Review Article

Customizing Treatment of Chronic Fatigue Syndrome and Fibromyalgia: The Role of Perpetuating Factors

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Background: *Syndromes characterized by chronic, medically unexplained fatigue, effort- and stress-intolerance, and widespread pain are highly prevalent in medicine.* **Results:** *In chronic fatigue syndrome (CFS) and fibromyalgia (FM), various perpetuating factors may impair patients' quality of life and functioning and impede recovery. Although cognitive-behavioral and graded-exercise therapy are evidence-based treatments, the effectiveness and acceptability of therapeutic interventions in CFS/FM may largely depend on a customized approach taking the heterogeneity of perpetuating factors into account.* **Conclusion:** *Further research should clarify the aim and outcome of different treatment strategies in CFS/FM, as well as the underlying mechanisms of change, including those facilitating neurobiological recovery.* (Psychosomatics 2008; 49:470–477)

Syndromes characterized by chronic, medically unexplained fatigue, effort- and stress intolerance, and widespread pain are highly prevalent in medicine, from general practice to several medical specialties. Such syndromes cause much individual and family suffering, and are often associated with serious physical, mental, and social/professional disability.[1]

Operational criteria have been formulated, defining these symptom-pictures as chronic fatigue syndrome (CFS)[2] and fibromyalgia (FM;[3] Table 1). However, since both syndromes largely overlap, some authors ("lumpers") argue that CFS and FM should be merged under the broad umbrella of "functional somatic syndromes," whereas others ("splitters") plead for maintaining CFS and FM as discrete entities.[4] Although the scientific literature on CFS and FM still follows distinct paths, there are increasing tendencies toward an integrative approach of these and other stress-related somatic syndromes.[5–7] In this article, we will assume the "lumper" point of view by using the abbreviation CFS/FM.

On the other hand, it has become evident that patients with a CFS/FM diagnosis are a heterogeneous group. In this respect, different subgroups have been proposed, for example, depending on type of onset (sudden or gradual, initiating infection or not, etc.),[8] activity patterns (passive or relatively active),[9] or putative biological mechanisms,[10] but no consensus has been reached on this issue.

Current evidence-based treatments for CFS/FM mainly consist of cognitive-behavioral therapy (CBT) and graded-exercise therapy (GET).[1] However, despite positive results in randomized, controlled trials (see metaanalyses[11–13]), the use of these treatments in routine clinical practice is still problematic—as, for example, reflected on websites of patient-support groups.[14] Moreover, many questions remain about the therapeutic aim, strategies, and outcome, as well as mediating and moderating processes underlying mechanisms of change in CFS/FM treatment.[15,16] Also, little attention has been paid to the role of perpetuating factors in explaining heterogeneity among CFS/FM patients and to the way in which this heterogeneity may influence treatment results.

Hence, the main aim of this article is to clarify the

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TABLE 1. Operational Diagnostic Criteria for Chronic Fatigue Syndrome (CFS)[2] and Fibromyalgia (FM)[3]

CFS
Medically unexplained, persistent fatigue, of new onset, not due to ongoing exertion, not substantially relieved by rest, and significantly reducing previous activity levels
Four-or-more additional symptoms, for at least 6 months, among which are
multiple muscle/joint pains
concentration/memory disturbances
non-refreshing sleep
headache (new onset)
sore throat
tender lymph nodes
post-exertional malaise
FM
History of widespread pain for at least 3 months
Pain in 11 of 18 tender point sites on digital palpation

rationale of CFS/FM treatment in light of the heterogeneity of perpetuating factors. We will first outline a biopsychosocial model of the etiology and pathogenesis of CFS/FM. Subsequently, we will review recent empirical evidence about the role of perpetuating factors in the illness. Finally, we will argue that, in clinical practice, the effectiveness and acceptability of therapeutic strategies in CFS/FM may largely depend on customizing interventions to the patient's personal set of perpetuating factors.

