Title: A systematic mapping review of clinical guidelines for the management of fatigue in long-term physical health conditions

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Abstract

Background: Despite a high prevalence of fatigue and its importance to patients, many people with long-term conditions do not receive fatigue management as part of their treatment. This review aimed to identify clinical guidance for the management of fatigue in long-term physical health conditions.

Methods: A systematic mapping review was conducted in accordance with Social Care Institute for Excellence systematic review guidance. Bibliographic databases and guideline repositories were searched for clinical guidelines for long-term conditions, published between January 2008 and July 2018, with a search for updates conducted in May 2023. Data were extracted on the recommendations made for managing fatigue and, where cited, the underlying research evidence used to support these recommendations was also extracted.

Results: The review included 221 guidelines on 67 different long-term conditions. Only 30 (13.6%) of the guidelines contained recommendations for managing fatigue. These were categorised as clinical (e.g. conduct further investigations), pharmacological, behavioural (e.g. physical activity), psychological, nutritional, complementary, environmental and multicomponent. The guidelines rated much of the evidence for fatigue management as fairly low quality, highlighting the need to develop and test fatigue-management strategies in high quality trials.

Conclusion: This review highlights that management of fatigue is a very important neglected area in the clinical guidelines for managing long-term conditions.

Key words: Fatigue; long-term conditions; systematic review; mapping review; clinical guidelines

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Introduction

Fatigue is a common and debilitating symptom of many long-term physical health conditions, including musculoskeletal, neurological, and cardiovascular conditions. It is not ordinary tiredness that is resolved by rest but is described by patients as overwhelming and for many it is the most troubling symptom of their disease[1-4]. Estimated prevalence of fatigue in people with long-term conditions ranges from about one fifth to over 90% (see Supplementary table 1).

Fatigue has a significant negative impact on quality of life across many long-term conditions[5-12]. It is an important predictor of healthcare utilisation[13] and mortality[14,15] and has a high economic cost to society as a major cause of work disability[2,16-18]. Treatment is therefore essential to help reduce symptoms and/or help people manage fatigue to lessen its impact on their lives. However, many people with long-term conditions do not receive treatment for fatigue. For example, a survey of adults with rheumatoid arthritis (RA) found that 89% of respondents experienced fatigue but only 2% had attended a fatigue management intervention[19]. A survey of people with multiple sclerosis (MS) found that 90.3% reported experiencing fatigue but only 30.8% reported being offered any pharmacological or non-pharmacological treatment for their fatigue[20]. Both of these reports[19,20] stressed the importance of clinical practice guidelines in guiding treatment and emphasised that the guidelines for these conditions need to be strengthened to clearly reflect the best available evidence for managing fatigue, summarising both beneficial and ineffective treatments.

Approaches to help manage fatigue include pharmacological and non-pharmacological interventions. There is evidence for the efficacy of some interventions[21-23], however, these interventions are not necessarily considered in clinical guidelines [24,25]. For example, a Cochrane review of biologic agents for fatigue in RA concluded, based on evidence they rated as moderate quality, that biologic agents produce small to moderate benefit[26]. A Cochrane review in RA concluded that physical activity interventions, which they rated as moderate quality, and psychosocial interventions (such as

cognitive behavioural therapy and mindfulness therapy) produce small beneficial effects, although evaluations of psychosocial interventions were rated as low quality[21]. A systematic review of aerobic exercise for people with systemic lupus erythematosus (SLE), in which most studies were rated to have low or very low risk of bias, reported significant reductions in fatigue with moderate to high effect sizes[27]. However, some recent SLE guidelines do not contain recommendations on managing fatigue[28]. Given these limitations, we wanted to review the recommendations for managing fatigue across other long-term health conditions to see if there could be any shared learning across the condition-specific guidelines on how to manage this frequently reported symptom, or whether lack of treatment recommendations is common across conditions.

The aim of this review was to identify and categorise the clinical guidance, both pharmacological and non-pharmacological, that exists for the management of fatigue in long-term physical health conditions and to identify any gaps in this guidance.

Materials and Methods

Design

A systematic mapping review was conducted in accordance with Social Care Institute for Excellence systematic review guidance[29]. This type of review does not aim to rate the evidence in an area but rather to provide a comprehensive description of the literature available on a topic and identify gaps in that literature[29].

Inclusion criteria

Clinical guideline documents were included if they related to the management of a long-term physical health condition in adults (≥18 years old).

To ensure that we were as inclusive as possible, we did not set exclusion criteria based on whether or not fatigue was a recognised symptom of the long-term condition. Instead, we referenced literature on fatigue prevalence data across all of the long-term conditions for which we identified guidelines (Supplementary table 1).

