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EFFECTS OF GRADED EXERCISE THERAPY AND MEDICAL CARE ON CHRONIC FATIGUE SYNDROME

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ABSTRACT

Purpose: *Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME) is a complex condition with debilitating symptoms that significantly impact individuals, particularly those in the working population. This study aims to investigate the effectiveness of Graded Exercise Therapy (GET) and Cognitive Behavioral Therapy (CBT) along with additional methods such as Graded Exercise Self-help (GES), Adaptive Pacing Therapy (APT), and Specialist Medical Care (SMC), in managing Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME) among the working population.*

Methods: *A systematic analysis of five randomized controlled trials conducted between 2013 and 2023, encompassing GET, CBT, APT, SMC, and GES was performed using PubMed.*

Results: *The selected studies consistently demonstrate that GET positively impacts physical functioning and reduces fatigue levels in working individuals with CFS. Additionally, CBT proves valuable, emphasizing the importance of addressing the mental aspects of CFS in occupational contexts.*

Conclusion: *This review underscores the need for further research, advocating for direct assessment methods like biomarkers to enhance our understanding of CFS and improve treatment outcomes. These insights are crucial for healthcare practitioners, researchers, and policymakers navigating the complexities of CFS within the workplace. Emphasizing the integration of psychological interventions with physical thera-*

pies is essential for a comprehensive approach to managing CFS among the working population.

Keywords: *Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, CFS/ME, graded exercise therapy, cognitive behavioral therapy, adaptive pacing therapy, specialist medical care, working population.*

UČINKI STOPNJEVANE VADBENE TERAPIJE IN ZDRAVSTVENE OSKRBE NA SINDROM KRONIČNE UTRUJENOSTI

IZVLEČEK

Namen: *Sindrom kronične utrujenosti (CFS)/mialgični encefalomielitis (ME) je zapletena bolezen z izčrpavajočimi simptomi, ki močno vplivajo na posameznike, zlasti na delovno aktivno prebivalstvo. Namen te študije je raziskati učinkovitost stopnjevane vadbene terapije (GET) in kognitivno-vedenjske terapije (CBT) skupaj z dodatnimi metodami, kot so stopnjevana vadba za samopomoč (GES), terapija s prilagojenim tempom (APT) in specialistična zdravstvena oskrba (SMC), pri obvladovanju sindroma kronične utrujenosti (CFS)/mialgičnega encefalomielitisa (ME) med delovno populacijo.*

Metode: *Sistematična analiza petih randomiziranih nadzorovanih raziskav, opravljenih med letoma 2013 in 2023, ki vključujejo GET, CBT, APT, SMC in GES, je bila opravljena s pomočjo PubMeda.*

Rezultati: *Izbrane študije dosledno dokazujejo, da GET pozitivno vpliva na telesno delovanje in zmanjšuje stopnjo utrujenosti pri zaposlenih posameznikih s CFS. Poleg tega se CBT izkaže za koristno, kar poudarja pomen obravnave duševnih vidikov CFS v poklicnem kontekstu.*

Sklep: *V pregledu je poudarjena potreba po nadaljnjih raziskavah, pri čemer se zagovarja neposredne metode ocenjevanja, kot so biomarkerji, da bi izboljšali naše razumevanje CFS in izboljšali rezultate zdravljenja. Ta spoznanja so ključna za zdravstvene delavce, raziskovalce in oblikovalce politik, ki se spopadajo z zapletenostjo CFS na delovnem mestu. Poudarjanje vključevanja psiholoških intervencij v vadbene terapije je bistvenega pomena za celovit pristop k obvladovanju CFS med delovno aktivnim prebivalstvom.*

Ključne besede: *sindrom kronične utrujenosti/mialgični encefalomielitis, CFS/ME, stopnjevana vadbena terapija, kognitivno-vedenjska terapija, terapija s prilagojenim tempom, specialistična zdravstvena oskrba, delovna populacija.*

