; Buchwald *et al.* 1996). Jason *et al.* (2006) analyzed a group of 166 individuals who had died with ME/CFS (listed at a US ME/CFS memorial register). The mean ages of the ME/CFS patients dying from heart failure (20,1%), cancer (19.4%), and suicide (20,1%) were 58.7, 47.8, and 39.3 years, respectively. These ages are considerably lower than of those dying from heart failure (83.1 years), cancer (72.0 years), and suicide (48.0 years) in the general US population.

In spite of its chronicity and severity, ME/CFS remains highly controversial in the medical en political society. Despite several hundred studies demonstrating biological abnormalities in large subgroups, ME/CFS is still considered by many professionals to be a "medically unexplained syndrome" or a mental condition with a psychogenic/social origin. The psychosocial explanatory model for "medically unexplained disorders", disseminated by proponents of the (bio)psychosocial school, is the rationale for the combination of cognitive behavioral therapy (CBT) and graded exercise therapy (GET), which are supposed to eliminate the psychogenic "maintaining factors" and "deconditioning", respectively.

This review will show that:

a) the evidence-based success claim for CBT/GET is unjust, since the evidence base is lacking and CBT/GET is not significantly more effective than usual care; and
b) the exertion, and thus GET, can have numerous potential damaging physical effects on ME/CFS patients.

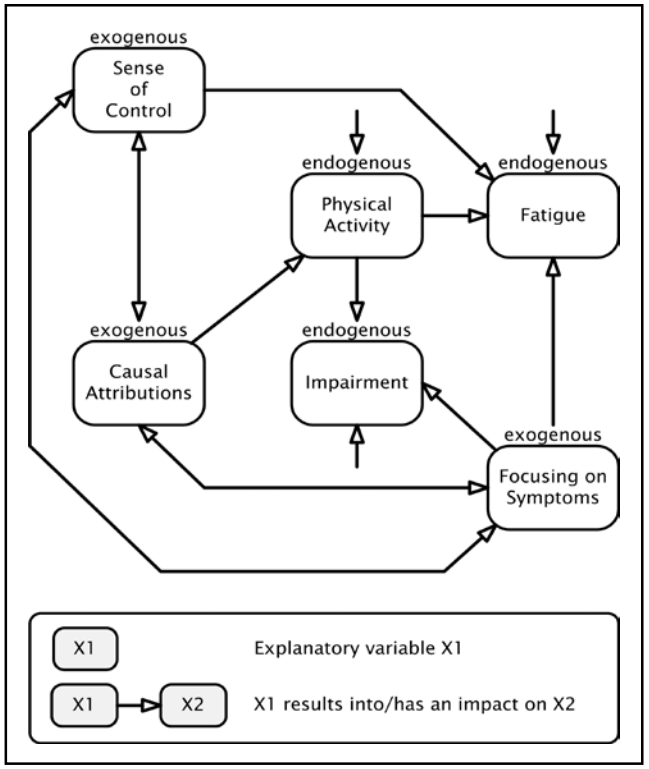

Figure 1. This figure shows the Vercoulen model as described by Song & Jason (2005).

The (bio)psychosocial model for ME/CFS

The (bio)psychosocial explanation for ME/CFS is based upon the hypothesis that psychogenic, cognitive and behavioral factors play an important role in the etiology and maintenance of ME/CFS.

According to the (bio)psychosocial school, one should make a clear distinction between predisposing factors, e.g. personality traits, genes; triggering factors, e.g. infections, vaccinations, injury; and maintaining factors, e.g. illness beliefs, stress, inactivity. This trichotomy incorporates the hypothesis that psycho-social factors are the main driving force of ME/CFS and biological factors are far less important in sustaining the illness.

The (bio)psychosocial view, based upon the premises that personality traits, "causal attributions", inactivity, kinesiophobia, somatizing etc. are the maintaining factors for ME/CFS, is best illustrated by the Vercoulen model (Song & Jason, 2005): ***Figure 1***.

The (bio)psychosocial therapy: CBT/GET

The model described above is the justification for the (bio)psychosocial "therapy" for ME/CFS: a combination of CBT and GET. 'CBT facilitates the identification of unhelpful, anxiety-provoking thoughts, and challenges these negative automatic thoughts and dysfunctional underlying assumptions'

(Price *et al.* 2008). 'CBT combines a rehabilitative approach of a graded increase in activity with a psychological approach addressing thoughts and beliefs .. that may impair recovery.' (Price *et al.* 2008).

Thus, this theory proposes that by eliminating the maintaining factors of ME/CFS, the patient can recover. The "illness beliefs" of the patient are challenged by CBT, while a graded increase in physical activity (GET) addresses "deconditioning".

The (bio)psychosocial model has been invalidated by research

However, the theoretical justification for CBT/GET, the (bio)psychosocial model (e.g. the Vercoulen model), has been invalidated. First of all, core elements of this model, i.e. the central role of "kinesiophobia" (fear of movement) and personality characteristics, have been disproved by research.

a) Two pillars of this model, i.e. "decreased exercise capacity is caused by kinesiophobia" and "physical deconditioning is a perpetuating factor in ME/CFS", have been invalidated by research results. For example, Nijs *et al.* (2004b) proved there is no correlation between kinesiophobia and exercise capacity, activity limitations, or participation restrictions, at least in patients with CFS with widespread muscle or joint pain.

Gallagher *et al.* (2005) found that ME/CFS patients without a co-morbid psychiatric disorder do not have an exercise phobia.

The conclusion of Bazelmans *et al.* (2001) that physical deconditioning does not seem to be a perpetuating factor in ME/CFS is at the least remarkable, since Bazelmans and her colleagues are outspoken advocates of the (bio)psychosocial explanation. Thus, an essential premise of the (bio)psychosocial model, i.e. that kinesiophobia is a perpetuating factor in ME/CFS, cannot be sustained.

b) Another misconception is the central role of specific personality traits presumed by the (bio)psychosocial model. According to various studies psychological factors play no role at all, or at the least a very minor one. Wood and Wessely, the captain of the (bio)psychosocial school, for example pointed out very clearly (Wood & Wessely, 1999) that no differences between patients with ME/CFS and rheumatoid arthritis in measures of perfectionism, attitudes toward mental illness, defensiveness, social desirability, or sensitivity to punishment (a concept related to neuroticism) were found. The authors stated their study also invalidated the 'stereotype of CFS sufferers as perfectionists with negative attitudes toward psychiatry'.

Le Bon *et al.* (2007) concluded that the personality structure does not appear to play a major role in the CFS.

