0.1% is a lower bound prevalence estimate

4.2.2.5 Epidemiologische und versorgungsrelevante Aspekte – Häufigkeit - Page 24

The IQWiG report states that there are approximately 70,000 adult ME/CFS patients in Germany. This is based on a 0.1% prevalence estimate found by Nacul and colleagues in the UK using the Canadian Consensus Criteria. [1]

This study, however, did not include a community-based screening of the entire population for cases of ME/CFS. Instead, Nacul and colleagues relied on general practitioners (GPs) for the detection of possible ME/CFS cases. The authors explained that this methodology might have underestimated the true prevalence rate of ME/CFS *"as some people may not consult their GPs, or do not receive a diagnosis."* The researcher highlighted that their estimate represents a "*lower range of the commonly assumed population prevalence for the UK."* For this reason, they referred to it as *"a minimum prevalence in primary care."* [1]

This view is confirmed by comparing the prevalence for the Fukuda 1994 case definition found by Nacul et al. with similar estimates found by other researchers. While Nacul and colleagues found a prevalence of 0.2%, other studies found significantly higher rates. A recent meta-analysis calculated a prevalence of 0.89% for the Fukuda case definition of ME/CFS, or more than 4 times higher than the estimate found by Nacul et al. [2]

The IQWiG report uses a lower limit of ME/CFS prevalence estimates without acknowledging that this is likely an underestimation of the true prevalence rate. We recommend adding an explanation that clarifies that the prevalence of ME/CFS may be significantly higher than 70,000 adult patients in Germany and that this figure represents a lower bound estimate.

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The pediatric prevalence found by Jason et al.

4.2.2.5 Epidemiologische und versorgungsrelevante Aspekte – Häufigkeit - Page 24

The prevalence of pediatric ME/CFS was estimated by Jason and colleagues in 2020. [1] The authors screened 10,119 youth, aged 5–17 in the greater Chicago area. Diagnoses were made after medical examination by an experienced team of physicians. The prevalence of pediatric ME/CFS was estimated to be 0,75%, more than 7 times the estimate the IQWiG report uses for adults. A British study of children (aged 11-16) using data from school-based clinics, found a similar but higher prevalence estimate of 1% using the 2007 case definition specified by the National Institute for Health and Care Excellence (NICE). [2]

It is unclear why the estimate of 0.75% for young people is not mentioned anywhere in the IQWiG report. The report only states that the results by Jason et al. 2020 are not reliable ("nicht zuverlässig") without providing further explanation.

The IQWiG report also states that extrapolation of the data by Jason et al. 2020 is not possible due to lack of information on age standardization. We believe that the figure of 0.75% should still be mentioned in the report. In addition, we recommend contacting the research team of Prof. Leonard Jason at the DePaul University of Chicago for more information on the age distribution of patients in his study.

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Outdated case definitions

4.3.2 Ergebnisse zu Therapieoptionen – Page 30

The IQWiG report included trials that selected patients with outdated case definitions such as the Oxford criteria if 80% of the trial participants experienced PEM. However, patients selected with these case definitions, even if they experienced PEM, may still differ substantially from patients selected with modern diagnostic criteria. The Oxford definition for example requires that chronic fatigue is the “principal symptom” of the syndrome, which may not be the case for many ME/CFS patients. [1] Studies have shown that only approximately half of patients selected with the Fukuda-criteria met more recent case definitions such as the Canadian Consensus Criteria (CCC). [2] The relevance of such studies to ME/CFS, as it is currently defined, is therefore questionable. Requiring 80% of patients to experience PEM does not fully address this issue as it is only one of several core features of ME/CFS.

We recommend using a stricter threshold where at least 80% of included participants meet modern diagnostic criteria for ME/CFS such as the CCC, the International Consensus Criteria, or the 2015 National Academy of Medicine criteria. This would ensure that results are applicable to ME/CFS as it is defined and diagnosed today.

References

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Non-blinded studies with subjective outcomes

5 Nutzenbewertungen – Page 98

The evidence for GET and CBT was extracted from 3 trials: PACE, GETSET, and the Dutch study by Janse et al. All 3 trials used subjective measurements as their main outcomes while patients and therapists could not be blinded to treatment allocation. Consequently, these studies are at high risk of response bias and have limited validity. Patients who know they are receiving an active intervention rather than a passive control might be more optimistic about

its effect on their health or report symptoms according to what they think will please the investigators. Patients in the GET or CBT group might thus have rated their health as better than patients in the control group even if the treatment did not actually improve their health.

