

## **Is cognitive behaviour therapy with a graded activity protocol effective for chronic fatigue syndrome and Myalgic Encephalomyelitis? An analysis of five Dutch hallmark studies.**

### **Reference**

**An analysis of Dutch hallmark studies confirms the outcome of the PACE trial: Cognitive behaviour therapy with a graded activity protocol is not effective for chronic fatigue syndrome and Myalgic Encephalomyelitis.**

FNM Twisk, LAMM Corsius.

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<http://www.oatext.com/pdf/GMO-1-117.pdf>

### **Introduction**

Advocates of the [\(bio\)psychosocial explanatory model for 'ME/CFS'](#) and the 'behavioral interventions' based on this model (CBT: [cognitive behavioral therapy](#) and GET: [gradual exercise therapy](#)) often refer to the results of the PACE trial and studies from the Netherlands.

The prestigious [PACE trial](#) has been [controversial](#) from the very first moment. Recently, the Journal of Health Psychology published [a special issue](#) to address the [methodical shortcomings](#) and [disappointing outcomes](#) of the PACE trial.

Various analyzes of the [PACE trial](#) and follow-up studies have made it clear

- that the PACE trial suffers from various serious [methodological flaws](#),
- that the patient group studied were not [CFS](#) patients, let alone people with [ME](#), but people with [chronic fatigue](#) (CF),
- that the effects of CBT and GET on subjective measures were (very) modest,
- that, looking at the [PACE trial protocol](#), there is [no question of recovery](#), and
- there was [no objective change](#) in the (hopeless) situation of patients.

A second important pillar of the 'evidence-base' for CBT and CBT+ in 'ME/CFS' are the studies of the Dutch [Expertise Center for Chronic Fatigue](#) (NKCv). CBT+ stands for CBT combined with/aimed at an incremental increase of activities.

## Is the claim of the NKCv that CBT+ is effective for CFS and ME justified by the data reported by five high-profile studies of the NKCv?

For a [study recently published in General Medicine Open](#),

five studies of the NKCv were selected on the basis of four criteria. The studies

- are [frequently cited in the scientific literature](#) and/or
- have, partly due to press releases of the NKCv, received a lot of [media attention](#),
- examined CBT+ in different variants (individually or in group sessions, face-to-face or through the internet/e-mail contact, for adults or adolescents) and
- have a strong influence on [medical policies for ME and CFS in the Netherlands](#).

To establish if the suggested effectiveness of CBT+ for CFS is supported by the (reported) data, the following five studies (and related secondary outcome studies, follow-up studies, commentaries and editorials) were analysed thoroughly:

- the prestigious [Prins et al., 2001](#) trial published in the Lancet,
- the [Bazelmans et al., 2005](#) trial that investigated CBT+ 'delivered' in groups,
- the [Stulemeijer et al., 2005](#) trial which studied CBT+ in adolescents,
- the [Knoop et al., 2007](#) study that claimed impressive recovery rates and
- the [Nijhof et al., 2012](#) (FITNET)-trial that studied internet CBT+ in adolescents.

The most important topics in the analysis of the studies were:

- the patient group investigated: [ME](#), [CFS](#) and/or chronic fatigue (CF)?
- the subjective and objective measures used to assess the effects of CBT+
- the cut-off threshold scores for the subjective measures, such as 'fatigue' and 'impairment' used as criteria to define 'clinical improvement' or 'recovery',
- the consistency of definitions of 'patient', 'improvement' and 'recovery', and
- the objective effects of CBT+, e.g. effect on the number of hours worked.

The results of that analysis are (briefly) described in the following pages.

For a detailed analysis of the studies, you are referred to the [article](#).

## The five studies suffer from serious methodical flaws

The five studies examined have various serious methodological shortcomings, relating to the participants, the research methods used and the outcomes.

Methodological shortcomings with regard to [participants](#) include:

- self-selection of the participants (patients who do not sign up for these trials), because [patients are very skeptical about psychological interventions](#),
- the observation that 'average' and 'serious cases' were not able to participate,
- the fact that a number of studies do not relate to [CFS](#), but to CF or CFS/CF,
- the observation that CBT+ has never been studied in a group of [ME](#) patients,
- the use of strongly fluctuating criteria to define and to select participants,
- the fact that [substantial group of eligible patients didn't want to participate](#), and
- the [high percentage of drop-outs/withdrawals](#) during the trails.