Vollmer-Conna *et al.* (2008) recently concluded that genetic variations (IFN-γ +874T/A and IL-10 -592C/A polymorphisms) largely determine the impact of a Epstein-Barr virus, a Coxiella burnetii (Q fever), or a Ross River virus (epidemic polyarthritis) infection. These cytokine genotypes, especially when combined, significantly affect the acute sickness response (illness severity, cytokine protein levels), and the duration of illness/recovery. More important, the authors established that psychosocial and environmental factors (including personality, coping style, mood, and psychiatric history) have no significant effect on illness outcomes. According to this study post viral ME/CFS is almost exclusively genetically determined.

Johnson *et al.* (2008) investigated the association of neuroticism and coping styles with ME/CFS symptoms, "fatigue" and physical functioning, and role functioning over a period of 18 months. The authors concluded that their findings support a very limited role for personality and coping factors in CFS.

According to Courjaret *et al.* (2009) the prominent absence of any significant difference in personality disorder characteristics between the female Flemish general population and the CFS samples suggest only a minor etiological role for personality pathology, as defined by the DSM-IV Axis II, within ME/CFS. Thus, it can be concluded that personal traits do not play a significant role in ME/CFS.

c) The validity of the Vercoulen model in its entirety has been disproved by Song & Jason (2005). Song established that 'Vercoulen model adequately represents chronic fatigue secondary to psychiatric conditions but not ME/CFS'.

The above justifies the conclusion that the Vercoulen model and other variants of the (bio)psychosocial model are not applicable to ME/CFS.

The evidence-based success claim for CBT/GET is unjust

Giving the fact that the theoretical foundation of CBT/GET has been challenged repeatedly, it is not surprising that CBT/GET prove to be not significantly more effective than usual care. The claim that CBT/GET is the only effective evidence-based therapy for ME/CFS, with proclaimed success rates as high as 69%, e.g. Knoop *et al.* 2007), is contradicted by numerous studies.

a) The evidence base for the success claim is almost non-existent

Proponents derive their evidence-based claim from proven effectiveness in randomized controlled trials (RCTs) and controlled trials (CTs).

The 2007 York Review on treatment and management of ME/CFS (Bagnall *et al.* 2007) analyzed all trials for CBT and/or GET. This review identified only 5 trials for CBT/GET for ME/CFS (according to the review GET is considered an integral part of CBT), totaling 480 participants, 2 RCTs and 3 CTs for "modified CBT" (CBT without GET or another graded activity program), totaling 383 participants, and five RCTs for GET, totaling 460 participants (all including controls). Three of the RCTs for CBT/GET and 3 of the RCTs for GET used the Oxford criteria (Sharpe *et al.* 1991) which, by definition, include all people who "present with a principal complaint of disabling fatigue of uncertain cause" (i.e. idiopathic chronic fatigue). According to this definition "psychiatric disorders (including depressive illness, anxiety disorders and hyperventilation syndrome) are not necessarily reasons for exclusion". Since the CFS defining Fukuda criteria (Fukuda *et al.* 1994) require at least 4 out of 8 additional (e.g. post-exertional malaise, cognitive difficulties, and muscle pain), the Oxford criteria basically select "chronic fatigued people" and certainly not patients with ME/CFS. Since 1 RCT for CBT/GET used a local set of criteria, the "evidence-base" for CBT/GET consists of only 1 RCT, and for GET of only 2 RCTs. For positive effects of CBT/GET on the long-term there is no evidence base at all. The only RCT follow-up study (using the Oxford criteria) showed that the effect on physical functioning and fatigue was diminished after 5 years.

b) The "effectiveness" of CBT/GET is negligible

The abovementioned Cochrane review (Price *et al.* 2008) concluded that, solely based upon fatigue scores, the clinical response to CBT was 40% in contrast with 26% in usual care. However, many participants in the underlying studies were "chronic fatigued people" and not ME/CFS patients. Taking into account the placebo effects and the fact that fatigue is not an objective measurement and is just one of the ME/CFS criteria, one can conclude that the effectiveness of CBT/GET in treating ME/CFS is non-existent.

c) In clinical practice CBT/GET has proven to be counterproductive

Moreover, if one considers objective measures of the effects of CBT/GET in clinical practice, the situation is even worse: CBT/GET has proven to be counterproductive.

For example, the evaluation of the CBT/GET therapy offered by the Belgium CFS Reference Centers in the period 2002–2004 (Council of approval with regards to rehabilitation contracts with CFS reference centres for patients suffering from Chronic Fatigue Syndrome, 2006) established that the exercise capacity (VO2max, aerobic threshold, etc) had not improved and that the occupational participation had even decreased after the "rehabilitation therapy" with CBT/GET. According to the Belgian Minister of Health CBT/GET are not to be considered curative therapies (Official minutes of Assembly of the Commission of Health, Environment and Social Innovation, Belgian House of Representatives, 24th October 2007. 5th session, 51th term). Thus, the Belgian Ministry of Social Affairs and Health, who carried out this evaluation, has provided evidence that CBT/GET has no significant efficacy in the treatment of ME/CFS (Maes & Twisk, 2009).

Based upon evidence-based criteria and clinical experiences the claim that CBT/GET is the only effective treatment cannot be substantiated.

CBT/GET is most likely to be harmful for many ME/CFS patients

CBT could be considered harmless (talking doesn't hurt), but much worse, according to the findings in numerous studies, GET must be considered potentially harmful for the majority of the CFS patients. This assertion is justified by many observations of biological abnormalities for large subgroups and the effect of exertion on those anomalies.

In the following paragraph we will discuss the physical complaints of ME/CFS patients, the biological aberrations that could explain these complaints, and the many negative effects of exertion on symptoms and pathophysiological factors as well.

a) Reduced exercise capacity and post-exertional malaise in ME/CFS

Most clinical cardiopulmonary exercise test studies have established a significantly reduced exercise capacity of ME/CFS patients (VO2max, maximal exertion, anaerobic threshold etc), when compared to sedentary controls (e.g. De Becker *et al.* 2000; Sisto *et al.* 1996; McCluskey & Riley, 1992; Farquhar *et al.* 2002; VanNess *et al.* 2007). According to some studies ME/CFS patients are capable of performing at the same level as sedentary controls (LaManca *et al.* 1999; Sargent *et al.* 2002; Bazelmans *et al.* 2001; Takken *et al.* 2007). However, when looking at the "high" performance levels of the ME/CFS patients in these latter studies, the deviant findings are most likely the result of differences in test samples, e.g. high participation rate of "less severe cases".

Many patients suffer from post-exertional malaise and "recover" very slowly.