The General Methods handbook by IQWiG version 6.1 offers several options to evaluate evidence of trials where blinding of patients and therapists was not possible. On page 171, section 9.1.4 it states that "If a blinded collection of outcomes is not possible, an objective endpoint should be chosen that can be influenced as little as possible in terms of its characteristics and the stringency of the recording by the person who collects the endpoint." [Original quote in German: "Falls eine verblindete Zielgrößenerhebung nicht möglich ist, sollte ein möglichst objektiver Endpunkt gewählt werden, der in seiner Ausprägung und in der Stringenz der Erfassung so wenig wie möglich durch diejenige Person, die den Endpunkt (unverblindet) erhebt, beeinflusst werden kann."]

Objective outcomes such as the 6-minute walking test or actigraphy, however, did not indicate a clinical effect for GET or CBT. Other reviews have demonstrated that, in contrast to subjective measurements, objective outcomes of GET and CBT trials do not indicate improvements. [1-2]

The General Methods handbook by IQWiG also states in section 3.2.4 on Patient-reported outcomes (PROs), page 61: "Since information on PROs is subjective by its very nature, open-label, ie unblinded, studies in this area are of limited validity. The size of the observed effect is an important decision criterion for the question of whether an indication of a benefit of an intervention with regard to PROs can be derived from open studies." [Original quote in German: "Da Angaben zu PROs aufgrund ihrer Natur subjektiv sind, sind offene, d. h. nicht verblindete Studien in diesem Bereich nur von eingeschränkter Validität. Für die Frage, ob sich aus offenen Studien ein Hinweis auf einen Nutzen einer Intervention bezüglich PROs ableiten lässt, ist die Größe des beobachteten Effekts ein wichtiges Entscheidungskriterium."]

A 2014 review by Hróbjartsson et al. on randomized trials that compared blinded and non-blinded groups found that the average difference in effect size for PROs was 0.56. [3] In other words, in groups where patients were not blinded, the reported effect sizes were inflated by approximately half a standard deviation. This is similar to the effect size found in trials on GET and CBT. [3] It is therefore doubtful if the differences found in such trials constitute a true treatment effect. For fatigue, for example, the SMD reported by IQWiQ was −0,48 [−0,71; −0,25] for the comparison CBT versus SMC at the 52-week follow-up and −0,37 [−0,54; −0,19] for GET versus SMC at the 12-weeks assessment. For the other primary outcome, physical function, the SMD was 0,32 [0,09; 0,55] for the comparison CBT versus SMC at the 52-week follow-up and 0.19 [0.02; 0.37] for GET versus SMC at the 12-weeks assessment. These effects could have fully been the result of bias due to a lack of blinding.

There are several reasons to think that response bias was particularly strong in trials of GET and CBT. First, as part of the treatment, patients were encouraged to interpret their ME/CFS symptoms as the reversible result of deconditioning, stress, anxiety, or disrupted sleep patterns rather than an unknown disease that cannot yet be treated. Such instructions might have led them to view their symptoms as more benign than patients in the control group who were not primed in this way. According to therapist manuals used in the PACE trial "participants are encouraged to see symptoms as temporary and reversible, as a result of their current physical weakness, and not as signs of progressive pathology." [4] The CBT used in the trial by Janse et al. was based on similar principles as it focused on correcting patients'

unhelpful beliefs about their illness. Therapists were encouraged to suggest that recovery is possible to raise patients' expectations which in turn would lead to a change in the perception of symptoms as well as disability. [5]

Second, therapists were explicitly instructed to encourage optimism and instill the belief that patients could get better through GET or CBT if they committed themselves to the treatment. The therapist manual on GET for example stated: "it is important that you encourage optimism about the progress that they may make with this approach. You can explain the previous positive research findings of GET and show in the way you discuss goals and use language that you believe they can get better." [4] Similarly, the PACE trial manual for participants in the CBT arm stated that: "Cognitive behaviour therapy (CBT) is a powerful and safe treatment which has been shown to be effective in a variety of illnesses" and that "many people have successfully overcome CFS/ME using cognitive behaviour therapy". [6] Such statements might have persuaded patients that GET and CBT were effective, even before treatment started.