Criticism relating to the [research methods](#) used include:

- the fact that the NKCVC consistently use the label cognitive behavioral therapy (CBT), while [gradual expansion of activities](#) is the [goal of the therapy](#) (CBT+),
- the fact that patients know that they are subjected to therapy ('lack of blinding'),
- the risk that the outcomes will be (strongly) influenced by, among other things, by [a response bias](#), the [placebo effect](#) and the [bias of the researchers](#), especially if (almost) only subjective outcome measures are used,
- the [lack of a control group](#), in particular a non-intervention group, since [non-intervention](#) also seem to have a [positive effect in many patients](#), and
- [not reporting data](#) or [reporting data much later](#), especially objective outcomes.

Methodological criticism with regard to the [outcomes](#) include:

- the use of subjective measures to determine the effect of CBT+, especially since the NKCVC stipulates that increased activity and [resuming work](#) are the goals,
- the use of [incorrect statistical methods](#) to determine 'normal values',
- [defining recovery/improvement afterwards](#) ('post hoc') and
- the use of various different definitions of recovery and improvement, so that someone meets the criteria for recovery [in one study](#) of the NKCVC, while he/she meets the admission criteria for 'severe fatigue' of [another study](#).

In this context it is impossible to review all methodological flaws extensively. In this summary only a number of relevant shortcomings will be discussed.

Some trials studied CFS patients are investigated, other studies investigated CF patients or a mix of CF and CFS patients, but the effect of CBT+ in (a group of) ME patients has never been established

Two or three (?) trials investigated the effect of CBT+ in a group of [CFS](#) patients, a [fourth study](#) explored CBT+ in patients with chronic fatigue, while the [fifth study](#) evaluated CBT+ in a group of patients with the diagnosis CFS or chronic fatigue.

With regard to [one of the three studies](#) into the effects of CBT+ in [CFS](#), serious question marks can be raised about the correctness of the diagnosis of CFS. Some participants experienced ('comorbid') medical/psychological disorders which could plausibly explain 'fatigue', an exclusion criteria for a diagnosis CFS. On the other hand, only a few patients reported other ('comorbid') disorders, such as bowel problems, while [80% of the CFS patients experience co-morbidities](#).

The effect of CBT+ on ME patients has never been examined or reported (so far). So the effectiveness claim for CBT+ in ME lacks any scientific justification. By definition, [ME](#), a neuromuscular ('polio-like') disease, is [not a synonym of CFS](#).

In the case of 'ME/CFS', CBT is not the equivalent to cognitive behavioral therapy, but behavioral therapy combined with gradual expansion of activities, hence: CBT+.

[Cognitive behavioral therapy](#) (CBT) is a psychotherapy aimed at 'dysfunctional cognitions' (e.g. 'fear of movement') and subsequent behavior (e.g. avoiding activities).

But in the case of 'ME/CFS' 'CBT' refers to a combination of cognitive behavioral therapy (CBT) and 'rehabilitation therapy': [gradual expansion of the activity levels](#), which, according to the NKCVC, should ultimately result in [work resumption](#).

Looking at recent studies into energy production and metabolism, in particular

- a [study](#) showing that the energy production under pressure is largely inadequate,
- a [study](#) that found a deviant response of isolated muscle cells to exercise, and
- a [study](#) that observed metabolic abnormalities (a survival mechanism?),

one could raise several questions regarding the medical ethics of the researchers.

The five studies are largely based on subjective measures which are very sensitive to placebo effect, response bias, bias of researchers etc.

The NKCVC employs a wide range of subjective measures in its studies. Subjective measures are incomparable in time and in-between patients.

Moreover, these subjective measures introduce a high risk of a [response bias](#) (giving a socially desirable answer), a [placebo effect](#), a [buy-in effect](#) (related to the expectations that the patient has before the therapy), the [effect of the individual therapist](#), the [therapist-patient relationship](#), but above all, the [effect of bias of the researchers](#) ('researcher allegiance').