If a guideline was superseded by a more up to date guideline from the same organisation, only the most recent guideline was included.

Exclusion criteria

We aimed to examine clinical guidelines for the comprehensive management of a long-term condition and therefore guidelines that had a narrow focus for example, solely on imaging administration of a pharmacological agent or surgical guidance for a long-term condition were excluded.

Guidelines were excluded if they related to long-term conditions resulting from accident or injury, rather than disease, mental health conditions or developmental disorders. Guidelines relating to cancer were excluded because a systematic review of clinical guidelines for the management of cancer-related fatigue has already been published[30]. Guidelines for myalgic encephalomyelitis/chronic fatigue syndrome were also excluded as fatigue is the illness itself rather than an effect of a distinct long-term condition.

Search methods.

The following databases were searched from January 2008 to July 2018 to identify published clinical guidelines:

- AMED
- Embase
- EBM Reviews – ACP Journal Club

- CINAHL
- Medline

A period of ten years was considered sufficient to identify current guidelines. An update was conducted in May 2023, when all included guidelines were checked to ensure that the latest version had been identified.

The following electronic repositories were also searched:

- Australian National Health and Medical Research Council clinical practice guidelines[31]
- Canadian Medical Association InfoBase of clinical practice guidelines[32]
- Guidelines International Network[33]
- National Institute for Health and Care Excellence[34]
- New Zealand Guidelines group[35]
- Scottish Intercollegiate Guidelines Network[36]

The search terms are described in Appendix A. Terms relating to long-term conditions included the MeSH term 'chronic disease' and 'chronic illness'. The individual conditions were also searched in all fields; the names of all known long-term conditions could not be included as this would be unmanageable therefore common long-term conditions and those known to have high prevalence of fatigue were included. Guideline* or guidance was searched in the Title.

The clinical guidelines repositories were searched for each of the individual conditions listed in the search in Appendix A. A search for 'fatigue' was also conducted in the clinical guidelines databases.

Data Extraction (Selection and Coding)

Selection of Studies

Studies identified in bibliographic databases were imported into Rayyan systematic review software[37] and duplicates removed. Guidelines identified in the clinical guideline repositories were entered into an Excel file. Two review authors (KH and KM) independently screened studies using the inclusion and exclusion criteria, first applied to title and abstract screening, and then to the full-texts of papers that had not been excluded on title and abstract. Disagreements were resolved through discussion.

Data Extraction and Management

Data extraction was performed by one reviewer with 10% checked by a second reviewer, using a data extraction sheet developed by the research team. Data were extracted for:

- Authors
- Country of origin
- Publication date
- Guideline body
- Global/National/Local Guideline
- Long-term condition
- Guideline recommendations made for managing fatigue and, where cited, the underlying research evidence used to support these recommendations was also extracted. If a guideline included recommendations for treating children and adults, only recommendations relating to adults were extracted. Recommendations relating only to the acute phase of a disease (e.g. in the emergency room) were not extracted.

Data synthesis

A narrative synthesis was conducted. The number of guidelines and percentage that made fatigue recommendations were summarised numerically for each LTC. The recommendations for managing

fatigue were categorised by the type of intervention recommended. Categorisation was conducted by KM and checked by LR.

Risk of Bias (Quality) Assessment

A quality assessment of the identified guidelines, such as AGREE II[38], was not conducted. AGREE II criteria are designed to be applied to the full guideline and would therefore not reflect the quality of specific guidance in relation to fatigue. Furthermore, it is not an aim of this review to make treatment recommendations. Mapping reviews aim to provide a comprehensive description of the literature on a topic and identify gaps in the evidence rather than to rate the evidence; it is therefore not usual to include quality assessments in mapping reviews[29].

Results

Searches identified 4444 publications, of which 221 guidelines relating to 67 different long-term conditions met the inclusion criteria (figure 1).

figure 1 about here

Only 30 (13.6%) guidelines, relating to 19 (28.4%) long-term conditions, contained recommendations for managing fatigue (figure 2). If we exclude guidelines related to long-term conditions where no data on fatigue prevalence were found (30 guidelines related to 21 long-term conditions – see Supplementary table 1), this still gives only 30/191 (15.7%).

figure 2 about here

The 30 guidelines that contained fatigue recommendations (table 1) mostly related to cardiovascular (n=6 guidelines), post-infection (n=5) and neurological conditions (n=5). Guidelines with no fatigue recommendations are listed in Supplementary table 2.

