Myalgic encephalomyelitis / Chronic fatigue syndrome (ME/CFS)

Current state of knowledge[1]

EXTRACT

IQWiG Reports – Commission No. N21-01

[1] Translation of the research question, discussion and conclusion of the final report N21-01 *Myalgische Enzephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) – Aktueller Kenntnisstand* (Version 1.0; Status: 17 April 2023 [German original], 26 May 2023 [English translation]). Please note: This document is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Myalgic encephalomyelitis / Chronic fatigue syndrome (ME/CFS) – Current state of knowledge

Commissioning agency

Federal Ministry of Health

Commission awarded on

11 February 2021

Internal Project No.

N21-01

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

The present report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter 11 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Erika Baum, Biebertal
- Wolfgang Eich, Heidelberg
- Carmen Scheibenbogen, Berlin

IQWiG thanks the external experts for their collaboration in the project.

Involvement of patients and other people affected

Six patients and other people affected were consulted before the preparation of the report. IQWiG would like to thank them for participating in the discussion about their experiences with disease and its treatment as well as their treatment goals. They were not involved in the preparation of the actual report.

IQWiG employees

- Katharina Doni
- Katrin Dreck
- Sebastian Grümer
- Dennis Fechtelpeter
- Daniel Fleer
- Andrea Kamphuis
- Klaus Koch
- Ulrike Lampert

- Christoph Mosch
- Gunnar Plinke
- Anke Schulz
- Sonja Siegert
- Beate Zschorlich

Keywords

Fatigue Syndrome – Chronic, Scoping Review, Evidence Map, Benefit Assessment, Health Information

Table of contents

List of abbreviations

Abbreviation	Meaning
AHRQ	Agency for Healthcare Research and Quality
CBT	cognitive behavioural therapy
CCC	Canadian Consensus Criteria
CDC	Centers for Disease Control and Prevention
CFQ	Chalder Fatigue Questionnaire
CFS	chronic fatigue syndrome
COVID	coronavirus disease
GET	graded exercise therapy
HTA	health technology assessment
IoM	Institute of Medicine
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ME	myalgic encephalomyelitis
ME / CFS	myalgic encephalomyelitis / chronic fatigue syndrome
MUS	medically unexplained symptoms
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PEM	post-exertional malaise
RCT	randomized controlled trial
SF-36 PF	Short Form-36 Physical Function
SMC	standard (specialist) medical care

Research question

The aims of the present project are

- to systematically review the current state of knowledge on myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS),
- to map the evidence on treatment options relevant to health care,
- to assess the benefits of 2 specific treatment interventions based on the evidence mapping, and
- to produce health information communicating the relevant knowledge in an easily understandable way.

Discussion / Classification of work results

Establishing the diagnosis ME/CFS

The criteria sets for diagnosis have evolved over time (see Section 4.2.2.3[2]). Therefore, when selecting studies, it was necessary to ensure that the patients included also sufficiently fulfilled the currently recommended criteria sets [1], such as the Canadian Consensus Criteria (CCC) [2,3] and the criteria of the US Institute of Medicine (IoM) [4]. For evidence mapping, this meant that only those studies were included in which the reported proportion of post-exertional malaise (PEM) in the study population was at least 80%. Following the approach described for the evaluation of the ME/CFS diagnosis (see Section 4.3.2.1), only 6 of the 55 non-drug randomized controlled trials (RCTs) and 2 of the 30 drug RCTs out of the total of 85 RCTs analysed in the report by the UK National Institute for Health and Care Excellence (NICE) of 2021 were used for the presentation of results in the evidence mapping. From these 8 RCTs used, 2 treatment options were finally selected for the benefit assessments as described in Section 4.3.4, which were examined in a total of 3 studies. In historical retrospect, it is noteworthy that, due to unclear diagnostic criteria, about 90% of the previous studies on ME/CFS included patient populations for which it is not clear what proportion actually had ME/CFS. Therefore, the interventions for patients with ME/CFS investigated in these studies must be considered unevaluated according to the current state of knowledge.

Whereas in Janse 2018 [5,6], CFS was diagnosed using the Fukuda criteria (US Centers for Disease Control and Prevention [CDC] 1994 [7]), in the PACE study [8-13], CFS was primarily diagnosed using the Oxford criteria (Sharpe 1991 [14]). Common to both classifications is that they do not include PEM as a mandatory criterion for ME/CFS diagnosis. As the respective publications indicated that more than 80% of the patients considered had PEM at baseline

[2] In the following text, unless otherwise stated, all references to sections and tables refer to sections of the full German-language IQWiG report N21-01 on ME/CFS.

(Janse 2018: 90% / PACE: 84% [in the study arms used]), the studies were included in the present assessment. This decision was supported by the results of an exemplary sensitivity analysis of the data on fatigue (cognitive behavioural therapy [CBT] vs. standard (specialist) medical care [SMC]) from PACE at 52 weeks (see Section 5.6.15).