For example, in [one study](#) the SIP 8 score was one of the two criteria to be eligible. The effect of CBT+ in this study was largely insufficient to achieve 'normal values'. The SIP8 score is not included in the 'general' and 'strict' definition of 'recovery'. These definitions 'justify' the 'recovery rates' that are mentioned in the media (70%).

### Studies use widely varying 'cut-off values' for recovery and improvement

The five studies are characterized by a wide range of subjective measures with strongly fluctuating cut-off values for 'clinical improvement' and 'recovery'. The (arbitrary) cut-off values fully determine the outcomes of a study, e.g. recovery rates. As [a study by the NKCV](#) stipulates: 'Recovery is a construction'.

The use of highly fluctuating 'cut-off thresholds' for the three most commonly used measures, the [CIS F](#) score for 'the level of fatigue' and the [SIP 8](#) and [SF-36 PF](#) score for the 'functional/physical limitations', are illustrated in Figure 2, 3 and 4.

The use of various 'cut-off values' in the studies implicate that someone meets one of the criteria for 'recovery' in [one study](#), while he/she meets the eligibility criterion for 'severe fatigue' of [another study](#).

### Objective criteria are used very sporadically

While the NKCV poses in [one study](#) that "It is important that [patients] jointly (re) formulate a definition of the objective of the treatment." and patients have repeatedly reported that CBT+ has no or a negative effect, the effect of CBT+ on objective measures, such as the level of activity, the number of hours worked and school performance, is rarely determined objectively.

This is very remarkable, to say the least, especially because these objective measures reflect the goals of CBT + according to the NKCV.

The objective assessment of the effects of CBT+ is also important, because [one study](#) conducted by the NKCV observed that self-reported activity levels don't correspond well with the objective determination thereof.

### Objective outcomes of the study protocol were not reported or reported much later

Contrary to what is indicated in the study or the protocol of the trial, the effects of CBT+ on a highly relevant objective measure, the activity level, sometimes are [not reported at all](#) or are only [reported many years later](#).

Given the [lack of impact of CBT+ on activity levels](#) observed in three studies, and the fact that an increased activity level is the goal of CBT+ according to the NKCV, not reporting these data or reporting data nine years later is a scientific 'mortal sin'.

**In summary, we can conclude that  
the five studies of the NKCV  
are characterized by  
serious scientific flaws.**

Figure 1.  
ME and CFS are two distinct, partially overlapping, diagnostic entities