Third, because patients were made to think that they were in large part responsible for the treatment effects of GET and CBT, they might have been reluctant to report no improvement on symptom questionnaires. It might have indicated that they, rather than the treatments, failed. As one PACE trial participant testified: "After repeatedly being asked how severe my symptoms were […] I started to feel like I had to put a positive spin on my answers. I could not be honest about just how bad it was, as that would tell the doctors I wasn't trying and I wasn't being positive enough. When I was completing questionnaires, I remember second guessing myself and thinking for every answer: 'Is it really that bad? Am I just not looking at things positively enough?'" [7] The therapist manual used in the GETSET trial stated: "It is essential that you demonstrate positive reinforcement when you work with patients. Often, patients may be more inclined to focus on what they have not achieved rather than what they have. It is therefore important that you emphasise and are very positive about what they have achieved. Every session you should positively reinforce all of their achievements." [8] Such instructions can severely distort how patients rate their improvement or complete symptom questionnaires.

We recommend focusing on objective outcomes in trials where patients nor therapists could be blinded. Small to moderate effect sizes on subjective measurements such as symptom questionnaires are not reliable indicators of treatment effects in unblinded trials. The IQWiG report on ME/CFS, however, seems, to have based its recommendations for GET and CBT mostly on such questionable outcomes.

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No control intervention

5 Nutzenbewertungen – Page 98

An additional concern is that the data on GET and CBT did not include a control intervention.

In the Dutch trial by Janse and colleagues, for example, patients in the control group were simply put on a waiting list to receive web-based CBT, the intervention that patients in the other 2 groups did receive. In the GETSET trial, specialist medical care (SMC) with guided graded exercise self-help compared with SMC alone. In other words, this trial design used an unfair comparison of 'A versus A + B' which is unsuited to measure the efficacy of an intervention. Something similar was true for the data extracted from the PACE trial. Patients in the control group only received SMC which patients in the intervention group also received, in addition to GET or CBT.

The General Methods handbook by IQWiG version 6.1 argues that a control group is the first requirement for assessing the benefits of interventions. It states that: "An indispensable condition for proving causality is a comparative experiment that must be designed in such a way that a difference between intervention groups - an effect - can only be attributed to a single influencing variable - the tested intervention." [Original quote in German: "Unverzichtbare Bedingung für den Nachweis von Kausalität ist ein vergleichendes Experiment, das so angelegt sein muss, dass ein Unterschied zwischen Interventionsgruppen – ein Effekt – nur auf eine einzige Einflussgröße – die geprüfte Intervention – zurückgeführt werden kann. Dieses Ziel macht für klinische Studien erhebliche Anstrengungen nötig, weil

es zahlreiche unerwünschte Einflüsse gibt, die einen Effekt vortäuschen oder auch verbergen können (Verzerrung).”]

This is not the case in these trials. Because the control group received no intervention, improved symptom scores might have resulted from patients’ expectations or increased attention and contact with their healthcare providers.

The data on CBT does not indicate a treatment effect

5.7 Zusammenfassende Bewertung der Ergebnisse - Vergleich CBT versus SMC– Page 149

The IQWiG report concludes on page 149: “When all results are weighed up across outcomes, there is a hint of a benefit of CBT compared to SMC for patients with mild to moderate ME/CFS severity, both in the short and medium term.” [Original quote in German: “Bei endpunktübergreifender Abwägung aller Ergebnisse ergibt sich für Patientinnen und Patienten mit leichtem bis moderatem ME/CFS-Schweregrad sowohl kurz- als auch mittelfristig ein Anhaltspunkt für einen Nutzen der CBT im Vergleich zur SMC.”]

In the appendix intended to appear on www.gesundheitsinformation.de, CBT is presented as a recommended treatment option. It is stated that studies have shown that CBT can help patients with mild to moderate ME/CFS to reduce their symptoms. The text states: “individual studies indicate that cognitive behavioral therapy and physical activation can help some people with mild to moderate ME/CFS to at least temporarily reduce certain symptoms.” [Original quote in German: “Studien deuten aber darauf hin, dass die kognitive Verhaltenstherapie und die körperliche Aktivierung einigen Betroffenen mit leichter bis mittelschwerer ME/CFS helfen kann, bestimmte Beschwerden zumindest vorübergehend etwas zu mindern.”] Both statements are incorrect and should be deleted.

The literature review on CBT identified only 2 randomized trials: the PACE trial and the Dutch study conducted by Janse and colleagues. Despite the risk of bias in both studies, most of the primary and secondary outcomes failed to show a clinical benefit of CBT. At long-term assessments, not a single outcome measure indicated a benefit of having received CBT. The control group performed just as well as the CBT group.

We recommend that the IQWiG report explains that there is no scientific evidence that CBT improves symptoms of ME/CFS. In the long run, the control group that did not receive an intervention performed just as well as the patients who received CBT. While ME/CFS patients should be able to receive psychological support if requested, IQWiG should clarify that there is no scientific evidence for using CBT to treat ME/CFS.