In the third study included, the GETSET study [15,16], the diagnosis of ME/CFS at baseline was based on the NICE 2007 criteria, which required the presence of PEM and/or delayed-onset post-exertional fatigue with a recovery period of several days as a mandatory criterion. Given the lack of international standardization in the recording of PEM (see Section 4.2.2.3), the initial recording of PEM in the studies was accepted as adequate in the present report, despite the uncertainties.

Study data on potential harm, such as induced PEM

In all 3 studies included, it is unclear to what extent the frequency of specific events of harm was recorded, such as the core aspect of harm in the form of repeated PEM events ("crashes") induced by intervention-related cognitive, emotional or physical exertion. One would expect that possible undocumented ME/CFS-specific events of harm, particularly PEM, would have had a major impact on other outcomes as well. However, this cannot be inferred from the studies, as for both interventions the results for the outcomes of fatigue, quality of sleep, physical function, return to school/work, mental status, general symptoms and feeling ill after exertion tended to favour the respective test intervention.

The reported proportions of study discontinuations (see Table 21) do not allow any conclusions to be drawn about harm, especially with regard to a group-specific higher frequency of PEM. On the one hand, for both comparisons no consistent direction of the proportions of study discontinuations was shown across studies. While in GETSET the proportion of study discontinuations was higher in the graded exercise therapy (GET) intervention group than in the control group (GET: 9.3%; SMC: 1.9%), in PACE the opposite was true, and proportionally more patients in the control group discontinued the study (GET: 10.0%; SMC: 13.8%). A similarly inconsistent picture was also seen across studies for the CBT comparison in the data from Janse 2018 (CBT: 1.6%; SMC: 5%) and PACE (CBT: 18.3%; SMC: 13.8%). Beyond that, no specific reasons for study discontinuations are reported in the studies, so that it remains unclear to what extent ME/CFS-specific events (in particular in the respective intervention groups) actually primarily led to the study discontinuations.

ME/CFS severity of study participants

None of the 3 studies relevant to the assessment contained explicit information on the disease-specific ME/CFS severity of the patients included. Information from validated scales (such as the Bell scale) or results differentiated by severity were not reported in the studies included. However, data on Short Form-36 Physical Function (SF-36-PF) reported in all 3

studies at baseline (see Table 21) indicate that, based on the mean values per arm, the patients included had mainly mild (Janse 2018: about 62 to 63 points) to at most moderate (PACE: about 37 to 39 points) limitations in physical function. The baseline data reported on the Chalder Fatigue Questionnaire (CFQ, see Table 21) between about 24 points (Janse 2018) and about 28 points (GETSET and PACE) can also be interpreted as an indication that fatigue was at most moderate at baseline [17]. Although there were no validated cut-off points for categorization for these 2 scales (SF-36 PF and CFQ), it can be inferred from these data that the available evidence relates to patients with mild to at most moderate ME/CFS severity. This interpretation of the data is supported by the settings of the studies in the sense that participation in these 3 studies required that patients at least were able to attend ME/CFS outpatient clinics or specialist clinics in order to be recruited into a clinical trial there. As a result, patients with severe to very severe ME/CFS who are unable to leave their home environment or who are bed bound, i.e. approximately 25% of all ME/CFS patients [18], were excluded from participation in the study from the outset. It is therefore very difficult, if not impossible, to apply the results of this study to patients with severe or very severe ME/CFS.

Comparison of results with other health technology assessment (HTA) reports

Several HTA reports or systematic reviews and (clinical practice) guidelines were identified in the course of report preparation / information retrieval that correspond to the research question of the present benefit assessments.

This section first presents the results of key HTA reports on ME/CFS and then compares them with the results of the present report.

HTA report of the Agency for Healthcare Research and Quality (AHRQ) 2014 / 2016

The US AHRQ report from 2014 [19] assesses and summarizes the research findings on the benefits and harms of various drug and non-drug treatments for ME/CFS. In July 2016, an addendum was added to the original report. This included an investigation of the impact that studies using the Oxford criteria (Sharpe 1991 [14]) had on the conclusions of the AHRQ report.

- The results on CBT show an improvement in the outcome of fatigue through CBT with and without the inclusion of 1 Oxford-criteria-based study with a low strength of evidence.
- In the original analyses with 4 studies on GET, there is an improvement in 3 outcomes through GET. In 1 study, the GET group had the highest number of study discontinuations and in 1 other study, the GET group had the highest number of adverse events. In the addendum, the exclusion of 3 Oxford-criteria-based studies leaves no evidence for the effectiveness of GET for any of the outcomes analysed.

Larun 2019

The Cochrane review by Larun 2019 on exercise therapy for CFS states that, compared with passive control, "Exercise therapy may moderately improve physical functioning at end of treatment, but the long-term effect is uncertain because the certainty of the evidence is very low. Exercise therapy may also slightly improve sleep at end of treatment and at long term" [20].

At the time of publication in 2019, Cochrane announced a full update of their review (publication date is unknown).