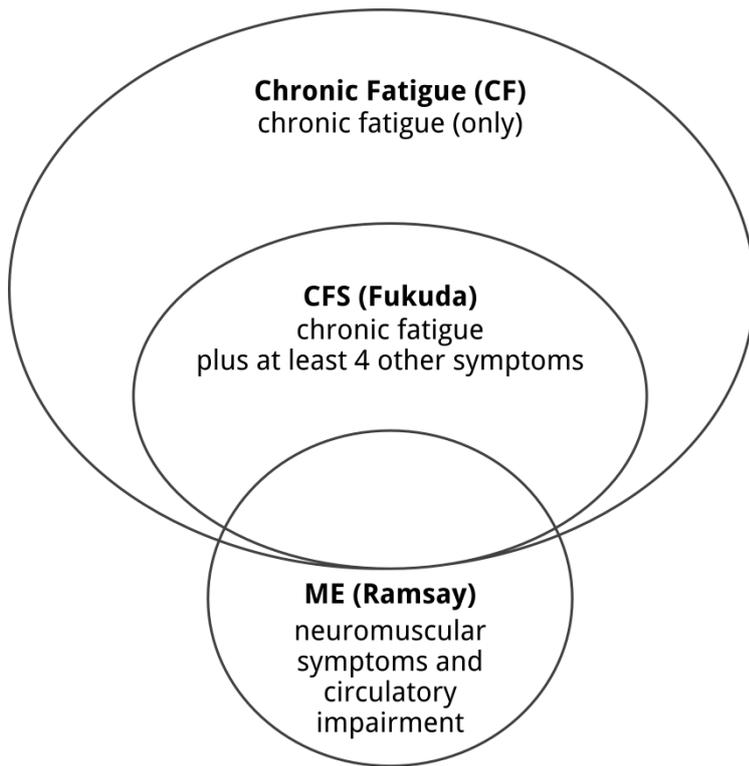
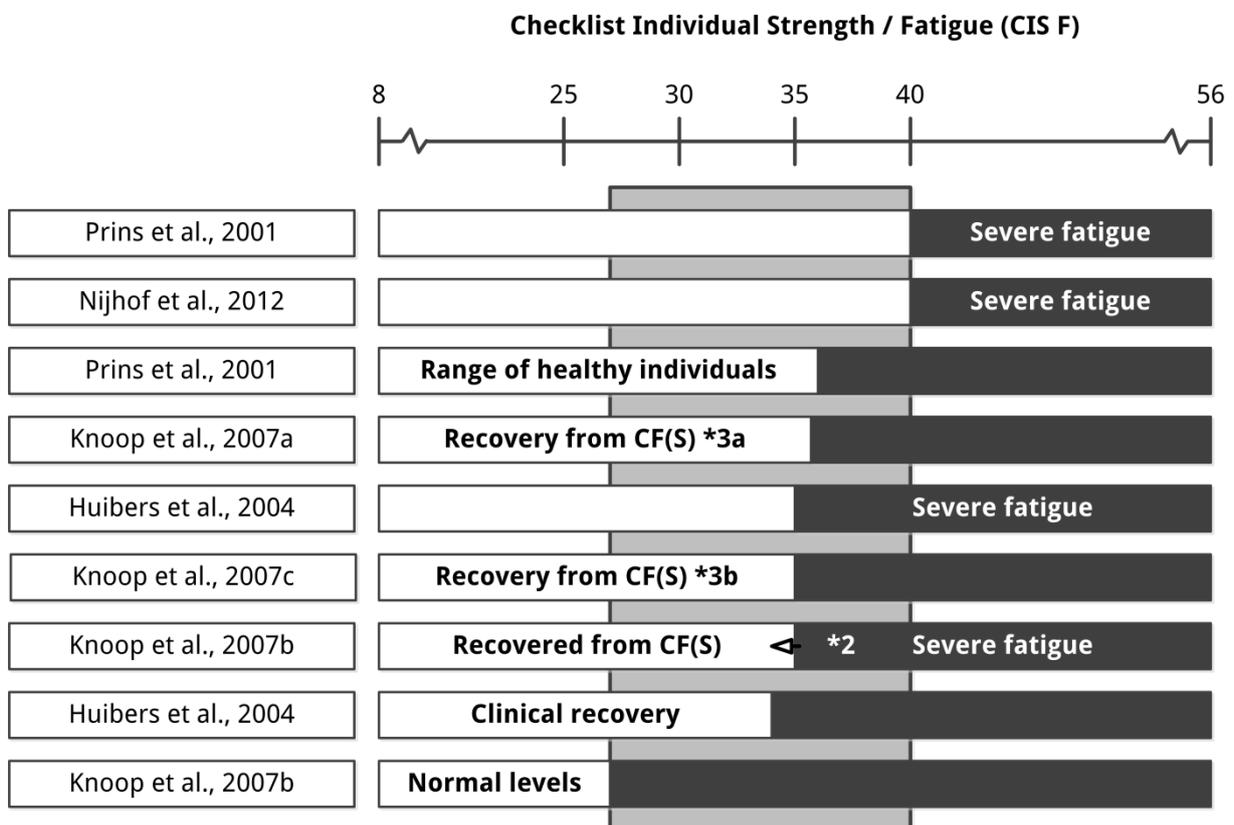
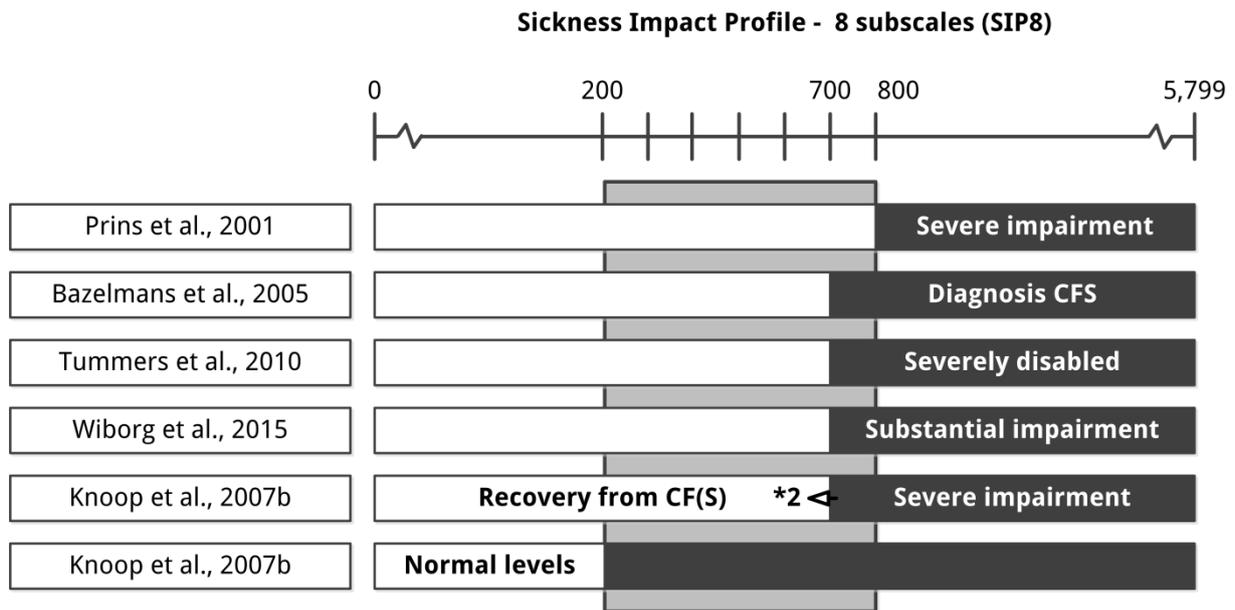