VanNess *et al.* (2006) showed that, even when ME/CFS patients are able to achieve a level comparable with sedentary controls, this exertion has serious consequences for the physical condition 24 hours later. Considering the fact that all severe ME/CFS patients, patients fulfilling the more strict Holmes criteria (Holmes *et al.* 1988), and 60% of the less severe patients report post-exertional malaise, that is an aggravation

of symptoms after minor exertion, (Peckerman *et al.* 2003), it is not surprising that exercise has a very negative effect on most ME/CFS patients. The capacity to "recover" from exertion is decreased, while the "recovery time" is prolonged.

Studies that have examined the rate of recovery and the effect of exercise on the performance at a second exercise test 24 hours later (repeated exercise tests) show important clinical differences between ME/CFS patients and sedentary controls. Eighty-five % of the sedentary controls recovered within 24 hours, for the remaining controls it took 48 hours to recover, whereas none of the ME/CFS patients recovered within 24 hours and only 5% within 48 hours (Stiles *et al.* 2007). Repeated exercise tests show that the first exercise test has an enormous effect on the exercise capacity 24 hours later (VanNess *et al.* 2006; Ciccolella *et al.* 2007). The anaerobic capacity of most patients was strongly reduced, i.e. the average anaerobic threshold of the patient group had declined with 25%, and the average VO2max had decreased with 30%. These test-retest studies are at the moment being repeated on a larger scale.

This slow rate of "recovery" is most likely to be the reason why ME/CFS patients are not able to increase their physical activities for a long time (Black *et al.* 2005a). The aim of the latter study was to sustain an increase in daily physical activity in ME/CFS patients for 4 weeks and assess the effects on fatigue, muscle pain and overall mood. The results suggest that a daily "activity limit" may exist in this patient population.

Black *et al.* (2005b) concluded that ME/CFS patients may develop exercise intolerance as demonstrated by reduced total activity after 4–10 days. The inability to maintain target activity levels, associated with pronounced worsening of symptomology, suggests that ME/CFS patients had reached their activity limit.

To prevent patients from sustained relapses (8–12 days) Lapp (1997) recommended mild to moderate exercise be limited to less than 5 minutes followed by rest.

b) Neurocognitive abnormalities and the negative effects of exertion

The effects of exercise are not limited to psychical complaints, exercise also seem to have important consequences for the neurocognitive performance.

Neurocognitive impairment have been demonstrated by various researchers over time. e.g. quantitative and qualitative differences in activation of the working memory network (Caseras *et al.* 2006), significant decreases in motor speed and impairment in working memory (Majer *et al.* 2008), and greater efforts, i.e. the use of more extensive regions of the verbal working memory system network, to process auditory information (Lange *et al.* 2005).

Several studies suggest hypoperfusion of (specific areas of) the brain, e.g. (Yoshiuchi *et al.* 2006; Costa *et al.* 1995; Ichise *et al.* 1992) and/or reduced oxidative metabolism e.g. (Tirelli *et al.* 1998; Mathew *et al.* 2009). Hypoperfusion and reduced energy levels are plausible explanations for the "brain fog" often reported by ME/CFS patients.

Several studies strongly suggest that the neurocognitive problems of ME/CFS patients are aggravated by exercise.

LaManca *et al.* (1998) showed that ME/CFS patients had significant impaired cognitive processing compared with healthy individuals immediately after and 24 hours after physically demanding exercise.

Exercise also seems to negatively influence the reaction time, i.e. simple reaction time and three levels of choice reaction time (VanNess *et al.* 2007).

Siemionow *et al.* (2004) found altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue.

Exertion has an negative impact on perfusion of the left prefrontal lobe and cerebral oxygenation, which very well could explain the sustained negative effect of exercise on neurocognitive performance (Patrick Neary *et al.* 2008).

c) Inflammation, immune dysfunction and immune system impairment and the additional negative consequences of exertion

The immune system seems to play a key role in the pathogenesis of ME/CFS.

An inflammatory response has been established in many ME/CFS patients (Maes, 2009), while the immune system also seems to be dysfunctional and depressed (Lorusso *et al.* 2009).

Over time researchers have shown various immune system abnormalities, like decreased natural killer cell activity (Saiki *et al.* 2008; Nijs & de Meirleir, 2005; Klimas *et al.* 1990), reduced perforin levels in cytotoxic T and NK cells (Maher *et al.* 2005), defects in T- and NK cell activation (Mihaylova *et al.* 2007; Maes *et al.* 2006), a significant decrease in the suppressor inducer subset of CD4+CD45RA+ cells (Klimas *et al.* 1990), a significant bias towards Th2- and Tc2-type immune responses (Skowera *et al.* 2004), and dysregulation of the RNAse L pathway (Suhadolnik *et al.* 1997; Englebienne & de Meirleir, 2002; Tiev *et al.* 2003).

A central role for immune system abnormalities, inflammation and immune dysfunction, in the pathophysiology of ME/CFS have also been implicated by several gene expression studies (Kaushik *et al.* 2005; Kerr *et al.* 2008; Broderick *et al.* 2006; Aspler *et al.* 2008, Gow *et al.* 2009).

Inflammation, leading to permanently increased oxidative and nitrosative stress, on the one hand, and a chronically depressed and dysfunctional immune system on the other hand, adequately explain many biological abnormalities found in ME/CFS, resulting into typical ME/CFS complaints.

This will be described more extensively in an publication in the near future.

Several studies have established a correlation between the immune system dysfunction (inflammation and impairment) and the severity of physical symptoms.

Cruess *et al.* (2000) concluded that elevations in T-helper/inducer cells, activated T-cells, an elevated CD4/CD8 ratio and reductions in the (percentage of) T-suppressor/cytotoxic cells were directly associated with greater severity of several symptoms.

According to Meeus *et al.* (2008) RNAse L and elastase activity are related to daily functioning.

Suhadolnik *et al.* (1999) demonstrated a negative correlation between Karnofsky Performance Score and bioactive 2-5A or RNAse L activity and positive correlations between Metabolic Screening Questionnaire and RNAse L activity and between interferon- and low molecular weight (LMW) RNAse L, which according to the authors of this study more firmly establishes the dysregulation of the 2-5A synthetase/RNAse L pathway in CFS.

According to Maes (2009) key phenomena of intracellular inflammation established in many ME/CFS patients are an increased production of nuclear factor kappa-B (NF-kB), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS). Maes *et al.* (2007a) and Maes *et al.* (2007b) found that intracellular inflammation is strongly correlated to aches and pain, muscular tension, "fatigue", and the subjective feeling of infection; and that oxidative and nitrosative damage to fatty acids and proteins is related to aches and pain, muscular tension and "fatigue".

The reduced exercise capacity seems also to be correlated with (intracellular) immune system abnormalities.