GET data shows that it is not an effective treatment for ME/CFS

5.7 Zusammenfassende Bewertung der Ergebnisse - Vergleich GET versus SMC – Page 150

The IQWiG report concludes on page 150: “When all results are weighed up across outcomes, there is a hint of a benefit of GET compared to SMC for patients with mild to moderate ME/CFS severity in both the short and medium term”. [Original quote in German: “Bei endpunktübergreifender Abwägung aller Ergebnisse ergibt sich für Patientinnen und Patienten mit leichtem bis moderatem ME/CFS-Schweregrad sowohl kurz- als auch

mittelfristig ein Anhaltspunkt für einen Nutzen der GET im Vergleich zur SMC."] This is an incorrect statement that cannot be justified by the evidence summarized in this review. In fact, the evidence review by IQWiG suggests the opposite, namely that GET is not an effective treatment for ME/CFS.

Only two randomized trials on GET were identified by the literature search: the PACE and GETSET trials, both conducted by the research team of Prof. Peter White in the UK. Despite the high risk of bias in both studies, the evidence review conducted by IQWiG found no hint of a benefit on the primary outcomes of the PACE and GETSET trials, namely fatigue and physical function. This was the case for the short-term, medium- and long-term assessments. The same was true for almost all secondary outcomes namely pain, sleep, mental status, physical activity, physical performance results, cognitive function results, and social participation. The only exceptions where GET temporarily showed a hint of an effect compared to SMC were the global clinical improvement (GCI) scale and the outcome 'feeling sick after exertion'.

The GCI scale was a secondary outcome in both the PACE and GETSET trial and is problematic as it arbitrarily reduces a 7-point scale to a percentage improvement score. The GCI scale allows participants to indicate how they felt after treatment using 7 options: very much better, much better, a little better, no change, a little worse, much worse or very much worse. The data used was the percentage of patients reporting the first two options (very much better or much better) in the GET versus SMC group. The option "a little better" was disregarded. Nonetheless, there was only an apparent effect of GET at the 12 weeks short-term assessment. For the medium and long-term assessments, no hint of a benefit could be derived.

The IQWiG report reviewed more than 10 outcome measures at 3 different assessment periods for the comparison of GET versus SMC, without applying a correction for multiple comparisons. At 12 weeks, the PACE trial was still ongoing, and patients only received half of their treatment sessions. It is therefore improbable that the higher percentage of improvers in the GET versus SMC group at 12 weeks reflects a true treatment effect.

The measurement 'feeling sick after exertion' was only used in the PACE trial. It was not assessed post-treatment or at long-term follow-up, only at the assessment 52 weeks after randomization. This measurement was not among the 14 primary or secondary outcomes measurements registered in the PACE trial protocol or statistical analysis plan. [1-2] It seems to have been added post-hoc by the PACE researchers and may thus have been the result of cherry-picking. The IQWiG report should not have included this outcome to assess the efficacy of GET.

The data summarized above fails to provide reliable evidence for the effectiveness of GET. Both the PACE and GETSET trial reported that the SMC group performed equally well as the GET group at the longest available follow-up. We recommend that the IQWiG report informs healthcare professionals in Germany that, despite two large trials conducted in the UK, there is no reliable evidence that GET improves ME/CFS symptoms or disability.

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Biased assessment of results

A2.3.3.6 Aussagen zur Beleglage – Page 180

The IQWiG report uses statistical significance to determine the strength of evidence. Table 54 on page 180, for example, shows that evidence is interpreted differently if results are statistically significant. We believe this has resulted in a bias where IQWiG undervalues trial results in which the data indicates, with sufficient precision, that there is no clinical difference between treatment arms.

An example may illustrate this point more clearly. The long-term follow-up results of GET versus SMC for the outcome of physical function resulted in an estimate of 2,0 [−4,0; 7,9] on the subscale SF-36 PF. The IQWiG report only notes that this was not a statistically significant result and therefore it is largely ignored in the rest of the document.

The confidence interval, however, excludes what is considered a 'minimal clinically important difference (MCID)' for this scale (usually around 8-10 points). [1] It thus indicates with sufficient precision that there is no clinical effect of GET compared to SMC at long-term follow-up. However, because this finding indicates no difference between groups rather than a treatment effect, it is disregarded in the rest of the report. There are other examples of this in the evidence review, depending on what one considers to be the MCID on the relevant outcome measure.