THE BIOPSYCHOSOCIAL MODEL

Etiological Factors

Although the etiology of CFS/FM is still uncertain, various precipitating, predisposing, and perpetuating factors have been identified, suggesting that multiple pathways may lead to the causation and persistence of the illness (Figure 1).[1,17]

More concretely, a whole range of physical and psychosocial stressors seem to play a precipitating role; familial-genetic factors, traumatic experiences, personality/lifestyle factors, and previous episodes of depression may increase vulnerability to CFS/FM, and various physical, perceptual-cognitive, affective, personality-related, behavioral, social, and iatrogenic factors may perpetuate the illness.[1,17]

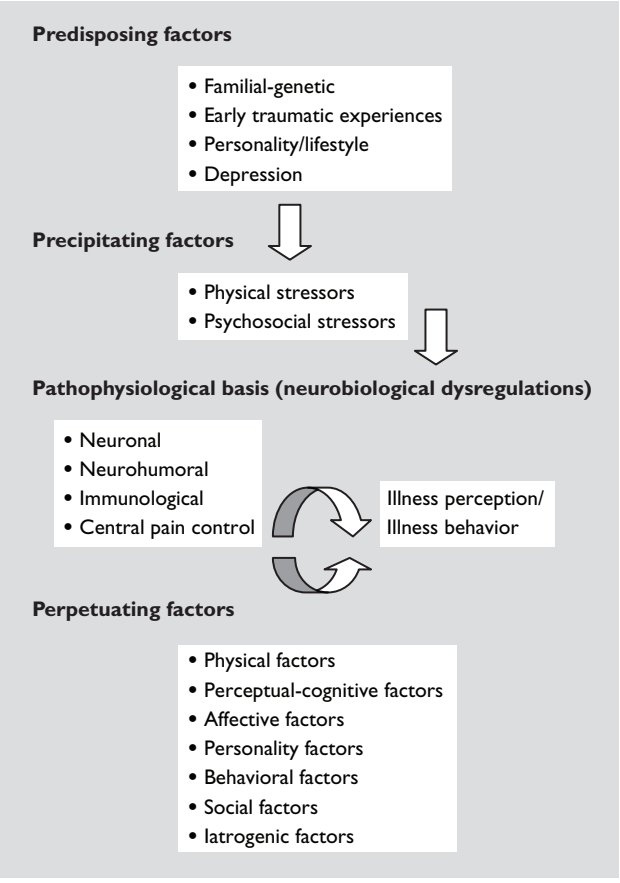
Pathophysiological Hypothesis

The exact pathophysiology of CFS/FM remains unclear, yet it has become very probable that the illness has a neurobiological substrate including subtle disturbances in physiological regulatory systems; notably, the neurohormonal stress system, different neurotransmitter systems, the immune system, and the central pain-processing system.[1,17]

Most neurobiological findings point to a hypo-(re)activity of the hypothalamic–pituitary–adrenal (HPA) axis, which may not only impede a normal stress response, but also foster abnormal inflammatory activity.[17–19] Also, the widespread pain and pain hypersensitivity of CFS/FM patients (allodynia) may be based on central sensitization, in which cytokine-mediated inflammation, as well as genetically-determined disturbances in neurotransmitter balance, lead to decreased central pain inhibition.[17–20]

Many questions remain, however, about the causal significance of these neurobiological findings.[1,21,22] Nonetheless, the illness-narrative of most CFS/FM patients,[23] as well as retrospective studies,[1,17] suggest that a dysfunction of the stress system may be the *primum movens* of the illness, whereby, after a long period of overburdening, a

FIGURE 1. Biopsychosocial Model of Chronic Fatigue Syndrome/ Fibromyalgia



"switch" from hyper- to hypofunctioning might take place, which, in turn might provoke a cascade of further neuronal, neurohormonal, and immunological dysregulations. This hypothesis nicely fits within McEwen's "allostatic load" paradigm,[24] and it has recently received preliminary support from a metaanalysis[25] and a population-based study.[26]

Finally, perpetuating factors may—often via vicious circles—not only reinforce symptoms and disability, but presumably also impede recovery by interacting with the pathophysiological basis of the illness, and/or negatively influencing the patient's associated illness-perceptions and illness-behavior. These factors, listed in Table 2, will be discussed below.

PERPETUATING FACTORS

Physical Factors

Deterioration of CFS/FM patients' physical condition logically results from their decreased activity due to fatigue and pain. In turn, loss of muscle power and endurance (cardiopulmonary functioning) reinforces and perpetuates symptoms and makes daily functioning still more problematic.[27]

However, research findings about the precise role of physical deconditioning in CFS/FM are equivocal. Taken together, findings converge to suggest that the degree of physical deconditioning varies significantly among patients and that—in contrast with previous theories—this factor does not seem to play a specific pathophysiological role in the illness.[27]

Furthermore, persistent sleep problems may make symptoms and functional limitations in CFS/FM patients worse, often also through circular interactions. Nonetheless, the perpetuating role of disturbed sleep in CFS/FM and the contribution of perceptual factors in this respect remain unclear.[28–30]