INTRODUCTION

Chronic Fatigue Syndrome (CFS) / *Myalgic Encephalomyelitis* (ME) is a medical condition characterized by profound fatigue and a range of associated symptoms, such as musculoskeletal pain, sleep disorders, cognitive impairments including concentration and memory deficits, headaches and a low tolerance for physical activity affecting individuals for six months or more (Prins, van der Meer, & Bleijenberg, 2006). Despite its significant impact, effective medical responses are hindered by the lack of standardized diagnostic tests and a comprehensive understanding of its pathophysiology (Sandler & Lloyd, 2020). The etiology of CFS remains elusive, encompassing various theories related to viral infections, immune imbalances, hormonal factors, genetic predispositions, and psychological stress (Sandler & Lloyd, 2020). Recent epidemiological studies have highlighted a high prevalence of CFS, particularly among adults (Johnston, Brenu, Staines, & Marshall-Gradisnik, 2013) and predominantly affecting women (Faro et al., 2016). While there is no universal tool for assessing CFS patients comprehensively (Bergner et al., 1976), specific questionnaires, such as the *Chalder Fatigue Questionnaire* (CFQ), are frequently used to assess the severity of symptomatic fatigue (Chalder et al., 1993), which has been shown to reliably discriminate between clinical and nonclinical conditions (Cella & Chalder, 2010), and the *Multidimensional Fatigue Inventory* (MFI-20) for comprehensive fatigue assessment (Shahid, Wilkinson, Marcu, & Shapiro, 2012). Additionally, various interventions have been proposed for managing CFS symptoms, including *Cognitive Behavioral Therapy* – CBT, *Graded Exercise Therapy* – GET, *Adaptive Pacing Therapy* – APT, *Specialist Medical Care* – SMC, and *Graded Exercise Self-help* – GES. CBT addresses the cognitive, behavioral, and symptomatic aspects of CFS, guiding participants to develop coping strategies (White, Goldsmith, Johnson, Chalder, & Sharpe, 2013). GET gradually increases physical activity to improve fitness in CFS/ME treatment (Sharpe et al., 2015). APT manages energy through activity assessment and pacing (Walwyn et al., 2013), while SMC offers explanations, guidance, and medical recommendations (Clark et al., 2017) and GES involves a six-step exercise program (Clark et al., 2017). Given the significant impact of CFS/ME on the working population (Valdez et al., 2019), there is a critical need to analyze existing research and interventions specifically designed for this condition. Therefore, the aim of this article is to provide a concise yet comprehensive examination of the current research and interventions aimed at managing CFS/ME symptoms within the working population, highlighting the impor-

tance of addressing the unique challenges faced by working individuals with this condition.

METHODS

The research methodology is based on a descriptive approach, involving the analysis of previous studies conducted between 2013 and 2023 using the PubMed domain using the words "CFS" OR "GET" OR "CBT" "APT" OR "SMC" OR "working population". The search specifically focused on randomized controlled trials and the literature review concentrated on studies incorporating the working population as a subject due to their increased vulnerability to this condition. The inclusion criteria were that participants involved in the study must have a diagnosed with CFS, belong to the working population, and the intervention in the treatment or prevention of CFS consisted of GET, CBT, APT, SMC, or GES. Additionally, the articles had to be written in the English language and the full text must be accessible. The exclusion criteria comprised studies addressing other forms of fatigue, those that did not specifically apply to research on the influence of physical activity on CFS, studies involving adolescents, and those assessing physical fitness after the administration of specific supplementation or medication.

RESULTS

The following results were obtained through the research of the PubMed database, based on keyword search and their combination, adhering to the inclusive and exclusive criteria. A total of 61 articles were identified through data research, from which 19 abstracts were reviewed. All the identified articles were read in full to assess eligibility and quality. In the end, a total of five articles were included in the review. An overview of the search and selection methodology procedure is described in Figure 1 through a Prisma diagram.

Based on the results presented in *Table 1* regarding the use of different programs in the treatment of CFS, the outcomes for patients receiving GET or GES treatment combined with CBT indicated a reduction in fatigue, with patients reporting an improvement in physical and cognitive functioning. SMC and APT showed improved outcomes in long-term follow-ups.