We recommend that IQWiG report no longer uses the arbitrary threshold of statistical significance to determine the strength of evidence. Evidence should be evaluated based on factors such as risk of bias or precision, not on the type of hypothesis it supports. Evidence that a treatment is not effective is also valuable information that should be shared with the public and healthcare professionals.

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Reports of harms incorrectly dismissed

6 Diskussion / Einordnung des Arbeitsergebnisses - Umgang mit kritischen Anmerkungen zu ME/CFS-Studien - Argument: „fehlende Berücksichtigung von Patientenbefragungen" – Page 157

In multiple surveys, ME/CFS patients reported that GET worsened their health. The IQWiG report dismisses these reports using several questionable arguments.

First, the IQWiG report questions that the surveys indicate harm. It uses the 2011 review by Tom Kindlon to argue that an almost equally large proportion of respondents reported that

GET improved their health. Between 28.1% and 82.0% of those questioned stated that their condition had deteriorated after GET while 13.1% to 60.8% stated that GET had improved their health. We find this comparison somewhat misleading as the percentage of participants reporting harm was quite consistently higher than the percentage saying GET was helpful if each survey is looked at separately. The 2017 overview provided by Geraghty et al. shows that when respondents to all surveys on GET were added together, 57% reported deterioration after GET while only 26% found it helpful. [1] More recent studies have only strengthened this view. In a 2019 survey developed for the NICE Guideline Development Group and conducted by researchers from Oxford Brookes University, for example, 85% of respondents reported that GET worsened their symptoms. [2]

Second, the IQWiG report suggests that reports of harm were due to inappropriate implementation of GET and that exercise should therefore be supervised by an experienced physiotherapist. The data, however, strongly speaks against this hypothesis. The 2019 survey by Action for ME, for example, found that *"even when people are supported by an M.E. specialist, only one in 10 reported that GET helped manage symptoms, while nearly half reported a worsening effect*." [3] Similarly, in a 2015 survey by the ME Association, *"GET courses held by therapists stated to have an ME/CFS specialism made symptoms worse for 57% of respondents."* [4] In an earlier survey by Action for ME there was little difference in the reported rate of harms by GET whether the treatment was delivered by an NHS specialist (31%), the GP (45%) or others (29%). [5] To our knowledge, there is no data to support the claim that reports of harm are mainly due to improper implementation of GET. This argument seems to originate from two papers by Clark & White in which they misinterpreted the results of a small Action for ME survey from 2003. Kirke later clarified this misunderstanding, explaining that in the 2003 survey:*"only 1 of 12 patients who did GET with 'no professional' reported a negative outcome, compared to 12 of 18 patients who did GET with the supervision of a physiotherapist."* [6]

Third, the IQWiG report claims that surveys are "are methodologically unsuitable for deriving reliable statements on the benefit or harm of a treatment" [Original quote in German: "Grundsätzlich sind Befragungen (Querschnittsstudien, retrospektive Vorher-Nachher Untersuchungen) in der Regel methodisch ungeeignet, zuverlässige Aussagen zum Nutzen oder Schaden einer Behandlung abzuleiten"]. While this may be true for measuring the benefits of treatments, the detection of adverse effects frequently relies on observational studies. [7] Harms are often poorly recorded in randomized treatment trials. According to a 2014 report by the Agency for Healthcare Research and Quality (AHRQ) *"observational studies are almost always necessary to assess harms adequately."* [8] The report clarified that observational studies include *"a broad range of study designs, including case reports, uncontrolled series of patients receiving surgery or other interventions, and others. All can yield useful information as long as their specific limitations are understood."* [8] Similarly, AMSTAR-II emphasizes that *"the failure to include non-randomised studies in a review of adverse outcomes of treatment may be a critical flaw."* [9]

It is quite unusual that surveys have consistently pointed towards adverse effects of GET for a period spanning almost three decades and in multiple countries including the United Kingdom, Norway, The Netherlands, and Australia. There is no clear explanation for why patients would report harms from GET but not from other interventions. In a 2010 survey by the ME Association, for example, GET was reported to be more harmful than pharmacological treatments with known side effects such as hydrocortisone, thyroxine or modafinil. [11] Similarly, in a 2014 survey by Action for ME, GET was rated as more

harmful than pain- and sleep medication. [12] This suggests that reports of harm following GET cannot be fully explained by selection bias.