Also, some biologically-oriented researchers have proposed that CFS/FM patients frequently suffer from opportunistic infections (e.g., chlamydia and mycoplasma microorganisms), which may be at least partly responsible for the persistence of some symptoms.[10] At this moment, however, there is no evidence either for the validity of this hypothesis or for the pharmacological therapy based on it (see, for example, the results of a large antibiotic trial in patients with Gulf-War syndrome who showed CFS-like symptoms.[31])

TABLE 2. Potential Perpetuating Factors in Chronic Fatigue Syndrome (CFS)/Fibromyalgia (FM)

- Physical Factors
  - Physical deconditioning[26]
  - Sleep disturbance[27–29]
  - Opportunistic infections[9]
- Perceptual-Cognitive Factors
  - Lack of information[31]
  - Somatic hypervigilance/preoccupation[32]
  - Rigid somatic attribution[1]
  - Catastrophizing[33]
  - Low self-efficacy[1]
- Affective Factors
  - Depression[34–40]
  - Anxiety disorders[37,38]
  - Kinesiophobia[42,43]
  - Problematic affect regulation[44,45]
- Personality Factors
  - Perfectionism/dependency[22,46,51]
  - Introversion[46]
  - Alexithymia[48–50]
- Behavioral Factors
  - Lack of adaptation/acceptance[54,55]
  - Periodic overactivity[53]
- Social Factors
  - Lack of understanding[56–59]
  - Secondary gain/operant conditioning[61,62]
  - Membership in patient-support group[63]
- Iatrogenic Factors[64]

Perceptual-Cognitive Factors

Many CFS/FM patients are badly informed about their illness or lose their way in the labyrinth of diverse theories and opinions (for example, on the Internet). This uncertainty not only causes much stress, but also makes symptoms and disability worse, and hinders efficient coping.[32] Some patients focus excessively on even minimal signs of physical distress (somatic hypervigilance).[33] Others show a tendency toward rigid somatic attributions while vigorously rejecting psychological or psychiatric explanations,[1] or remain preoccupied with their functional limitations or catastrophize about the prognosis of their illness.[34] Such perceptual-cognitive biases may play an illness-perpetuating role by making patients feel helpless, leading to decreased self-efficacy.

Affective Factors

Chronic pain and fatigue are frequently associated with depression and anxiety, and there are indications of neurobiological and familial-genetic links between these different sets of symptoms and syndromes.[35–37] Most frequent are feelings of demoralization and frustration, in response to the loss of earlier capabilities, but some CFS/FM patients show manifest major depression, panic disorder, or posttraumatic stress disorder.[38,39]

Although the relationship between depression and chronic physical illness has been much studied in recent years,[40] the exact nature, prevalence, and therapeutic implications of comorbidity between depression and CFS/FM are still a matter of debate.[40–42] Nonetheless, it can be assumed that additional depressive symptoms in these patients may perpetuate the illness by reinforcing symptoms and increasing the risk of patients' negatively spiralling into more severe functional limitations.

To what degree fear of movement and associated activity-avoidance may play a perpetuating role in CFS/FM is unclear, but it seems fair to state that only a minority of patients are really "kinesiophobic."[43,44]

Finally it should be mentioned that, particularly in patients with FM, not only high levels of negative affect have been demonstrated,[45] but even more pronounced deficits in positive affects, increasing the risk of depression in response to illness-related stressors.[46]

Personality Factors

The role of personality in CFS/FM is largely *terra incognita*. Experienced clinicians have described CFS patients as conscientious, hard-working, somewhat "neurotic," and introverted individuals with high personal standards, a strong wish for social acceptance, and a life-history that is often characterized by exceeding physical limitations.[23]

However, systematic research on the role of personality in hampering adaptation to the illness—and thus perpetuating it—is still in its infancy.[47] Interesting research topics in this context would be the following: links between personality and comorbid depression in CFS/FM;[48] emotion regulation related to alexithymia,[49,50] including biological measures such as salivary cortisol;[51] the way in which some CFS/FM patients may create their own stress, for example, by being too perfectionistic;[52] and the role such personality and lifestyle factors may play in the prognosis of CFS/FM and other functional somatic syndromes.[53]

Behavioral Factors

CFS/FM patients who do not accept their limitations or have difficulty adapting are not only more emotionally distressed but may unintentionally perpetuate their illness. Indeed, as soon as they feel somewhat less fatigued, they may engage in inappropriate activities, putting their disturbed stress mechanisms under severe pressure and making recovery less probable. Patients with a history of an overactive lifestyle may be particularly prone to this "boom-and-bust" activity pattern.[54]

In chronic-pain patients[55] as well as in patients with a CFS diagnosis,[56] it has been found that "nonacceptance" is correlated with lower quality of life and more associated psychiatric symptoms, but whether this also results in a less favorable outcome of CFS/FM remains to be studied.