Nijs *et al.* (2005a) demonstrated that elastase activity is related to the reduction in oxygen uptake at a respiratory exchange ratio (RER) of 1.0, that protein kinase R activity is the principle factor related to the reduction in workload at RER=1.0, and elastase activity is the principle factor related to the reduction in percent of target heart rate achieved.

Snell *et al.* (2002) suggest that ME/CFS patients with elevated RNase L levels (63% of the ME/CFS patients studied) had a lower V02max.

The results of Snell *et al.* (2005) implicate abnormal immune activity in the pathology of exercise intolerance in ME/CFS and are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity.

Nijs *et al.* (2004a) offers a plausible explanation for the correlation between several immune intracellular immune deregulations (deregulation of the 2-5A synthetase/RNAse L pathway, activation of the protein kinase R, and subsequent NF-kB activation, excessive nitric oxide production), several types of infections, frequently identified in ME/CFS patients, and the abnormal exercise response.

In the next paragraph we will summarize important general immunological effects of exertion and the specific pathophysiological impact of exercise on ME/CFS patients.

Strenuous exercise has some well-known immunosuppressive effects, e.g. depression of the NK cell function (Pedersen, 1997; Malm *et al.* 1999; Pedersen & Ullum, 1994; Gleeson & Bishop, 2005; Hoffman-Goetz & Pedersen, 1994).

In addition, exercise also induces a number of inflammatory pathways.

Exercise induces the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) (Jiminez-Jiminez *et al.* 2008; Nieman *et al.* 2007).

Eccentric exercise also specifically increases the expression of specific intracellular inflammatory mediators, such as NF-kB (Bar-Shai *et al.* 2005), iNOS (Niess *et al.* 2000) and COX-2 (Nieman *et al.* 2007), which have been found already to be increased in ME/CFS (Maes *et al.* 2007a; Maes *et al.* 2007b).

Increased NF-kB production in muscles, as during acute exercise, plays a role in muscle damage and protein breakdown (Bar-Shai *et al.* 2005).

Exertion also induces increases the production of the pro-inflammatory and pyrogenic prostaglandins (PGs) (Bradford *et al.* 2007).

In light of the abnormalities described above, (frequent) exercise has important negative consequences for the immune system of many ME/CFS patients, which is already impaired and activated at rest. In addition to these general extra negative effects of exercise on immune dysfunction and inflammation, the negative impact of exertion by ME/CFS patients on specific immunological components have also been established.

White *et al.* (2004) investigated the effect of exercise on the immune system. Travelling from home to the hospital alone was sufficient for significantly elevated TGF-β concentrations. There also was a sustained increase in plasma TNF-α after exercise in ME/CFS patients, not in controls.

In another study (Sorensen *et al.* 2003) it was shown that exercise induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the ME/CFS group. Differential gene activity confirms a prolonged abnormal response of the lectin complement pathway to exertion (Sorensen *et al.* 2009).

After sustained moderate exercise, ME/CFS patients showed greater increases than control subjects in gene expression for interleukin-10 (IL-10), Toll-like receptor 4 (TLR4) and CD14 (a co-receptor, along with TLR4, for the detection of bacterial lipopolysaccharide) in a study by Light *et al.* (2009). These increases lasted from 0.5 to 48 hours. According to the authors greatly enhanced upregulation of SNS receptors alpha-2A, beta-1, beta-2, and COMT after moderate exercise also suggests pow-

erful upstream signaling to the immune system in ME/CFS.

d) Oxidative and nitrosative stress and the additional negative impact of exercise

There is sufficient evidence that the induction of oxidative and nitrosative stress are important phenomena in the pathophysiology of ME/CFS.

An significant increase of oxidative and nitrosative stress and early intracellular acidosis have been demonstrated with various methods and indicators, like thiobarbituric acid-reactive substances and ascorbic acid (Jammes *et al.* 2005) 31P MRS (Chaudhuri *et al.* 2004), and oxidative damage to DNA and lipids in muscle specimens (Fulle *et al.* 2000).

Vecchiet *et al.* (2003) showed a significant correlation between increased oxidative stress/decreased antioxidant defenses and the severity of muscle pain.

An IgM-mediated immune response against neoepitopes formed by damage by O&NS to fatty acids and proteins was established by Maes *et al.* (2008).

According to Smirnova & Pall (2003) elevated protein carbonyl levels confirm earlier reports suggesting that oxidative stress is associated with CFS/ME.

Kennedy *et al.* (2005) found significantly increased levels of isoprostanes and oxidized low-density lipoproteins indicative of a free radicals attack on lipids.

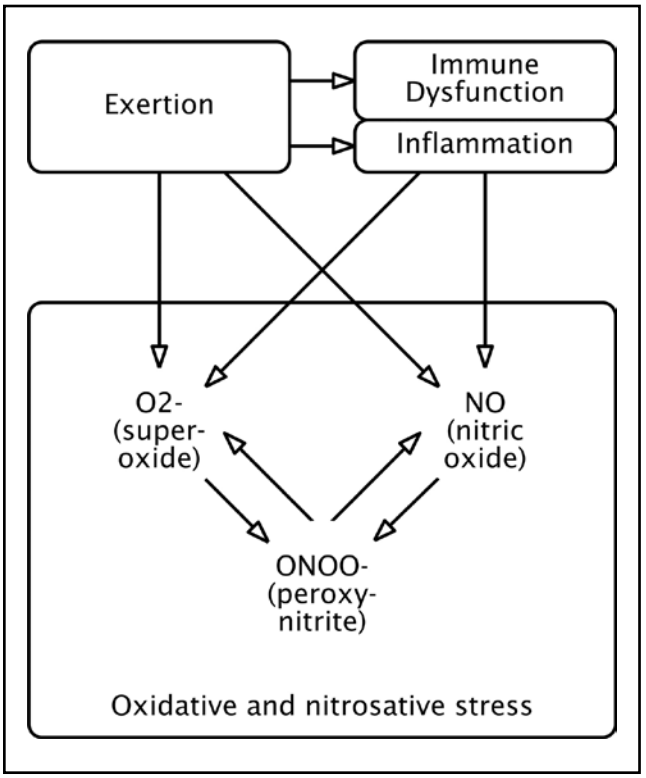

Figure 2. This figure illustrates the causal relations between inflammation, immune dysfunction, exertion and oxidative and nitrosative stress.

Evidence of oxidative damage with significant increases in 2,3-diphosphoglyceric acid (2,3-DPG), methemoglobin and malondialdehyde and significant more stomatocytes was also found by Richards *et al.* (2007).

Differentially expressed genes in a recent study by Gow *et al.* (2009) indicate pathophysiological key roles for immune modulation, oxidative stress and apoptosis.