HTA report of the National Institute for Health and Care Research (NIHR) 2020

The UK NIHR 2020 report [21] assesses the clinical effectiveness of several interventions for patients with medically unexplained symptoms (MUS) or functional somatic syndromes (FSS), including patients with chronic fatigue (including, but not limited to CFS). Thirteen different behavioural modification interventions are examined, such as both high- and low-intensity CBT and graded activity (including, but not limited to GET). The setting in which the studies were conducted was restricted to primary care.

However, the NIHR report combines the results of all health conditions within MUS (e.g. chronic fatigue, chronic pain and irritable bowel syndrome) in the analyses by outcome. Therefore, the results of the NIHR report cannot be compared with the results of the present report.

HTA report of NICE 2021

The current UK NICE guideline for ME/CFS is based on an HTA report on the benefits and harms of CBT and GET (see Section 3.3 "Benefits and harms" in [22]). The comparison of CBT versus SMC shows

- in adults, a benefit of CBT for 3 outcomes (activity levels, general symptom scales and exercise performance) and
- in children and young people, a benefit of
  - both face-to-face CBT and web-based CBT for 3 outcomes (general symptom scales, fatigue and physical function),
  - web-based CBT for 1 outcome (return to school), and
  - face-to-face CBT for 2 outcomes (cognitive function and pain).

For the comparison of GET with SMC, the NICE assessment shows a benefit of GET for 4 outcomes in adults (general symptom scales, fatigue, activity levels and exercise performance).

In a re-analysis, NICE also evaluated whether the original assessment of the evidence should be corrected because of previously unconsidered information on PEM (see Appendix G of the non-pharmacological interventions in [23]).

For the comparison of CBT with SMC, no additional information on PEM was identified that required re-analysis.

For the comparison of GET with SMC, the PEM reanalysis (for a selection of the outcomes originally assessed) found a benefit for the PEM subgroup (see Section 4.3.2.1) for 2 out of 5 outcomes (general symptom scales and fatigue).

In summary, NICE found a benefit for both CBT and GET for several outcomes.

Summary comparison with the findings of the present report

Overall, the assessments of the other HTA reports presented here are basically similar to the present report: for CBT, AHRQ and NICE 2021 found a benefit (like in the present report); for GET, either a benefit was found (Larun 2019 and NICE 2021) or insufficient evidence was reported (AHRQ). The present report also found outcome-specific benefits for GET based on RCT data. The most striking difference lies in the (partly considerably) larger study pool of the other HTA reports compared to the present report. The other HTA reports mainly analysed studies in which the PEM proportion of the study population was not reported and therefore did not meet the inclusion criteria (PEM proportion at least 80%) of the present report.

Overview of current recommendations in international guidelines

During the hearing on the preliminary report, it became clear that conclusions on benefit drawn in the present report were often misunderstood as recommendations for the interventions studied. In Germany, however, the formulation of treatment recommendations is reserved for scientific societies within the framework of (clinical practice) guidelines.

Guidelines differ from HTA reports such as the present report in that they formulate clear recommendations, for example on diagnostic procedures and treatment. In addition, other aspects such as the clinical expertise of experts and aspects of the structure of the health care system are considered in guidelines. It is possible to deviate from guidelines in justified cases. The applicability of a guideline or individual recommendations must be evaluated in the specific situation [24]. This is all the more important for a disease with such individual characteristics as ME/CFS.

German S3 guideline on fatigue

In the current German S3 guideline on fatigue (as of 11/2022) [25], the section on ME/CFS has been extensively revised compared with the previous version. Among other things, it describes the IoM criteria and the CCC, the epidemiology, and patients' situation of care. For

various reasons, however, the guideline does not strictly represent the usual type of guideline issued by the German Society for General Medicine and Family Medicine (DEGAM) and reference is made to other sources for more detailed information.

One recommendation is made for the diagnosis:

- Medium strength of recommendation: If unexplained fatigue has persisted for at least 3 months, the IoM criteria for ME/CFS should be checked to establish a tentative diagnosis, which should be re-evaluated after 6 months.

Two treatment recommendations for behavioural and/or symptom-orientated activation measures are given (explicitly excluding ME/CFS). In addition, 1 treatment recommendation is given specifically for ME/CFS:

- High strength of recommendation: Physical activation based on the deconditioning concept should not be offered for ME/CFS. Exertion intolerance with varying latency should be taken into account. Behavioural therapy can be offered, especially to treat concomitant symptoms.

The S3 guideline on fatigue largely follows the treatment recommendations of the current NICE guideline (see below). The comments in the S3 guideline with regard to ME/CFS end with a dissenting opinion from the scientific societies involved in the guideline development, which, among other things, criticizes the strong orientation towards the NICE guideline. Further details on the dissenting opinion and the replies can be found in the guideline report [26].

Also in the context of the extremely limited treatment options, such an absolute negative recommendation as stated above seems questionable according to the German Patients' Rights Act. This Act stipulates that when informing patients, alternatives must be mentioned if several medically equally indicated and common methods can lead to markedly different burdens, risks or chances of cure, so that the patient can make a well-considered decision on consent [27].