table 1 about here

Of the 30 guidelines that included fatigue recommendations, the amount of guidance given was mostly minimal. Only seven of the guidelines laid out what might be considered fairly comprehensive guidance[39-45]. The guidance that addressed fatigue focused on a number of different approaches, which we grouped into categories, based on the type of intervention recommended, and guided by similar categories reported elsewhere in the literature[46,47]. The categories were:

- Clinical – e.g. investigations, referrals
- Pharmacological – guidance re medications
- Information/education - provision of basic information about fatigue
- Psychological / Psychosocial e.g. coping skills, cognitive behavioural therapy
- Behavioural (focused on change in patients' behaviour) e.g. activity pacing, physical activity, dietary behaviour (such as advice about fasting during Ramadan)
- Nutritional e.g. taking dietary supplements
- Environmental (physical) e.g. warmth
- Complementary therapies (defined as "treatment that falls outside of mainstream healthcare"[48]) e.g. acupuncture

The findings for these categories are summarised below:

Clinical – Of the 30 guidelines that made fatigue recommendations, 17 (56.7%) recommendations were classified as 'Clinical'[39,40,43,44,49-61]. These mostly involved recommendations to consider modifiable contributory factors, to conduct further investigations and/or to refer for further input.

Pharmacological – sixteen guidelines (53.3%)[39-45,50,55,57,62-67] made recommendations classified as 'Pharmacological', most of which related to the review/adjustment of medication that may have contributed to symptoms of fatigue. Eight guidelines, for, fibromyalgia[41], HIV[55], MS[68], post-polio syndrome[67], Sjogren's syndrome[42], SLE[57], and Stroke[44,45] made recommendations about 19

pharmacological agents for the treatment of fatigue. Supplementary figure 1 plots the strength of guideline recommendation for each treatment according to whether it should/should not be given or could be considered for some patients/situations and the strength with which each recommendation was made. It can be seen that all of the strong recommendations related to treatments that should not be given, while the recommendations in favour of treatments were weak or not classified. Only hydroxychloroquine and modafinil were recommended for consideration in more than one long-term condition - hydroxychloroquine for SLE in patients with normal renal and liver function[57] and in selected situations for Sjogren's Syndrome[42] and modafinil in MS[68] and stroke[44,45] (but for the latter, one guideline advised it should only be provided in the context of a clinical trial).

Supplementary figure 2 plots the strength of guideline recommendations/quality of evidence reported for non-pharmacological treatments, which are summarised below.

Information – Five guidelines (16.7%), on heart failure[51], multiple sclerosis and stroke[44,45,60] recommended provision of information regarding fatigue, including potential fatigue triggers.

Psychological – Eight guidelines (27.6%) made recommendations classified as 'Psychological' [39-41,44,45,51,69,70]. These included relaxation therapy[51 45], coping strategies[40 45], stress management[39], psychotherapy[39], mindfulness-based training[44,70], cognitive-behavioural therapy/techniques[44,69], building acceptance and adjustment [45] and communication of needs to others[44]. The guidelines were for heart failure, inflammatory bowel disease, cholestatic liver disease, fibromyalgia, stroke and COPD. Guidance for psychological treatments mostly consisted of weak recommendations based on low quality evidence.

Behavioural – seventeen guidelines (58.6%) made recommendations classified as 'Behavioural'. The most common was regarding physical activity[39,41-45,50,51,61,67,70,71], which was recommended across

several long-term conditions, including heart failure, inflammatory bowel disease, post-polio syndrome, fibromyalgia, RA, Sjogren's syndrome, MS, stroke and chronic obstructive pulmonary disease (COPD). Several fatigue-specific physical activity recommendations were based on limited or low-quality evidence, as rated by the guideline authors. Two exceptions were for COPD, where pulmonary rehabilitation was strongly recommended based on evidence from systematic reviews or randomised controlled trials (RCTs)[61] and for heart failure, where aerobic endurance or interval training was recommended for people in New York Heart Association (NYHA) Classes II-III, based on Level 1 (systematic review) evidence[51]. Exercise was advised against in some patients with heart failure.

Other behavioural recommendations included pacing of rest and activity[44,45,67,72], and sleep hygiene practices[40,44,69].

Specific dietary advice was given regarding diabetes[73] and ALS[58]. Advice for diabetes was to break fasting during Ramadan if symptoms of hyperglycaemia, such as fatigue, were experienced; the evidence on which this was based is unclear. Advice for ALS was to eat several small meals a day, which was considered a good practice point.

Some behavioural advice was vague, for example, self-management education was recommended for COPD but without specifying how fatigue-management should be addressed[70].