In the study conducted by White et al. (2013), commonly known as the PACE study (Table 1), the effectiveness of different treatments for CFS in achieving

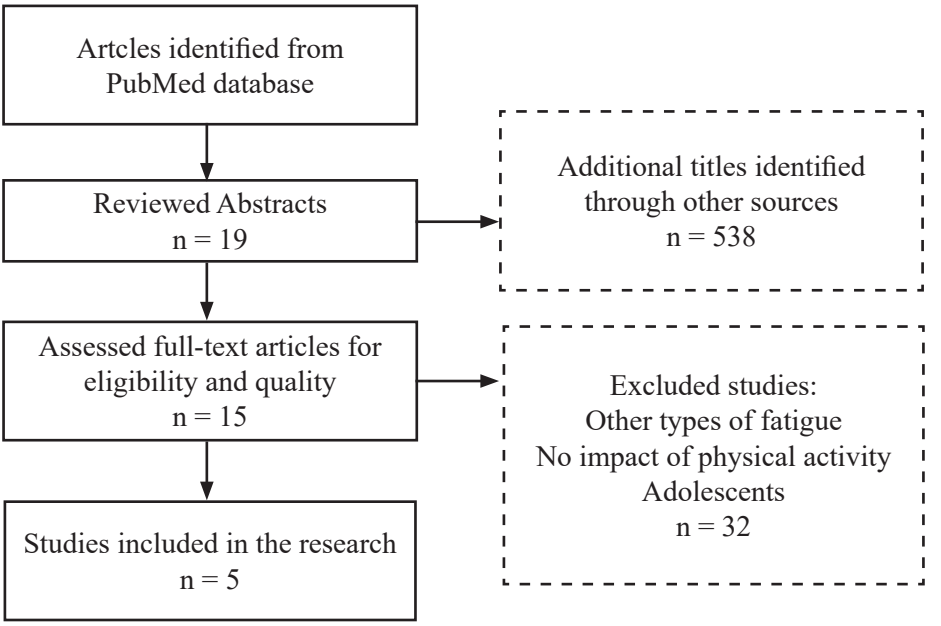

Figure 1. An overview of the search and selection methodology procedure.

recovery was compared in a sample of 641 participants over 52 weeks. The average age of the participants was 38 years, with 77% being female. The study included four treatment groups: cognitive-behavioral therapy (CBT), graded exercise therapy (GET), and adaptive pacing therapy (APT), combined with specialist medical care (SMC), as well as SMC alone. Physicians specializing in CFS were responsible for treating participants in the SMC program. Occupational therapists oversaw SMC and APT, clinical psychologists SMC and CBT, and physiotherapists SMC and GET. The primary goal was to determine how many participants in each treatment group achieved complete recovery based on different criteria. Specialist doctors explained the symptoms of the syndrome to the patients and ways to manage their condition, prescribing medications to alleviate symptoms such as pain and insomnia. APT involved carefully matching activity levels to the energy levels of the participants. CBT examined the connection between thoughts and behaviors, encouraging participants to try new ways to cope with their condition. GET gradually increased the volume and intensity of physical activity to improve fitness and reacquaint the body with activity. The method of self-assessment using the standardized CFQ

Table 1. Articles Included in the Analysis of the Impact of GET and CBT in the Treatment of CFS.

Study	**Journal**	**Study type**		
1. White et al., 2013	Psychological Medicine	RCT		
2. Sharpe et al. 2015	Lancet Psychiatry	Pre-post trial		
3. Clark et al., 2017	The Lancet	RCT		
4. Wilshire et al., 2018	BMC Psychology	RCT		
5. Clark et al., 2021	Journal of Psychosomatic Research	Pre-post trial		
↓ Sequence number	Interventions			
1. CBT, GET, SMC, APT				
2. CBT, GET, SMC, APT				
3. GES, SMC				
4. CBT, GET				
5. GES, SMC				
Study sequence number →	1	2	3	4	5
n	641	641	211	641	211
Duration	52 weeks	2 years	12 weeks	52 weeks	12 months
Results	↓ fatigue, ↑ physical and cognitive functioning	↓ fatigue, ↑ physical and cognitive functioning	↓ fatigue, ↑ physical and cognitive functioning	↓ fatigue, ↑ physical and cognitive functioning	↓ fatigue, ↑ physical and cognitive functioning, ↑ overall health

Legend: n-number of participants; ↓- decrease; ↑-increase; SMC – Specialist Medical Care; CBT – Cognitive Behavioral Therapy; GET – Graded Exercise Therapy; APT – Adaptive Pacing Therapy, GES – Graded Exercise Self-help

questionnaire was used to measure the participants' fatigue levels, and the SF-36 physical fitness assessment scale was used to assess physical and cognitive functionality. The study found the following percentages of participants who met the recovery criteria: CBT: 22%, GET: 22%, APT: 8%, and SMC alone: 7%. When comparing CBT and GET with APT and SMC alone, the chances of achieving recovery were significantly higher for CBT and GET.