Centers for Disease Control and Prevention (CDC)

The statements on the US CDC web pages on ME/CFS are not interpreted as recommendations in the sense of a guideline, as there are disclaimers stating that the content of these web pages is for informational purposes only.

With regard to the treatment of ME/CFS, the CDC states that “Any activity or exercise plan for people with ME/CFS needs to be carefully designed with input from each patient. While vigorous aerobic exercise can be beneficial for many chronic illnesses, patients with ME/CFS do not tolerate such exercise routines. Standard exercise recommendations for healthy

people can be harmful for patients with ME/CFS. However, it is important that patients with ME/CFS undertake activities that they can tolerate…" [28].

NICE 2021 guideline

The treatment recommendations in the current UK NICE guideline on ME/CFS are based on the HTA report described previously. In addition to evidence reviews of the effectiveness of non-drug and drug interventions such as CBT and GET, the HTA report also includes a cost-effectiveness review and a review of qualitative studies of experiences with both non-drug and drug interventions.

The recommendations of the current NICE guideline describe that CBT for the treatment of ME/CFS "aims to improve wellbeing and quality of life, and may be useful in supporting people who live with ME/CFS to manage their symptoms and reduce the distress associated with having a chronic illness" [29]. In addition, "The [guideline] committee noted that none of the evidence included or reflected the needs of people with severe or very severe ME/CFS. They recognised that CBT could be supportive for people with severe or very severe ME/CFS but because of the severity of their symptoms it is important to be more flexible and adapt the delivery of CBT to accommodate the limitations of those with severe or very severe ME/CFS" [22].

With regard to physical activity or exercise programmes such as GET, "The committee noted that some people with ME/CFS have found physical activity programmes can make their symptoms worsen, for some people it makes no difference and others find them helpful" [22]. The guideline concludes that ME/CFS patients should not be offered programmes using "fixed incremental increases in physical activity or exercise, for example, GET" or "physical activity or exercise programmes that are based on deconditioning and exercise avoidance theories as perpetuating ME/CFS" [29].

With regard to self-management, "The committee discussed that pacing is the main self-management tool used by many people with ME/CFS and noted pacing is often used as one of the first steps of interventions such as CBT to stabilise a person's activity levels. The committee considered the evidence regarding the best self-management strategy is unclear and that in their experience people with ME/CFS use their own individual self-management strategies without the need for a specific intervention. Taking this into account the committee did not make a recommendation for any particular self-management strategy identified in the evidence included in this review" [22]. Furthermore, the committee "recognised the benefits of self-management strategies" and "acknowledged that some people found that technologies, such as activity trackers helpful and recommended that people could use the tools they already have. In response to the lack of research in activity management strategies

and the high interest in how tools can be used to support people with ME/CFS the committee made a research recommendation" [22].

Criticism of the NICE methods for guideline development

It should be noted that some people have criticized the way in which NICE has interpreted the results of the evidence reviews on the effectiveness of non-drug and drug interventions on the one hand and the qualitative evidence on experiences with such interventions on the other. Only a few weeks before the final guideline was published, some members of the guideline committee stood down, suggesting "divisions within the committee over the guideline's final content" [30]. According to a joint statement by medical leaders, among others, from the UK Royal College of Physicians, "There is considerable disquiet in the medical profession and some patient groups about the way the data and evidence have been assessed…" [31]. For example, according to the expert group, "GET as defined in the guidance is not reflective of the personalised paced exercise programmes that are currently used in the NHS [National Health Service] and termed GET" [31]. According to Turner-Stokes and Wade, "NICE has chosen simply to downplay the evidence supporting GET and CBT, with the worrying consequence that these interventions will not be available in the future, even to those who would benefit. The updated guideline could have unintended adverse consequences for large numbers of patients..." [32]. Flottorp et al. note that since the publication of the NICE 2007 guideline, which recommended CBT and GET, "more randomised trials and systematic reviews have provided additional evidence supporting these recommendations." They further note that "The new guideline presents strengthened evidence, but a major shift in interpretation" and that "NICE decided that evidence from clinical trials of CBT and GET showing improvement in subjective symptoms would be considered unreliable" [33]. NICE also preferably used "anecdotal evidence from patient group surveys and qualitative studies…" and "disregarded the best available research evidence…" [33]. In line with Turner-Stokes und Wade, Flottorp et al. conclude that "this guideline denies patients treatments that could help them…" [33].

Comparison of CBT with GET

For the direct comparison of CBT with GET, only data from the PACE study were available. No further data or relevant studies on this comparison were identified beyond the results of the evidence mapping. No conclusions on effects with regard to this comparison were drawn in the PACE study reports. However, according to the calculations of the authors of NICE 2021 (Section E.2.7 in [23]), there was no statistically significant difference between the intervention groups for any of the outcomes analysed at the longest available follow-up (see Section 4.3.2.2.1). A detailed presentation of the results on this comparison was dispensed with in the benefit assessments, as no gain in information was expected compared to the evidence mapping.