Since levels are very likely to be increased in ME/CFS already, the oxidative and nitrosative stress as a result of exercise has an additional negative impact on the patient's condition.

This thesis is supported by a study of Light *et al.* (2009). The authors established significant greater increases in gene activity for the B-1, B-2 and COMT adrenergic genes after sustained moderate exercise in ME/CFS. b-Adrenergic receptors are normally associated with cardiovascular function: activation of B-1 receptors is known to enhance heart rate and contractility, and activation of B-2 receptors allows dilation of arteries and arterioles feeding skeletal muscles, thereby maintaining sufficient blood flow to the skeletal muscles during exercise. This increased blood flow prevents excessive accumulation of metabolites (e.g. lactate).

In a study by Jammes *et al.* (2009) 9 ME/CFS patients and 9 gender-, age- and weight-matched healthy sedentary subjects performed an incremental cycling exercise continued until exhaustion. The response of ME/CFS patients to this exertion associated early and accentuated TBARS (thiobarbituric acid reactive substances) increase accompanying reduced changes in RAA (reduced ascorbic acid) levels. This and other markers indicate a lengthened and accentuated oxidative stress in response to incremental exercise.

At rest F(2)-isoprostanes were higher in ME/CFS patients compared to sedentary male controls. This difference persisted immediately and 24 hours after an incremental exercise test to exhaustion in a study by Robinson *et al.* (2009).

Besides modulating the inflammatory pathways, exercise also increases oxidative and nitrosative stress (Peake *et al.* 2007). Inflammation and oxidative and nitrosative stress (O&NS) traditionally have been associated with fatigue and impaired recovery from exercise.

A short term supramaximal anaerobic exercise induces O&NS pathways, as shown by damage to macromolecules and reduced plasma levels of gluthation, a strong antioxidant (Cuevas *et al.* 2005).

Also, translational research experiments have shown that acute exercise increases macrophage phagocytic activity, peroxide release, nitrite production and iNOS expression (Silveira *et al.* 2007).

Prolonged exercise in Sprague-Dawley rats induces inflammation and oxidative and nitrosative stress (IO&NS) pathways, which in turn may cause delayed-onset muscle damage (Aoi *et al.* 2004).

In conclusion, ME/CFS is accompanied by (intracellular) inflammation and an activation of the O&NS pathways, pathways that are related to fatigue, muscle pain, reduced exercise capacity and exercise intolerance, post-exertional malaise, and a delayed "recovery" after exercise. Exercise may further induce the IO&NS pathways causing more muscle damage and consequently atrophy.

The effects of immune dysfunction and inflammation and the additional effects of exertion are illustrated by ***Figure 2***.

e) Muscle abnormalities in ME/CFS and the negative consequences of exertion

Metabolic dysfunction and structural damage to mitochondria in muscle cells has been demonstrated by various researchers.

Kuratsane *et al.* (1994) demonstrated a deficiency of serum acylcarnitine in ME/CFS patients, which is likely to have a negative effect on muscular metabolism.

According to Plioplys & Pliopsys (1995) ME/CFS patients have lower serum total carnitine, free carnitine and acylcarnitine levels. They also established a significant correlation between serum levels of total and free carnitine and clinical symptomatology.

Several of the differentially expressed genes found in people with post-EBV ME/CFS by Vernon *et al.* (2006) relate to mitochondrial functions, including fatty acid metabolism and the cell cycle.

Another gene expression study by Kaushik *et al.* (2005) also demonstrated perturbation of neuronal and mitochondrial function.

Behan *et al.* (1991) examined muscle biopsies of 50 patients with post-viral fatigue syndrome (a variant of ME/CFS) and found branching and fusion of mitochondrial cristae in 35 specimens and mitochondrial degeneration with swelling, vacuolation, myelin figures and secondary lysosomes in 40 samples.

Other structural muscle abnormalities have also been demonstrated, e.g. type II fibre predominance, muscle fibre necrosis and mitochondrial abnormalities (Jamal *et al.* 1985), with abnormal SFEMG results for 75% of the CFS patients.

Pietrangelo *et al.* (2009) analyzed biopsy samples by determining fibre-type proportion (using myosin isoforms as fibre type marker and gel electrophoresis as a tool to separate and quantify myosin isoforms), and contractile properties of manually dissected, chemically made permeable and calcium-activated single muscle fibres. The fibre-type proportion was significantly altered in ME/CFS samples, showing a shift from the slow-twitch to the fast-twitch phenotype. An altered composition of muscle tissue might contribute to the early onset of fatigue/weakness typical of the skeletal muscles of ME/CFS patients.

Teahon *et al.* (1988) showed significantly lower levels of intracellular RNA, suggesting that ME/CFS patients have an impaired capacity to synthesize muscle protein, a finding which, according to the authors, cannot be explained by misuse.

Exercise does increase muscle complaints experienced by (many) ME/CFS patients (pain, weakness). In addition to all findings described above, there are various other studies which support or explain these clinical complaints.

According to Behan & Behan (1988) the distinguishing characteristic of ME/CFS is severe muscle fatigability, which is worsened by exercise. The authors stated that it 'had become apparent that any kind of muscle exercise can cause patients to be almost incapacitated and usually to be confined to bed.'

Lengthened and accentuated oxidative stress together with alterations of the muscle membrane excitability after exercise is described by Jammes *et al.* (2005).

A more recent study by Jammes *et al.* (2009) also established M-wave (muscle potential) alterations in the vastus lateralis of ME/CFS patients, in response to maximal exercise, indicative for reduced muscle membrane excitability.

McCully *et al.* (1996) measured muscle oxidative capacity as the maximal rate of post-exercise phosphocreatine (PCr) resynthesis using the ADP model (Vmax) in the calf muscles using 31P magnetic resonance spectroscopy. PCr resynthesis post-exercise was significantly reduced in ME/CFS patients.

Lane *et al.* (1998) found that patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibers.

McCully & Natelson (1999) reported that, compared with sedentary controls, the time to fully recover oxygen delivery was significantly reduced in ME/CFS patients, both after exercise and after cuff ischemia. Oxidative metabolism was reduced by 20% in ME/CFS patients, and a significant correlation was found between oxidative metabolism and recovery of oxygen delivery.

Arnold *et al.* (1984) used 31P nuclear magnetic resonance to demonstrate abnormally early intracellular acidosis during exercise of forearm muscles. According to the authors the excessive lactic acid formation could reflect metabolic abnormalities.