Social Factors

Lack of recognition and understanding is a perpetuating factor that cannot be overestimated. Concretely, many CFS/FM patients complain of a skeptical attitude or even disbelief from their family members ("You don't look ill!"), as well as from private or governmental insurance agencies ("[This illness] does not exist!").[57–60] Such reactions not only cause extra stress for the patient and diminish his or her quality of life, but may also encourage illness-behavior: in the words of Hadler:[61] "when you have to prove you are ill, you cannot get well."

Some CFS/FM patients—like other chronically ill patients—welcome the sickness status because it provides them with a range of advantages, such as a solicitous partner.[62] In classical terms, this has been called "secondary gain," but this illness-reinforcing mechanism can also be formulated in terms of operant conditioning.[63]

Opinions differ as to whether membership in a CFS or FM patient-support group might play a role in the prognosis of the illness. Nevertheless, a recent investigation found that active—as compared with nonactive—support-group members had more serious symptoms and showed a less favorable illness outcome.[64]

Iatrogenic Factors

A final perpetuating factor may be the inadequate treatment behavior of doctors and therapists.[65] Some practitioners seduce the patient into undergoing various investigations (e.g., sophisticated immunological tests) or interventions with dubious benefit (among them, the replacement of dental amalgam fillings or long-lasting treatment with antibiotics or nutritional supplements). Others impose unfounded beliefs onto patients, making them catastrophize even more ("Your immune system is a total loss!"). Such messages may decrease patients' self-efficacy beliefs and active coping efforts, which, as studies discussed below demonstrate, are crucial requirements for recovery.

FROM PERPETUATING FACTORS TO THERAPY

Aims, Strategies, and Outcome

The rationale of current treatment interventions in CFS/FM can be formulated as follows: since the pathophysiology underlying the illness cannot be actively (e.g., pharmacologically) corrected, treatment should aim at creating optimal conditions for "natural" stress-system recovery by tackling illness-perpetuating factors.

In this respect, cognitive-behavioral therapy (CBT) and graded-exercise therapy (GET) have shown moderate efficacy in CFS/FM via randomized, controlled trials (RCTs).[11–13] However, the effect sizes for individual CBT are significantly higher than those for CBT-based group programs.[66,67] This may, at least partly, be due to the heterogeneity of perpetuating factors, implying that individual treatment may be better able to address this heterogeneity. Also, therapeutic effects are not always maintained in the long-term, and drop-out rates are fairly high,[11,68,69] which may also be related to insufficiently individualized treatment. Furthermore, we cannot ignore the resistance of some researchers and patient organizations to CBT and GET—particularly when they follow a fixed protocol.[10,14]

It seems crucial, therefore, that the clinical application of CBT/GET should not be based on a "one-size-fits-all" approach, but should be carefully tailored to the patient's personal needs.[1,68] The recently-published NICE (British National Institute for Health and Clinical Excellence) guidelines for CFS/ME, similarly, recommend a customized therapy.[70]

Finally, opinions differ as to what might be an attainable therapeutic outcome in CFS/FM. Should these patients, in the first place, accept their ailment and learn to cope optimally with symptoms and functional limitations, or should they strive for real recovery? And, in the latter case, how should "recovery" be defined? Should patients, after a symptomatic and functional improvement, stop defining themselves as CFS or FM patients, or should they take account of their—possibly lifelong—vulnerability? These are questions for which no definitive answer has yet been given. (Several investigators[15,16,71] have offered more extensive discussions.)

THERAPEUTIC PROCESSES

There is a manifest lack of knowledge about factors that could account for and predict successful treatment in CFS/FM.[1,68] What are the core therapeutic ingredients of CBT and GET in these patients? Is therapeutic success initially dependent on correcting cognitive-perceptual errors and behavioral adaptation, or are there more fundamental factors at work, such as changes in emotional processing?[72] Are some perpetuating factors more difficult to influence than others? Are there contraindications for these treatment strategies ? How can these treatments lead to enduring adjustments of personality traits, lifestyle, and life goals—rather than producing only temporary changes, such as a deactivation of maladaptive cognitive-affective schemas that could easily be reactivated by new stressors?[73]