Handling of criticism of ME/CFS studies

A large number of critical publications can be found on the methods and results of ME/CFS studies, especially on the PACE study. The main points, which are repeatedly mentioned, are discussed by Friedberg et al. in a publication from 2020 [34]. On the basis of these points, it is explained below how the methods used in the present report consider the weaknesses of studies such as PACE.

Argument "lack of blinding"

Friedberg et al. noted that the studies of CBT and GET were not blinded and failed to consider the "potential biasing effects of subjective measures" [34]. This criticism is particularly directed at the PACE study. In addition, they found no convincing results on outcomes described as objective, such as the 6-minute walk test or return to work. They also note that "it has been suggested that patient-reported improvements on subjective measures may reflect improved coping, stress reduction, or improved adjustment to ongoing limitations, rather than robust gains in physical and role functioning" [34].

Apart from the fact that coping with the disease and stress reduction can also represent relevant improvements for patients, "blinding" / "lack of blinding" is always an aspect in the Institute's benefit assessments when assessing the risk of bias [35]. In the present report, for example the PACE study was rated as having a high risk of bias. This contributes to the fact that in the overall weighing of all results across all outcomes, conclusions on the benefits and harms of CBT or GET were classified in the lowest level of certainty of conclusions ("hint").

Argument: "inadequate inclusion criteria"

Friedberg et al. question the use of the Oxford diagnostic criteria as inclusion criteria for PACE. As stated in the present report, a study population diagnosed according to these criteria can only be considered relevant if, in addition, PEM, as a mandatory symptom of ME/CFS, is present in a sufficient number of patients. This is the case in PACE. The presence of PEM is reported in approximately 86% of study participants (see Table 21).

Argument: "definition of the outcome: recovery"

Friedberg et al. question the appropriateness of the combined outcome of recovery recorded in PACE, noting the "use of a recovery definition that did not require restoration of health" and "changes to recovery criteria" during the PACE study [34]. Due to inappropriate operationalization (including the use of the Oxford and CDC diagnostic criteria), the results of the outcome of recovery were not considered in the present benefit assessments.

Argument "disease model"

In terms of the disease model, Friedberg et al. point out that the theories underlying the PACE study – deconditioning and the fear-related avoidance of activity – have led to the neglect of

the neurological, immunological, autonomic and metabolic impairments of ME/CFS, giving the impression of a primarily psychological ailment. This criticism has no influence on the conclusions of the present report on the benefits and harms of CBT or GET as an add-on therapy to SMC. In IQWiG's benefit assessments, underlying hypotheses about mechanisms of action are generally not taken into account when assessing benefits and harms.

Argument: "Lack of consideration of patient surveys"

In general, Friedberg et al. criticize the restriction to clinical trial data and the insufficient consideration of patient surveys to assess possible harms of CBT and GET. These should be taken into account to a greater extent, especially when there are considerable discrepancies between clinical data and survey results. The authors refer to a publication of the Irish ME/CFS Association, which showed that "over 50% of patients reported that CBT and GET not only fell short of delivering significant improvements but often led to worsened health ..." [36].

This publication is an international survey of patients with ME/CFS summarizing 9 surveys with self-evaluations after use of GET or CBT.

However, by emphasizing patient surveys, Friedberg et al. do not take into account that such surveys must also be subjected to (the same) critical methodological evaluation as other study types. In general, surveys (cross-sectional studies, retrospective before-and-after studies) are methodologically unsuitable for drawing reliable conclusions about the benefits or harms of a treatment [37]. This is because, for example, the very decision to participate or not can distort the results of the survey. In the case of ME/CFS, regarding the selection of participants for the survey, there is also the question of what criteria set (with or without PEM) was used for the diagnosis of participants. Furthermore, the publication of the Irish ME/CFS Association [36] does not provide any information on serious adverse events (especially PEM events). Only subjective improvements or deteriorations were reported: In the cited patient surveys on GET, between 28.1% and 82.0% (mean: 51.2%) of the more than 4000 respondents reported that their condition had worsened after GET, but between 13.1% and 60.8% (mean: 32.2% to 32.9%) of respondents reported that their condition had improved. In the patient surveys on CBT, between 7.1% and 38.0% (mean: 19.9%) of the more than 1800 respondents reported that their condition had worsened after CBT, and between 7.0% and 56.9% (mean: 28.6%) of respondents reported that their condition had improved.[3]

The results of more recent patient surveys, such as Geraghty 2019 [38] or OxCATTS 2019 [39], which were submitted during the hearing on the preliminary report, point in a similar direction

[3] The ranges specified in percent were extracted from Kindlon 2011. The mean values given were submitted by the study author during the hearing on the preliminary report. The calculation method was not specified.

for both interventions. However, the information also does not allow a reliable quantification of the risk of harm from the treatments.