The next study conducted by Sharpe et al. (2015), a follow-up investigation of the effects of the previously mentioned PACE study was conducted at least 2 years after randomization (Table 1). The aim was to assess additional treatments that participants received after the study and explore whether there were long-term effects in the context of recovery within and between the original groups exposed to different CFS treatments initially included in the PACE study. Of the 641 participants involved in the original PACE study, 75% of them returned the long-term follow-up questionnaire. Additional treatment had been received by 44% of the participants, with those originally assigned only SMC or APT, as opposed to GET or CBT, being more inclined to seek additional treatment. Improvement in terms of reduced fatigue and better physical and cognitive functionality reported by participants originally assigned CBT or GET methods was sustained in the long-term follow-up compared to one year. Participants initially assigned SMC or APT methods showed improvement in long-term follow-up compared to one year in the context of reduced fatigue and improved physical functionality. To measure the participants' fatigue levels, the method of self-assessment using the standardized CFQ questionnaire was again employed, and the SF-36 physical fitness assessment scale was used to assess physical functionality.

In the study by Clark et al. (2017), the researchers conducted a study called GETSET to investigate the impact of SMC compared to SMC with the addition of the modified Graded Exercise Self-help (GES) method, described in a self-help manual outlining a six-step graded exercise therapy, with an expected duration of approximately 12 weeks. Of the total 211 participants (adults aged 18 and above), 107 were assigned to the GES group, and 104 to the control group. The study aimed to compare the effects of the GES method combined with SMC versus SMC alone in the treatment of chronic fatigue syndrome, hypothesizing that the combined method would yield better results in terms of reducing fatigue and improving physical functionality. With the GES manual, participants had the option to conduct up to four guided sessions with a physiotherapist over 8 weeks, totaling 90 minutes. After 12 weeks, compared to the control group, 34% of the GES group showed 8 points of improvement on the SF-36 physical fitness assessment scale and 3 points of

improvement on the CFQ questionnaire, compared to a 14% improvement in the control group.

In study number 4 (Table 1), the authors Wilshire et al. (2018) conducted a reanalysis of the previously mentioned PACE study (White et al., 2013), primarily focusing on the effects of the GET and CBT methods. They noted that the original authors had not consistently adhered to the procedures outlined in the published protocol, and it is unclear whether the conclusions drawn are entirely justified by the evidence, suggesting that the impact of the applied methods in CFS therapy is limited to self-assessment. After the reanalysis of the self-assessment questionnaire results, the GET group had better ratings for physical function compared to the control group but not in fatigue self-assessment, while the CBT group showed better ratings in self-assessment of fatigue but not in physical function.

In a study conducted by Clark, McCrone, Pesola, Vergara-Williamson, and White (2021), the long-term effects of the GETSET research in the treatment of CFS were investigated. The aim of this study was to examine the effects of the GES study compared to SMC alone in the context of improved physical functioning and reduced fatigue, with an assessment of the long-term clinical and economic outcomes. Primary outcomes were evaluated through the CFQ questionnaire and SF-36 survey, with questionnaires mailed 12 months after the completion of the GETSET study. In the study, 78% of the participants returned the questionnaires 15 months after the study's commencement, with previously recorded improvements following GES being sustained in the long-term follow-up but without additional improvement and no significant difference compared to the control group.

DISCUSSION

Based on the existing research presented in *Table 1*, the results indicate that the application of GET improves physical functioning and reduces the perception of fatigue more than SMC alone in adults diagnosed with CFS (Clark et al., 2017). It can be stated that the GET method has consistent evidence of benefits in the treatment of CFS, supported by a conducted meta-analysis showing moderate evidence of improved physical functionality and reduced fatigue severity (Smith et al., 2015). In clinical practice, GET precedes activities involving adaptation, which includes identifying the threshold beyond which the prolonged worsening of symptoms occurs. Subsequently, a 'pacing' approach to activities is implemented to maximize the utilization of limited energy reserves (Sandler