In a study of Paul *et al.* (1999) patients and controls performed 18 maximum voluntary contractions (MVCs) (10 seconds contraction, 10 seconds rest). This was followed by a recovery phase of 200 minutes, in which quadriceps strength was evaluated at increasing intervals, and a follow-up session at 24 hours post-exercise involving three 10 seconds MVCs. Recovery was prolonged in the patient group, however, with a significant difference compared to initial MVCs being evident during the recovery phase and also after 24 hours.

These findings also support the complaint of delayed recovery after exercise.

Some studies specifically investigated the relationship between the presence of viruses and the response to exercise.

Lane *et al.* (2003) for example, analyzed quadriceps muscle biopsies from 48 patients with ME/CFS and used RT-NPCR to detect enterovirus RNA. Samples from 20.8% of the patients were positive for enterovirus sequences. The authors established an association between an abnormal lactate response to exercise, reflecting impaired muscle energy metabolism, and the presence of enterovirus sequences in the muscles. This is a good example of different subgroups reacting differently to exercise.

f) The (muscoskeletal) pain in ME/CFS patients and the negative impact of exercise

The widespread (muscle and joint) pain experienced by most ME/CFS patients may be explained by hypoperfusion, mitochondrial dysfunction and/or an induction of inflammatory pathways and/or increased oxidative and nitrosative stress. A hypersensitive central nervous system and cardiovascular abnormalities also seem to be play a role in the pathophysiological explanation for pain.

Nijs *et al.* (2005b) concluded that excessive nitric oxide leads to central sensitization, which may account for the chronic widespread pain.

Vecchiet *et al.* (1996) challenges this central sensitization theory. According to the authors the significant lower pain thresholds of the deltoid, trapezius and quadriceps to electrical stimulation corresponds to fiber abnormalities seen in muscle biopsies of the quadriceps. The assessment that hyperalgesia is absent in skin and subcutis contradicts with the idea of heightened perception of physiological signals.

Almost all ME/CFS patients report that the pain they experience, is aggravated by exercise.

Even if exercise has strict limitations (very low intensity, very short duration), musculoskeletal pain and bodily pain in general increase immediately post-exercise. This situation is retained 24 hours after exercise (Nijs *et al.* 2008).

This increase of (muscle) pain after exercise can be explained by various mechanisms: impaired oxygenation due to disturbed vasodilatation/vasoconstriction homeostasis, accentuated oxidative and nitrosative stress, additional induction of inflammatory pathways, altered muscle membrane excitability, reduced aerobic metabolism, hypoperfusion, and dysfunction of central anti-nociceptive mechanisms.

Nijs *et al.* (2005b) hypothesizes post-exertional malaise, including pain, originates from immune system dysfunction. Activation of PKR and subsequent NF-kB activation might account for the increased production of nitric oxide, while infectious agents frequently associated with ME/CFS, might initiate or accelerate this process. Elevated nitric oxide is known to induce vasodilatation, which may limit ME/CFS patients to increase blood flow during exercise, and may even cause enhanced post-exercise hypotension.

Jammes *et al.* (2005) concluded that a lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability in response to incremental exercise are sufficient to explain muscle pain and post-exertional malaise reported by ME/CFS patients.

Another plausible explanation for prolonged muscle pain after exercise has been described by Bounous & Molson (1999). Glutathione (GSH) precursors are utilized by the immune system, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia (muscle pain).

Exercise also affects the pain thresholds of ME/CFS patients. Pain thresholds, measured in the skin web between thumb and index finger, increased in control subjects with exercise, while it decreased in the ME/CFS patients (Whiteside *et al.* 2004). According to the authors the increased perception of pain may result from dysfunction of a central anti-nociceptive mechanism.

Light *et al.* (2008) demonstrated that acid sensing ion channel (probably ASIC3), purinergic type 2X receptors (probably P2X4 and P2X5) and the transient receptor potential vanilloid type 1 (TRPV1) are molecular receptors in mouse sensory neurons detecting the metabolites (combinations of protons, ATP, and lactate), that cause acute muscle pain and possibly muscle fatigue. Light *et al.* (2009) also established recently that moderate exercise increases expression for the metabolite detecting receptors ASIC3, P2X4, and P2X5 in ME/CFS patients. These increases, lasting from 0.5 to 48 hours, highly correlated with the symptoms of physical fatigue, mental fatigue, and pain.

g) Impairment of the ion channel function in ME/CFS and potential effects of exertion

Channelopathy, i.e. abnormal ion channel function, also seems to play a central role in the pathogenesis of CFS.

Ion channel abnormalities were found by gene expression studies (Broderick *et al.* 2006; Fang *et al.* 2006).

Several authors have suggested that channelopathy may account for fluctuating fatigue, exercise intolerance and other symptoms (Chaudhuri *et al.* 2000; Englebienne *et al.* 2002; Snell *et al.* 2005).

Channelopathy seems to increase as a result of exertion.

According to a gene expression study of ME/CFS patients (Whistler *et al.* 2005) differences in ion transport and ion channel activity were evident at baseline and were exaggerated after exercise. This implicates that ion channel abnormalities are likely to increase as a result of exertion.

h) Stress response disturbances in ME/CFS and negative effects of exercise

Various studies have established hypothalamic-pituitary-adrenal (HPA) axis anomalies in ME/CFS, including an insufficient stress response.

Di Giorgio *et al.* (2005) demonstrated subtle alterations in HPA axis activity characterized by reduced adrenocorticotrophic hormone (ACTH) over a full circadian cycle and reduced levels of ACTH during the usual morning peak.

Significantly reduced baseline ACTH levels were identified by Gaab *et al.* (2002).

Van den Eede *et al.* (2007) described mild hypocortisolism, a blunted ACTH response to stressors and an enhanced negative feedback sensitivity to glucocorticoids.

The findings of a gene activity network analysis (Fuite *et al.* 2008) align with known mechanisms of chronic inflammation and support the notion that possible immune-mediated loss of thyroid function in ME/CFS is exacerbated by blunted HPA axis responsiveness.

When reviewing relevant studies it seems that a clear distinction can be made between ME/CFS, burnout and depression based upon HPA axis functioning.

According to Scott *et al.* (Scott & Dinan, 1998) patients with depression have urinary free cortisol (UFC) excretion values which were significantly higher than healthy controls, whereas UFC excretion of ME/CFS patients was significantly lower than the controls, in line with in hypotheses of hyperactivity and hypoactivity of HPA axis in depression and ME/CFS respectively. ME/CFS patients with co-morbid depressive illness retained the profile of UFC excretion of those with without, suggesting a different pathophysiological basis for depressive symptoms in ME/CFS.

Decreased UFC excretion in ME/CFS was also established by Cleare *et al.* (2001).