Overall, these aspects show that the methods used by IQWiG in general and in the present report are explicitly designed to take into account the methodological strengths and weaknesses of different studies when selecting studies and assessing results. This applies to all studies, regardless of the direction of the results.

Follow-up of patient reports on possible serious harms from activation therapies

Contradictions have arisen regarding the assessment of benefits and harms from GET, which could not be resolved within the scope of the present report. On the one hand, the results of the studies assessed indicate that GET has benefits for individual outcomes, while there is no indication of serious harm (see Sections 5.6 and 6.2). Furthermore, surveys of people affected on the benefits and harms of activation therapies such as GET do not provide a clear negative or positive picture: larger subgroups report deteriorations, while others report improvements (see previous section).

This contrasts with patient reports submitted in the hearing on the preliminary report, which, for example, mentioned activation therapies experienced in the context of rehabilitation therapy as the reason for a serious deterioration in their health (see Section 5.7).

This risk of harm is also recognized by scientific societies and experts in the field (see documentation of the hearing). It therefore remains incomprehensible why these patient reports have not yet led to a systematic examination of the risk of harm of the activation therapies applied in Germany (see Section 5.7).

In addition to a detailed medical history, such an examination should in particular collect the following information from a suitable group of patients with ME/CFS:

- What activation therapies were applied? What components did these treatments include?
- What other treatments have patients received?
- What proportion of people with ME/CFS have received these treatments without experiencing adverse events?
- Were current diagnostic criteria used when diagnosing the condition?

To make comparisons possible, both patients who report a permanent deterioration of their illness after GET and those who report no harms should be studied.

Conclusion

ME/CFS is a complex and chronic illness that, in very severe cases, can lead to permanent dependence on care. ME/CFS is difficult to define and diagnose for a number of reasons. These include the complexity of symptoms and the lack of an established biomarker. Different sets of diagnostic criteria have been proposed internationally, all of which are purely symptom-based. According to the most recent diagnostic criteria sets, ME/CFS is in particular characterized by the core symptom of PEM, as well as other symptoms such as severe and persistent fatigue, pain, sleep disturbance and cognitive impairment.

If the prevalence estimates from 4 studies based on criteria sets with PEM as the core symptom are applied directly to the German population, the number of patients with ME/CFS in Germany can be estimated to be in the range of about 140,000 to about 310,000. It seems plausible to assume that the prevalence of ME/CFS could increase as a result of the coronavirus disease (COVID) pandemic, since some patients with long COVID fulfil the diagnostic criteria for ME/CFS.

Although ME/CFS was included in the International Classification of Diseases (ICD) in 1969, the causes of the disease are still unclear, despite research in various fields.

The diagnostic inaccuracy, which makes distinction from other diseases difficult, and the limited consideration of ME/CFS in the training of health care professionals hamper the provision of appropriate care.

Evidence mapping and benefit assessment

A total of 85 RCTs on non-drug or drug treatment options were identified for the evidence mapping based on an up-to-date, high-quality systematic review. However, 77 of these studies neither used criteria sets for diagnosis including PEM as a component that is now considered mandatory, nor did they report the proportion of the population with PEM. It is therefore questionable to what extent patients with ME/CFS actually participated in these studies. The evidence mapping was therefore limited to the remaining 8 studies. From these studies, conclusions could be drawn on 7 interventions: CBT, GET, self-management (pacing), lightning process, vitamin D, valganciclovir and rituximab, especially in comparison with SMC. Only CBT and GET showed statistically significant effects in favour of the intervention compared to SMC (in 2 studies each). Separate benefit assessments were conducted for these two interventions.

For patients with mild to moderate ME/CFS, the benefit assessments based on 2 RCTs showed a hint (weakest certainty of conclusions) of benefit for CBT versus SMC in the short and medium term. For the longer term, there is no hint of a benefit of CBT versus SMC. A conclusion on benefit for the use of CBT in patients with more severe ME/CFS is not possible due to a lack of data.

It was not possible to reliably weigh the benefits and harms of GET versus SMC for patients with mild to moderate ME/CFS. Although the available study data suggest a benefit of GET for individual outcomes, the risk of serious side effects cannot be conclusively assessed. On the one hand, this risk was highlighted in the hearing on the preliminary report, although it remained unclear whether these comments related to inappropriate use of GET. On the other hand, the data collected in the available studies are insufficiently informative to exclude relevant harm due to serious side effects of GET. A conclusion on benefit for the use of GET in patients with more severe ME/CFS is not possible due to a lack of data.

Health information

Investigating the experiences of people with ME/CFS allowed comprehensive conclusions about information needs, perceptions and experiences. Patients and their relatives report many misunderstandings, barriers and stigmatization both in health care and in professional and private environments, which are an additional burden.

These results were the starting point for the development of health information on ME/CFS. In order to answer the questions raised, the results of the report sections on the current state of knowledge, evidence mapping of treatment options, and benefit assessments were mainly used. The health information includes 4 texts that provide an overview of the illness and more detailed information for patients and their relatives, particularly on the topics of diagnosis, treatment, and support in everyday life. This health information can also promote understanding for people with ME/CFS among the general public.