& Lloyd, 2020). Compared to passive controls (such as relaxation or flexibility exercises), GET reduces the fatigue levels at the end of treatment with moderate certainty (Larun, Brurberg, Odgaard-Jensen, & Price, 2019). The specific characteristics of the symptomatology of patients with CFS require a prompt adaptation of educational, healthcare, and social systems to prevent issues arising from the current systems (Nacul et al., 2011). In earlier studies, it is noted that the majority of individuals diagnosed with CFS/ME will experience or have already experienced periods when their symptoms relapse or worsen (Clark, 2009). Clark (2009) concluded that it is crucial to have a plan for coping with the return of the symptoms to preserve the progress that has been made and, above all, identifying the cause of the symptom recurrence is essential to reduce the likelihood of it happening again. The reviewed studies collectively contribute to our understanding of therapeutic interventions for CFS/ME within the working population. The PACE study (White et al., 2013) compared various treatments, revealing that CBT and GET increased the recovery chances significantly. The follow-up study (Sharpe et al., 2015) demonstrated sustained benefits in participants assigned CBT or GET, while those on SMC or APT also showed improvement. The GETSET study (Clark et al., 2017) introduced modified graded exercise self-help – GES alongside SMC, exhibiting superior outcomes compared to SMC alone. Wilshire et al.'s (2018) reanalysis criticized the PACE study's methodology, highlighting limitations in its conclusions. Clark et al.'s (2021) long-term investigation of GETSET showed sustained benefits but no additional improvement over SMC.

CONCLUSION

In this study, we underscore the importance of integrating psychological and physical interventions for comprehensive CFS management within the working population. The findings from the reviewed studies, encompassing a combination of CBT and GET, and either SMC or APT, emphasize the significance of personalized treatment approaches. The consistent positive outcomes of CBT and GET, maintaining their effectiveness in the long term, highlight the critical role of psychological interventions in effectively addressing CFS among the working population. Furthermore, the analysis of the available data and the recommended treatment for CFS/ME indicates that short-term changes can be expected, resulting in a temporary reduction in the sensation of fatigue and an improvement in physical and cognitive functioning (Wilshire et al., 2018). The studies reviewed also revealed a predominant reliance on indirect

measurement methods, primarily employing self-reported questionnaires. To address existing gaps, there is a noteworthy need for more research utilizing direct assessment methods, such as biomarkers, providing a direct measurement of physiological changes. Previous research (Maksoud, Magawa, Eaton-Fitch, Thapaliya, & Marshall-Gradisnik, 2023) identified potential blood-based biomarkers, encompassing genetic/epigenetic, immunological/mitochondrial/microbiome, endovascular/circulatory, neurological, ion channel, and physical dysfunction biomarkers. Notably, the use of lymphocytes as a model for investigating CFS/ME pathology is prominent among the immune system-based biomarkers (Maksoud et al., 2023). However, the heterogeneity shown in many of the included studies highlights the need for multidisciplinary research and standardized protocols to advance our understanding and management of CFS/ME. While numerous blood abnormalities show promise as potential biomarkers for CFS/ME, none can reliably differentiate individuals with CFS/ME from those with other health conditions or those in perfect health (Maksoud et al., 2023). The variability in findings across studies underscores the necessity for multidisciplinary research and standardized protocols. A continual overview and the transparent reporting of research methods are essential for developing a comprehensive understanding of CFS/ME and refining treatment strategies.

REFERENCES

Bergner, M., Bobbitt, R. A., Kressel, S., Pollard, W. E., Gilson, B. S., & Morris, J. R. (1976). The sickness impact profile: conceptual formulation and methodology for the development of a health status measure. *International Journal of Health Services, 6*(3), 393-415. https://doi.org/10.2190/RHE0-GGH4-410W-LA17.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research, 37*(2), 147-153. https://doi.org/10.1016/0022-3999(93)90081-P.

Cella, M., & Chalder, T. (2010). Measuring fatigue in clinical and community settings. *Journal of Psychosomatic Research, 69*(1), 17-22. https://doi.org/10.1016/j.jpsychores.2009.10.007.

Clark, L. (2009). *Graded Exercise Therapy: A self-help guide for those with chronic fatigue syndrome/myalgic encephalomyelitis*. London: Bart's and the London NHS Trust. Retrieved from https://www.researchgate.net/publication/256293990_Graded_Exercise_Therapy_A_self-help_guide_for_those_with_chronic_fatigue_syndromemyalgic_encephalomyelitis.