In patients with burnout, however, HPA-axis functioning is normal according to Mommersteeg *et al.* (2006).

HPA axis abnormalities seem to be more pronounced in females. e.g. Segal *et al.* (2005) and Nater *et al.* (2008). This assessment is important since approximately 70–85% of the CFS patients is feminine.

The ability to respond adequately to physical or emotional stress also seems to be impaired in ME/CFS patients.

Controlling for possible confounding variables, Gaab *et al.* (2002) found significantly lower ACTH response levels in the psychosocial stress test and the exercise test, and significantly lower ACTH responses in a insulin tolerance test, with no differences in plasma total cortisol responses.

Segal *et al.* (2005) investigated the stress response provoked by low dose synacthen tests. They found that ME/CFS patients had significantly lower mean serum cortisol levels during the test, lower peak cortisol, reduced cortisol area under the curve and longer time to peak cortisol.

Thambirajah *et al.* (2008) investigated the heat shock protein expression levels in ME/CFS patients before and after exercise. Basal HSP27 levels were higher among ME/CFS patients than in controls, decreased immediately post-exercise and remained below basal levels at day 1 post-exercise, while HSP27 levels remained relatively constant following exercise among control subjects. Similar patterns, i.e. declining HSP levels compared with basal levels, were also observed for HSP60 and for HSP90 at day 7 post-exercise. HSP60 levels in control subjects increased at day 1 and day 7 post-exercise compared to corresponding levels immediately post-exercise. The authors conclude that their preliminary findings suggest an abnormal or defective adaptive response to oxidative stress in CFS.

Delayed and marked reduction of heat shock protein 27 (Hsp27) and 70 (Hsp70) variations in ME/CFS in response to incremental cycling exercise until exhaustion were found by Jammes *et al.* (2009). Amongst others, heat shock proteins protect cells against the noxious effects of oxidative stress.

In addition to this, solely based upon established HPA axis – stress response aberrations, it seems very likely that the endocrine disturbances are caused or amplified by physical exertion.

i) GET can physically harm patients with ME/CFS

Based upon the abovementioned observations and various other studies, it can be alleged that – in ME/CFS – exertion and, by inference, GET, have an negative impact on pre-existing abnormalities, e.g. physical limitations, neurocognitive impairment, immune dysfunction, inflammation, oxidative and nitrosative stress, channelopathy, (muscle) pain, muscle weakness and defective stress responses. This is illustrated by ***Figure 3, next page***.

Discussion

When looking at the evidence-base, it can be claimed that the effectiveness of CBT/GET is negligible. If drop-outs etc. are taken into account, the effectiveness of CBT/GET (20–40%), compared to support groups, natural course, standard medical care etc. (20–30%) is only marginal. Especially if taken into consideration the fact that fatigue, which is not only subjective, but also insufficient for a ME/CFS diagnosis, was the only measure in most studies.

The evidence-based success claim of CBT/GET cannot be substantiated, since only a few randomized controlled trials for CBT/GET can be identified. Most of these studies explicitly excluded large groups of ME/CFS patients and/or included non-ME/CFS patients, due to the selection criteria.

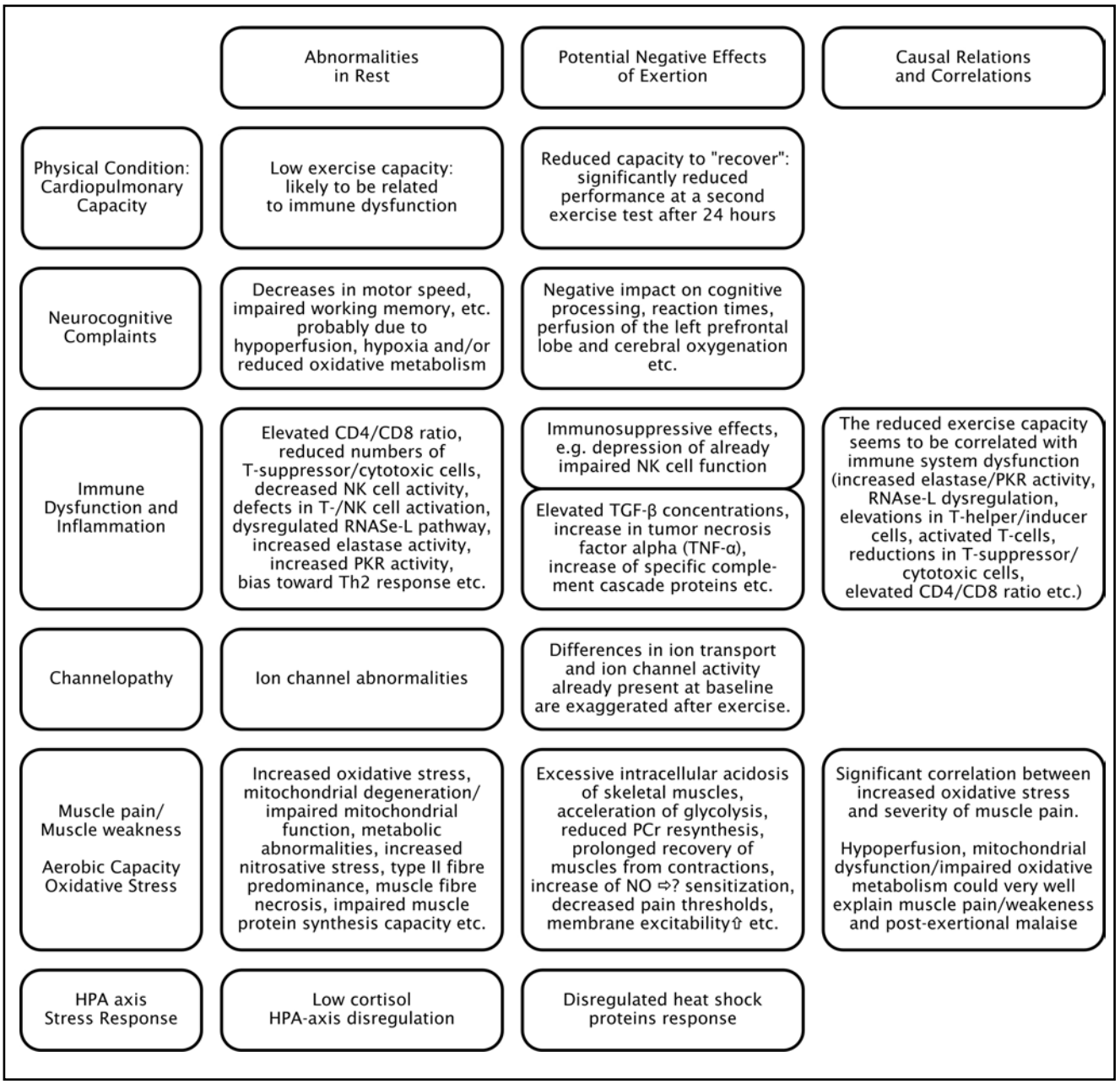

Figure 3. This figure summarize symptomology, biological abnormalities, correlations between symptoms and abnormalities, and the potential negative impact of on those symptoms and aberrations (not intended to be complete).