Recommendations for action

Several measures should be combined to improve the care and general life situation of people with ME/CFS. In the short term, this includes providing more objective information to both people affected and the general public, and integrating relevant teaching content into the education and training of health professionals.

A prerequisite for promising research is the definition and international consensus of diagnostic criteria with as clear a set of diagnostic parameters as possible. Building on this, increased research efforts are needed to clarify the aetiology of ME/CFS, as well as the type of treatment and care required. There is currently a lack of interdisciplinary research in all these areas. Appropriately designed studies should investigate the possible benefits and harms of activation therapies such as GET. In this context, it should also be clarified whether the risk of harm is primarily due to inappropriate application in individual patients. A first study to improve care with a rehabilitation concept specifically adapted to ME/CFS has already started in Germany. Given the lack of evidence, it also seems necessary to investigate the benefits and harms of pacing in comparative studies.

Until sufficient study results are available, the decision for or against a specific treatment (in particular activation therapy) should all the more be made on an individual basis, after providing appropriate information about possible benefits and harms and taking personal preferences into account.

References for English extract

Please see full final report for full reference list.

1. Nacul L, Authier FJ, Scheibenbogen C et al. European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe. Medicina (Kaunas) 2021; 57(5): 510. https://dx.doi.org/10.3390/medicina57050510.

2. Carruthers BM, Jain AK, De Meirleir KL et al. Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols. Journal of Chronic Fatigue Syndrome 2003; 11(1): 7-115. https://dx.doi.org/10.1300/J092v11n01_02.

3. Jason LA, Evans M, Porter N et al. The Development of a Revised Canadian Myalgic Encephalomyelitis Chronic Fatigue Syndrome Case Definition. American Journal of Biochemistry and Biotechnology 2010; 6(2): 120-135. https://dx.doi.org/10.3844/ajbbsp.2010.120.135.

4. Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness [online]. 2015 [Accessed: 07.06.2021]. URL: https://www.ncbi.nlm.nih.gov/books/n/nap19012/pdf/.

5. Janse A, Worm-Smeitink M, Bleijenberg G et al. Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry 2018; 212(2): 112-118. https://dx.doi.org/10.1192/bjp.2017.22.

6. Janse A, Worm-Smeitink M, Bussel-Lagarde J et al. Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial. BMC Neurol 2015; 15: 137. https://dx.doi.org/10.1186/s12883-015-0392-3.

7. Fukuda K, Straus SE, Hickie I et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121(12): 953-959. https://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009.

8. Bourke JH, Johnson AL, Sharpe M et al. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. Psychol Med 2014; 44(7): 1545-1552. https://dx.doi.org/10.1017/s0033291713002201.

9. Dougall D, Johnson A, Goldsmith K et al. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res 2014; 77(1): 20-26. https://dx.doi.org/10.1016/j.jpsychores.2014.04.002.

10. Sharpe M, Goldsmith KA, Johnson AL et al. Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. Lancet Psychiatry 2015; 2(12): 1067-1074. https://dx.doi.org/10.1016/s2215-0366(15)00317-x.

11. Walwyn R, Potts L, McCrone P et al. A randomised trial of adaptive pacing therapy, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome (PACE): statistical analysis plan. Trials 2013; 14: 386. https://dx.doi.org/10.1186/1745-6215-14-386.

12. White PD, Goldsmith KA, Johnson AL et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011; 377(9768): 823-836. https://dx.doi.org/10.1016/s0140-6736(11)60096-2.

13. White PD, Sharpe MC, Chalder T et al. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. BMC Neurol 2007; 7: 6. https://dx.doi.org/10.1186/1471-2377-7-6.

14. Sharpe MC, Archard LC, Banatvala JE et al. A report--chronic fatigue syndrome: guidelines for research. J R Soc Med 1991; 84(2): 118-121.

15. Clark LV, McCrone P, Ridge D et al. Graded Exercise Therapy Guided Self-Help Trial for Patients with Chronic Fatigue Syndrome (GETSET): Protocol for a Randomized Controlled Trial and Interview Study. JMIR Res Protoc 2016; 5(2): e70. https://dx.doi.org/10.2196/resprot.5395.

16. Clark LV, Pesola F, Thomas JM et al. Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. Lancet 2017; 390(10092): 363-373. https://dx.doi.org/10.1016/s0140-6736(16)32589-2.

17. Kedor C, Freitag H, Meyer-Arndt L et al. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nature Communications 2022; 13: 5104. https://dx.doi.org/10.1101/2021.02.06.21249256.

18. Pendergrast T, Brown A, Sunnquist M et al. Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. Chronic Illn 2016; 12(4): 292-307. https://dx.doi.org/10.1177/1742395316644770.

19. Smith MEB, Nelson HD, Haney E et al. Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [online]. 2016 [Accessed: 08.08.2022]. URL: https://www.ncbi.nlm.nih.gov/books/NBK379582/.