Randomized trials on GET have not reported an increase in adverse effects but the data they provided is quite limited. Adverse effects were only monitored in two trials, the PACE and GETSET trial. The GETSET trial did not assess the safety of GET but a self-help guide to exercise. Therefore, its findings may not be generalizable to full courses of GET in clinical practice. And as noted by Kindlon in 2017, data on harms in the PACE trial was not reported in accordance with its pre-specified protocol. [10] GETSET and PACE also did not provide objective evidence of adherence to GET.

We recommend that IQWiG takes the reports of harms from observational studies into consideration. Relying solely on randomized controlled trials to evaluate harms can be misleading, especially if there is a large and consistent literature that points to serious adverse effects.

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Statements on revalidation and return work unjustified

Appendix: Treatment of ME/CFS page 1 (page 287 of PDF)

The draft for www.gesundheitsinformation.de suggests that rehabilitation helps ME/CFS patients to maintain employability and that CBT can help patients return to school or work earlier. These are misleading statements that should be deleted.

Employment has been included in multiple randomized trials of rehabilitative interventions for ME/CFS. Almost all have reported that these treatments do not improve the ability to maintain employment or return to work. The most recent review of this subject by Vink & Vink-Niese concluded that *"cognitive behavioural therapy and graded exercise therapy do not restore the ability to work."* [1]

Of the randomized trials included in the IQWiG report, the PACE trial reported data on employment and welfare benefits. These showed no difference between the intervention groups (CBT and GET) and the control group (SMC). [2]

Incorrect statements suggesting that rehabilitative interventions such as GET or CBT help patients to maintain or return to work can have a dramatic impact on their lives. It may not only result in false hope or wasteful investments but can also lead to healthcare professionals questioning patients' recovery behavior and an unjust denial of disability benefits. We, therefore, recommend IQWiG to only make evidence-based statements on the topic of rehabilitation and ME/CFS.

References

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[2] McCrone P, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis.

The PACE trial, a questionable source of evidence

Umgang mit kritischen Anmerkungen zu ME/CFS-Studien - P 155

The evidence review by IQWiG heavily depends on the PACE trial; a controversial study that was criticized for having various methodological flaws. In evaluating the shortcoming of the PACE trial, IQWiG focuses on a paper by Friedberg and colleagues. This brief commentary, however, does not give an overview of all essential points of the debate.

It does not discuss, for example:

- that the PACE authors published a newsletter for participants that included positive testimonials from earlier participants about the benefits of the interventions.
- that the PACE trial used outcome thresholds for being within the normal range on the two primary measures of fatigue and physical function that demonstrated worse health than the criteria for entry.
- that the PACE authors failed to adhere to the Declaration of Helsinki.

To get a more comprehensive overview of the debate, we refer to a special issue of the Journal of Health Psychology on the PACE trial (Volume 22 Issue 9, August 2017).

Problems with the SMILE trial

4.3.2.1.4 Lightning Process – P 48

The SMILE trial included in the IQWiG also suffered from severe methodological shortcomings. As explained by Tuller D: "*The investigators recruited more than half of the participants before trial registration, swapped primary and secondary outcomes after gathering data from the early recruits, and then failed to disclose these critical details in the paper."* [1] These issues were not mentioned in the evidence review conducted by IQWiG.

References

[1] Tuller D. 2019. BMJ should retract flawed research paper on chronic fatigue syndrome. Statnews.com.
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No section on severe ME/CFS

Schweregrade der Erkrankung – P 9

The IQWiG report lacks a separate section devoted to the care of patients with very severe ME/CFS as was included in the NICE guidance. Patients with very severe ME/CFS need special care from healthcare providers. They require a low-stimulus environment and may suffer from extreme symptoms such as an inability to speak or swallow.

More information on this patient group was provided in a special issue "ME/CFS – the Severely and Very Severely Affected" of the Journal Healthcare (March 2021).

Longitudinal EBV-studies

4.2.2.4 Ätiologie / Ursachen – P 21

The IQWiG report understates the evidence that an Epstein-Barr Virus (EBV) infection can act as a trigger of ME/CFS. It states, for example on page 21, that "herpes viruses, Epstein-Barr viruses or SARS-CoV-2 are suspected to be triggers of ME/CFS." [Original quote in German: "Herpes-Viren, Epstein-Barr-Viren oder SARS-CoV-2 werden als Auslöser von ME/CFS vermutet."]

Multiple longitudinal studies, however, have confirmed an increased prevalence of ME/CFS following EBV infection. [1-4] This is one of the few findings on ME/CFS that were replicated by multiple research teams. We think this could have received more attention in the IQWiG report.

References

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