Figure 2.  
Threshold scores used for the definition of recovery, improvement and caseness (patient selection) in studies conducted by the NCKV (ECCF): CIS F fatigue score



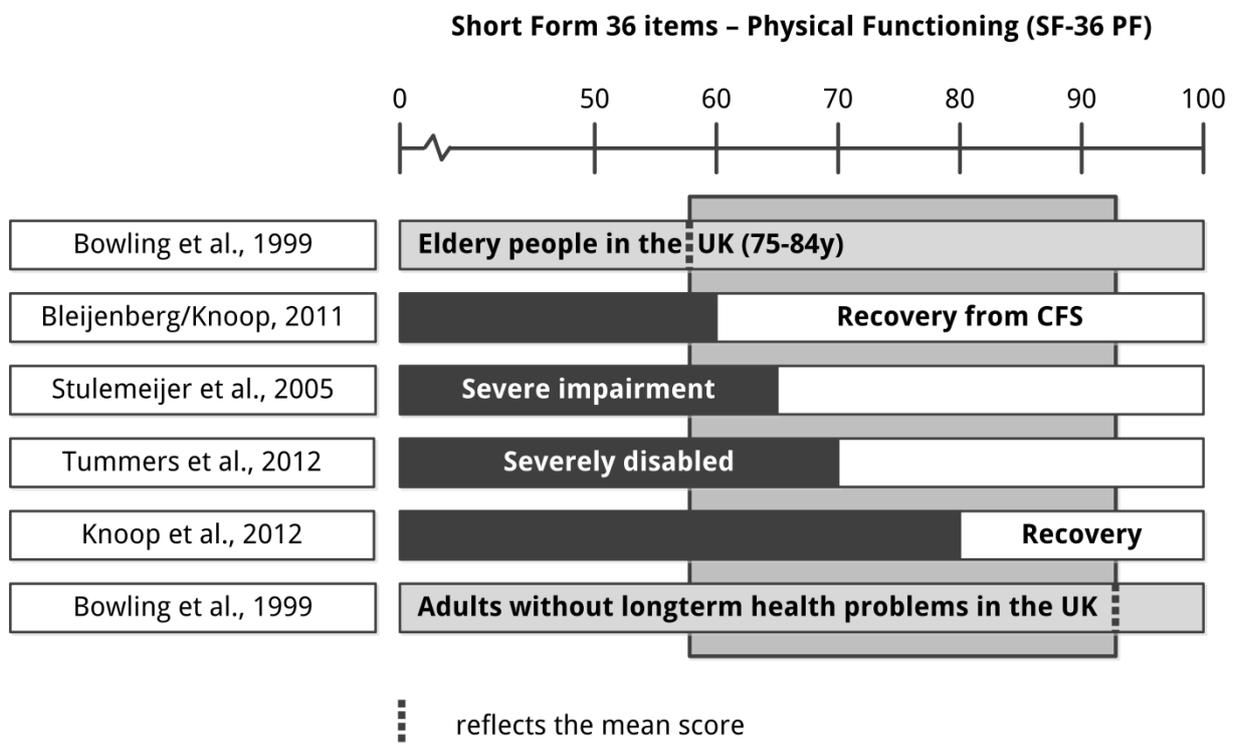
\*2 a small improvement is sufficient to recover on this aspect  
\*3 a) adolescents, b) adults