Such questions—which are crucial in view of individualizing therapy—should be studied via process-outcome studies, focusing on putative mechanisms of change. In this respect, the question "what works, and for whom?"[1,68] could be best addressed by using a conceptual framework distinguishing between predictors, mediators, and moderators.[74]

Today, such studies are still scarce. In FM, cognitive behavior and exercise treatments have been shown to be most effective in distressed patients in which the disorder has had a high impact on their daily life.[68] In CFS, some of the perpetuating factors discussed above (such as membership of a self-help group, receipt of sickness-benefits, low sense of control, strong focus on symptoms, emotional problems, and passivity) have been found to predict negative treatment-outcome of CBT,[1] whereas a decrease in symptom-focusing predicted a positive outcome for GET.[75] These findings are congruent with studies in chronic low-back pain showing that changes in catastrophizing and self-efficacy/helplessness in part mediated the effects of a multidisciplinary rehabilitation program.[76–78]

Finally, although it has been suggested that a favorable therapeutic outcome in CFS/FM might be paralleled by positive changes in the neurobiological substrate of the illness,[1] in line with recent evidence that CBT and exercise may increase resiliency of the HPA axis,[79–81] no definitive proof of such effects in CFS/FM patients has been given until now.

Therapeutic Practice

In the clinical setting, individualized treatment should consist of three components: First, adequate therapy of possible comorbid depression, anxiety, and sleep disturbances, as well as optimal pain control, should be carried out, to minimize patients' emotional and physical distress.[82] Although antidepressants certainly have a role to play in this respect,[35] it remains controversial whether these medications might also lead to lower levels of fatigue.[42]

Second, the patient should be offered a plausible illness theory that can be the starting-point for translating the therapeutic rationale into concrete practice. In accordance with the presumed pathophysiology of CFS/FM, a formulation in terms of "loss of stress-system resilience" could be useful, since it points to real, although subtle, biologically-based disturbances; it links physical and psychological factors, and has a nonstigmatizing and "nonpsychiatric" character, implying multiple "handles" for therapeutic change.

Third, we should discuss with patients which perpetuating factors will be concretely targeted during the therapy and what, in his or her particular case, might be realistic objectives. For most CFS/FM patients, it will be helpful to learn to pace their activities, instead of periodically exceeding their limits and provoking repeated setbacks manifesting as post-exertional malaise.[71] Also, some patients must be assisted to rebuild their physical condition, by overcoming "fear of movement," while, at the same time, respecting their dysfunctional recovery mechanisms.[27] Other persons must be confronted, for example, by means of a "Socratic dialogue," to abandon their erroneous or unfruitful illness-beliefs that foster catastrophizing and undermine self-efficacy, replacing them by more helpful approaches.[1] For some patients, stress-management techniques such as relaxation training may be useful, as well as counseling focused on acceptance-based[55,56,83] or affect-regulation[46,72] principles. Some patients should be treated together with their partner in order to find a common *modus vivendi* adapted to intended life-changes. Still others need active coaching in their efforts for progressive professional reintegration or search for medical/social compensation.[84] Also, many CFS/FM patients may benefit from gaining insight into personality and lifestyle factors that have contributed to their illness, since a better understanding of the past can help keep future stress levels within acceptable limits and help find a new equilibrium.[52,72]

It logically follows from the above that results of randomized, controlled trials in CFS/FM (such as the current therapeutic trial in the U.K. comparing CBT, GET, and pacing[85]) can guide, but never be simply translated into, clinical practice.[86] Thus, future process-outcome studies should randomize different subtypes of CFS/FM patients to different treatment conditions that should be customized in turn to individual patterns of perpetuating factors.

Finally, it may be expected that a more personalized therapeutic approach may foster the openness of patients and researchers to a pragmatic management of symptoms and functional limitations, and counteract perceptions of psychological or rehabilitative treatments as being inflexible and dogmatic.[10,14]

CONCLUSION

Next to precipitating and predisposing factors, various perpetuating factors seem to play a role in CFS/FM by interacting with neurobiological dysfunction and associated perceptual and behavioral disturbances.

From a therapeutic point of view, CBT and GET (as well as other interventions) should start from a plausible illness theory and focus on perpetuating factors in a tailored, patient-centered way. Under these conditions, psychological and rehabilitative treatments may improve quality of life and functioning in CFS/FM patients and optimize their chances of recovery.

Nonetheless, many uncertainties remain about the therapeutic aim, strategies, and outcome, as well as the mechanisms of change underlying the above-mentioned treatments, particularly with regard to the recovery of stress-system functioning. Long-term follow-up studies are needed to provide answers to these unsolved questions.

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