So, it can be concluded that the efficacy claim for CBT/GET is false. But what is more important, is the fact that numerous studies support the thesis that exertion, and thus GET, can physically harm the majority of the ME/CFS patients.

This assertion is confirmed by the outcomes of two large patient surveys in the UK and Norway, and two smaller surveys in Scotland and the Netherlands.

The results of the AfME survey in 2001, cited in (CFS/ME Working Group, 2002), with more than 2,180 patients responding, are very clear. Of the 1214 patients who had participated in a CBT/GET program, 34% considered CBT/GET to be helpful, 16% reported no change, while 50% responded CBT/GET made them worse. CBT (without GET) was considered to be helpful for 7%, 67% reported no change, and 26% responded it made them worse.

The AfME Scottish Survey from 2007 reported even worse results. GET had no effect for 14% of the patients and a negative effect for 74%. Only 12% considered GET to be helpful. Graded Activity (comparable with GET, but less strict) was helpful for 32% of the participating patients, 14% reported "no effect", and according to 54% Graded Activity made them worse. 39% reported CBT (without GET) had improved their situation, 44% responded it had had no effect, and 18% reported it had made them worse.

828 persons with ME/CFS participated in a Norwegian patient survey by Bjørkum *et al.* (2009). Pacing was evaluated as useful by 96% of the participants, rest by 97%, and 96% of the participants considered complete shielding and quietness to be useful. 57% of the participants who had received help to identify and challenge negative thought patterns (CBT) regarded this useful. Seventy-nine % of the participants with experience from graded exercise regarded this to worsen their health status. Overall, the results were similar, irrelevant of the severity of the condition. The results must be interpreted with care, according to the authors, since the sample may not be representative, due to the fact that participants were recruited through two Norwegian patient organizations.

The results of a patient survey conducted on the effect of CBT/GET in the Netherlands in 2008 (Koolhaas *et al.*) (100 patients) are in line with the thesis that CBT/GET is as effective as usual care and potentially harmful for a large subgroup. Only 2% of respondents reported they considered themselves to be completely cured upon finishing the therapy, 30% reported "an improvement", 30% reported no change, and 38% said the therapy had affected them adversely, the majority of them even reporting substantial deterioration. Participating in CBT/GET proved to have little impact on the number of hours people were capable of maintaining social contacts or doing household tasks. A striking outcome is that the number of those respondents who were in paid employment or who were studying while taking part in CBT/GET was adversely affected. The negative outcome in paid employment was statistically significant.

As described above, CBT/GET has also proven to be counterproductive in clinical practice of the Belgium CFS Reference Centers (Council of approval with regards to rehabilitation contracts with CFS reference centres for patients suffering from Chronic Fatigue Syndrome, 2006).

The assertion that GET is harmful for a large subgroup of ME/CFS patients is also supported by two recent studies of Jason *et al.* (2007) and (2008).

The success rate of CBT/GET according to a study of Jason *et al.* (2007) was 20% ("recovered ME/CFS patients" improved by only 20%). In a follow-up study Jason *et al.* (2008), using the SF-36 Physical Functioning Scale, divided the participants in two groups: patients which improved by CBT/GET, CBT, anaerobic exercise, and relaxation (42%), and patients who did not (58%). Physical functioning rates for those who improved versus those who did not were not significantly different at baseline, but were significantly different at afterwards. Those in the improved group changed from 43.9 to 66.0, whereas those who did not improve showed declining scores from 50.4 to 42.2. So, in most cases "non-improvement" was equivalent with "aggravation".

The authors concluded that overall, those who did not improve demonstrated alterations in lymphocyte subset distributions that suggested that their immune system had experienced prior immune stimulation and expansion of T and B cell subsets, relative to the improving group. ME/CFS patients with a dominance of the Type 2 over the Type 1 immune response, as indicated by the patterns of lymphocyte subset distributions, tended not to improve (read: to deteriorate) over time by all non-pharmacological treatments, including CBT/GET and anaerobic exercise.

Conclusions

If taken into account drop-out rates and the fact that efficacy is measured by fatigue only, which is very subjective and hardly sufficient for the diagnosis ME/CFS, the effectiveness of CBT/GET (20–40%), when compared to support groups, natural course, standard medical care, etc. (20–30%), is negligible.

Since only a few randomized controlled trials for CBT/GET can be identified and most of these trials, as a result of the selection criteria, excluded many ME/CFS patients and/or included non-ME/CFS patients, the evidence-based claim for proven effectiveness of CBT/GET for ME/CFS cannot be substantiated.

Not only is the evidence-based claim for CBT/GET unjust, there is compelling evidence that CBT/GET is potentially harmful for many ME/CFS patients. Numerous studies support the assertion that exercise and, consequently, GET, can aggravate several characteristic ME/CFS symptoms, e.g. neurocognitive complaints, reduced exercise capacity and widespread muscoskeletal pain, and amplifies pre-existing pathophysiological abnormalities in ME/CFS, e.g. immune dysfunction, induction of the IO&NS pathways, channelopathy and an impaired stress response. Large-scaled patient surveys and clinical practice show that CBT/GET often induces a deterioration of the clinical status of ME/CFS patients and is harmful for many patients.

Therefore, it is medically unethical to subject ME/CFS patients to CBT/GET programs or variants, like GET with limits (Nijs *et al.* 2008), without assessing biological abnormalities, monitoring functional impairment objectively and measuring the effect of exercise e.g. on the physical and neurocognitive performance (e.g. by using exercise test/retest measurements, blood analysis, and neurocognitive tests).

When one looks at the facts and the objective data, it is incomprehensible that CBT/GET is still promoted by many (semi) governmental agencies and professional organizations.

Des Turner MP, Chair of the All Party Parliamentary Group on ME (Group on Scientific Research into Myalgic Encephalomyelitis/M.E., 2006a), described the NICE (NHS – National Institute for Health and Clinical) guidelines, which recommends CBT/GET for ME/CFS to medical professionals, as 'not fit for man nor beast'. Dr Ian Gibson MP described the guidelines as

'useless' (Group on Scientific Research into Myalgic Encephalomyelitis/M.E., 2006b).

'I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.' (Hippocratic Oath)

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