Clark, L. V., McCrone, P., Pesola, F., Vergara-Williamson, M., & White, P. D. (2021). Guided graded exercise self-help for chronic fatigue syndrome: Long term follow up and cost-effectiveness following the GETSET trial. *Journal of Psychosomatic Research, 146*, 110484. https://doi.org/10.1016/j.jpsychores.2021.110484.

Clark, L. V., Pesola, F., Thomas, J. M., Vergara-Williamson, M., Beynon, M., & White, P. D. (2017). Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomized controlled trial. *Lancet, 390*(10092), 363-373. https://doi.org/10.1016/S0140-6736(16)32589-2.

Faro, M., Sàez-Francás, N., Castro-Marrero, J., Aliste, L., de Sevilla, T. F., & Alegre, J. (2016). Gender differences in chronic fatigue syndrome. *Reumatología Clínica (English edition), 12*(2), 72-77. https://doi.org/10.1016/j.reumae.2015.05.009.

Johnston, S., Brenu, E. W., Staines, D., & Marshall-Gradisnik, S. (2013). The prevalence of chronic fatigue syndrome/myalgic encephalomyelitis: a meta-analysis. *Clinical Epidemiology, 5*(1), 105-110. https://doi.org/10.2147/CLEP.S39876.

Larun, L., Brurberg, K. G., Odgaard-Jensen, J., & Price, J. R. (2019). Exercise therapy for chronic fatigue syndrome. *Cochrane database of systematic reviews*, (10). https://doi.org/10.1002/14651858.CD003200.pub8.

Maksoud, R., Magawa, C., Eaton-Fitch, N., Thapaliya, K., & Marshall-Gradisnik, S. (2023). Biomarkers for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review. *BMC Medicine, 21*(1), 189. https://doi.org/10.1186/s12916-023-02893-9.

Nacul, L. C., Lacerda, E. M., Pheby, D., Campion, P., Molokhia, M., Fayyaz, S., ... Drachler, M. L. (2011). Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. *BMC Medicine, 9*(1), 1-12. https://doi.org/10.1186/1741-7015-9-91.

Prins, J. B., van der Meer, J. W., & Bleijenberg, G. (2006). Chronic fatigue syndrome. *Lancet, 367*, 346-355. https://doi.org/10.1016/S0140-6736(06)68073-2.

Sandler, C. X., & Lloyd, A. R. (2020). Chronic fatigue syndrome: progress and possibilities. *Medical Journal of Australia, 212*(9), 428-433. https://doi.org/10.5694/mja2.50553.

Shahid, A., Wilkinson, K., Marcu, S., & Shapiro, C. M. (Eds.). (2012). *STOP, THAT and one hundred other sleep scales*. Springer Science & Business Media.

Sharpe, M., Goldsmith, K. A., Johnson, A. L., Chalder, T., Walker, J., & White, P. D. (2015). Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. *The Lancet Psychiatry, 2*(12), 1067-1074. https://doi.org/10.1016/S2215-0366(15)00317-X.

Smith, M. B., Haney, E., McDonagh, M., Pappas, M., Daeges, M., Wasson, N., ... Nelson, H. D. (2015). Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine, 162*(12), 841-850. https://doi.org/10.7326/M15-0114.

Valdez, A. R., Hancock, E. E., Adebayo, S., Kiernicki, D. J., Proskauer, D., Attewell, J. R., ... Proskauer, C. (2019). Estimating prevalence, demographics, and costs of ME/CFS using large scale medical claims data and machine learning. *Frontiers in Pediatrics, 6*, 412. https://doi.org/10.3389/fped.2018.00412.

Walwyn, R., Potts, L., McCrone, P., Johnson, A. L., DeCesare, J. C., Baber, H., ... White, P. D. (2013). A randomised trial of adaptive pacing therapy, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fa-

tigue syndrome (PACE): statistical analysis plan. *Trials, 14*(1), 1-23. https://doi.org/10.1186/1745-6215-14-386.

White, P. D., Goldsmith, K., Johnson, A. L., Chalder, T., & Sharpe, M. (2013). Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychological Medicine, 43*(10), 2227-2235. https://doi.org/10.1017/S0033291713000020.

Wilshire, C. E., Kindlon, T., Courtney, R., Matthees, A., Tuller, D., Geraghty, K., & Levin, B. (2018). Rethinking the treatment of chronic fatigue syndrome—a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. *BMC Psychology, 6*(1), 1-12. https://doi.org/10.1186/s40359-018-0218-3.