Figure 3.  
Threshold scores used for the definition of recovery, improvement and caseness (patient selection) in studies conducted by the NKCVC (ECCF): SIP 8 disability score



\*2 a small improvement is sufficient to recover on this aspect

Figure 4.  
Threshold scores used for the definition of recovery improvement and caseness (patient selection) in studies by the NKCVC (ECCF): SF-36 PF physical functioning score



**The five studies show that CBT+ is not effective for CFS,  
the effect of CBT+ for ME was never investigated/reported**

Even if we would accept the numerous methodical shortcomings,  
the claim that CBT+ is effective for CFS and ME cannot be substantiated.

CBT+ has a (modest) positive, no or a negative effect on subjective measures at group level, such as 'fatigue' and 'functional limitations'

CBT+ has a (modest) positive effect on a number of subjective measures,  
CBT+ has no significant effect on a various other subjective measures, and  
CBT+ has a [negative effect](#) on the primary subjective criterion in one study.

CBT+ has no effect whatsoever on objective measures relevant to the NKCVC

With one exception, CBT+ had no effect on the objective measures used,  
especially [activity levels](#), [cognitive test scores](#), and [number of hours worked](#).  
The latter is very relevant since work resumption is the goal according to the NKCVC.

The only objective positive effect was an improvement of school attendance,  
that was reported in [a study from 2005](#) and [a study from 2012](#).

However, most likely this positive effect is the result of 'activity substitution',  
doing a activity, school work, at the expense of another, for example sport,  
since an [NKCVC study from 2010](#) (analysing data of three trials) showed that  
CBT+ has no substantial effect on the activity levels as assessed by actometers.

In this context it is relevant that other studies of the NKCVC demonstrated  
that CBT+ has no (significant) effect on [cognitive test scores](#)  
that the [substantial drop of the IQ](#) is [not related to school absenteeism](#).

Impressive recovery rates are based on very loose, widely varying subjective criteria

The impressive percentages of patients who are supposed to improve or recover  
([Knoop and colleagues](#) report a recovery rate of 69% in 2007)  
are based on extremely loose and very strongly fluctuating subjective criteria,  
for example cut-off thresholds for the CIS F fatigue score and SIP 8 disability score,

- so that a [minimal improvement or a zero effect](#) is [sufficient to 'recover'](#),
- so that improvement is completely inadequate to achieve ['normal values'](#)  
( 'normal values' as defined by the NKCVC itself) and
- so that a ['recovered patient'](#) meets the [eligibility criteria of other NKCVC studies](#).

As indicated by [Knoop and colleagues](#), 'recovery is a construction'  
based on strongly fluctuating 'normal values' for ill-defined notions, like 'fatigue'.  
Extremely loose 'normal values' for subjective definitions of 'recovery'  
enable researchers to report very impressive 'recovery percentages'.

**In summary, we can conclude  
that CBT+ (in some cases) has a (small) positive effect on subjective measures,  
but that this effect is insufficient for patients to be qualified as 'recovered',  
that CBT+ has no effect on relevant objective indicators, and  
that the effect of CBT+ in ME was never investigated.**