20. Larun L, Brurberg KG, Odgaard-Jensen J et al. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2019; 10: CD003200. https://dx.doi.org/10.1002/14651858.CD003200.pub8.

21. Leaviss J, Davis S, Ren S et al. Behavioural modification interventions for medically unexplained symptoms in primary care: Systematic reviews and economic evaluation. Health Technol Assess 2020; 24(46): 1-489. https://dx.doi.org/10.3310/hta24460.

22. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management; [G] Evidence reviews for the nonpharmacological management of ME/CFS; NICE guideline NG206 [online]. 2021 [Accessed: 02.08.2022]. URL: https://www.nice.org.uk/guidance/ng206/evidence/g-nonpharmacological-management-of-mecfs-pdf-9265183028.

23. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management; [H] Appendices for the management of ME/CFS; NICE guideline NG206 [online]. 2021 [Accessed: 02.08.2022]. URL: https://www.nice.org.uk/guidance/ng206/evidence/h-management-of-mecfs-pdf-9265183029.

24. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Das AWMF-Regelwerk Leitlinien [online]. 2020 [Accessed: 23.02.2023]. URL: https://www.awmf.org/fileadmin/user_upload/dateien/downloads_regelwerk/20210215_AWMF-Regelwerk_2020_V2.0.pdf.

25. Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin. Müdigkeit; S3-Leitlinie [online]. 2022 [Accessed: 05.01.2023]. URL: https://register.awmf.org/assets/guidelines/053-002l_S3_Muedigkeit_2023-01_01.pdf.

26. Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin. Müdigkeit; S3-Leitlinie; Leitlinienreport [online]. 2022 [Accessed: 05.01.2023]. URL: https://register.awmf.org/assets/guidelines/053-002m_S3_Muedigkeit_2023-01_01.pdf.

27. Deutscher Bundestag. Gesetz zur Verbesserung der Rechte von Patientinnen und Patienten [online]. 2013 [Accessed: 27.02.2023]. URL: https://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&bk=Bundesanzeiger_BGBl&start=//*%5B@attr_id=%27bgbl113s0277.pdf%27%5D#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl113s0277.pdf%27%5D__1677500768382.

28. Centers for Disease Control and Prevention. Treatment of ME/CFS [online]. 2021 [Accessed: 19.12.2022]. URL: https://www.cdc.gov/me-cfs/treatment/index.html.

29. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management [online]. 2021 [Accessed: 02.08.2022]. URL: https://www.nice.org.uk/guidance/ng206/resources/myalgic-encephalomyelitis-or-encephalopathychronic-fatigue-syndrome-diagnosis-and-management-pdf-66143718094021.

30. Torjesen I. Exclusive: Four members of NICE's guideline committee on ME/CFS stand down. BMJ 2021; 374: n1937. https://dx.doi.org/10.1136/bmj.n1937.

31. Royal College of Physicians. Medical leaders sign joint statement in response to NICE guidance on ME/CFS [online]. 2021 [Accessed: 17.11.2022]. URL: https://www.rcplondon.ac.uk/news/medical-leaders-sign-joint-statement-response-nice-guidance-mecfs.

32. Turner-Stokes L, Wade DT. Updated NICE guidance on chronic fatigue syndrome. BMJ 2020; 371: m4774. https://dx.doi.org/10.1136/bmj.m4774.

33. Flottorp SA, Brurberg KG, Fink P et al. New NICE guideline on chronic fatigue syndrome: more ideology than science? Lancet 2022; 399(10325): 611-613. https://dx.doi.org/10.1016/S0140-6736(22)00183-0.

34. Friedberg F, Sunnquist M, Nacul L. Rethinking the Standard of Care for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Gen Intern Med 2020; 35(3): 906-909. https://dx.doi.org/10.1007/s11606-019-05375-y.

35. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 24.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

36. Kindlon T. Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome [online]. 2011 [Accessed: 30.08.2022]. URL: https://www.iacfsme.org/bulletins/.

37. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Welche Studienarten gibt es? [online]. 2020 [Accessed: 24.09.2022]. URL: https://www.gesundheitsinformation.de/welche-studienarten-gibt-es.html.

38. Geraghty K, Hann M, Kurtev S. Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys. J Health Psychol 2019; 24(10): 1318-1333. https://dx.doi.org/10.1177/1359105317726152.

39. Oxford Clinical Allied Technology and Trials Services Unit (OxCATTS), Oxford Brookes University. Evaluation of a survey exploring the experiences of adults and children with ME/CFS who have participated in CBT and GET interventional programmes. Final Report [online]. 2019 [Accessed: 07.03.2023]. URL: https://www.meassociation.org.uk/wp-content/uploads/NICE-Patient-Survey-Outcomes-CBT-and-GET-Oxford-Brookes-Full-Report-03.04.19.pdf.

The full report (German version) is published under

https://www.iqwig.de/en/projects/n21-01.html