Nutritional – Three guidelines (10.0%) made recommendations that we classified as 'Nutritional'. A guideline for neurological conditions[58], made a 'good practice point' recommendation for meal enrichment/oral supplementation for prevention of malnutrition in MS and, if weight loss progresses, in ALS. A MS guideline recommended explaining that there is no evidence for a specific diet to help

MS-related fatigue[68]. A guideline for COPD[70] recommended nutritional support to improve fatigue (level of evidence/strength of recommendation unclear).

Complementary – Two guidelines (6.7%), one for fibromyalgia[41] and one for stroke[45], made recommendations regarding complementary therapies. A guideline for fibromyalgia made a 'weak' recommendation for use of acupuncture and a weak recommendation against S-Adenosyl methionine, based on Level 1A evidence (systematic reviews). A stroke guideline[45] recommended that acupuncture should only be provided in the context of a clinical trial.

Environmental (physical) – One guideline (3.4%) for post-polio syndrome[67] recommended muscular training in a warm climate (Level B recommendation – 'probably effective').

Multicomponent – Two guidelines (6.9%), one for fibromyalgia[41] and one for MS[68], recommended multicomponent interventions that combine behavioural and psychological approaches. A weak recommendation for multicomponent therapies was made in fibromyalgia based on a systematic review of moderate quality trials. A recommendation to consider a combination of aerobic and moderate progressive resistance activity with cognitive behavioural techniques for multiple sclerosis was based on evidence that ranged from very low to high quality.

Of the non-pharmacological treatments, summarised above, only biofeedback and S-Adenosyl methionine were advised against, both in relation to fibromyalgia[41].

Discussion

Statement of principal findings

Only 13.6% of clinical guidelines for long-term physical health conditions provided recommendations for how to manage fatigue. Furthermore, in guidelines that did address fatigue, the

recommendations were often minimal, for example, advice to adjust medication if fatigue was a side-effect. Although recommendations for pharmacological treatment of fatigue were available for some conditions, the strong recommendations made were mainly about what treatments *not* to use whereas most of the recommendations for treatments to use were weak.

The most widely recommended non-pharmacological approach for fatigue was physical activity. The amount of advice given varied between guidelines, for example, in the type of exercise recommended and whether supervision is required but there was little advice on frequency or intensity of activity. The strength of recommendations varied, with few making strong recommendations; this does, however, suggest that guideline developers for other conditions should explore the evidence for physical activity on fatigue.

A variety of psychological approaches were recommended with no one dominant approach. No guideline advised against using psychological therapies, however, recommendations were mostly weak based on low quality evidence.

Interpretation within the context of the wider literature

Most of the identified guidelines did not contain any recommendations for managing fatigue. For some guidelines this is understandable because fatigue is not a major feature of those particular diseases. However, it should be borne in mind that while we did not identify fatigue prevalence data for all included long-term conditions (Supplementary table 1), this does not necessarily mean that people with those diseases do not experience fatigue. For example, it is widely recognised that people with thyroid disease experience fatigue[74], however, no prevalence data were found.

This review confirms that, where evidence is available, it has not always been incorporated into guidelines. As mentioned in the introduction, some evidence of benefit of interventions to alleviate fatigue exists in RA[21,26] and SLE[27], however, only one of the five RA guidelines and one of the four SLE guidelines identified in this review included recommendations for fatigue management. Some

recent trials have examined the effect of interventions on fatigue for people living with HIV but no guidelines were identified that have incorporated the findings[75,76]. A scoping review of systematic reviews reported that the anti-depressant fluoxetine was found to be ineffective for reducing fatigue in HIV and post-stroke, however, the HIV guidelines we identified did not advise against its use[46]. We have not reviewed evidence of efficacy of interventions to manage fatigue across all long-term conditions as this would be beyond the scope of this mapping review, however, these examples indicate that lack of guidance is not always due to non-availability of research evidence. It is also important that, where negative findings for treatments exist, they are incorporated into guidelines to advise on what not to do.

It is unclear why some guideline developers have not included recommendations in cases where evidence on the efficacy of interventions exists. Recommendations and checklists exist to help groups developing and updating clinical practice guidelines[77,78], and following these recommendations should help ensure that the included guidance is appropriate. However, it would seem that fatigue is not always identified by guideline developers as a priority. Patient involvement in the guideline development panel is crucial[79,80] but even where this occurred, for example in NICE RA guidelines[25], fatigue recommendations are not necessarily included. It is possible this omission arises because of an assumption that symptoms of fatigue will be alleviated if the disease is otherwise brought under control, for example, if inflammation is controlled. This view may be mistaken as, for example, in RA[81] and inflammatory bowel disease[82] the correlation between disease activity and fatigue is low. Where fatigue is a persistent symptom of a long-term condition, it is important that guidelines should offer specific advice on how best to manage it.

Implications for policy, practice and research

The scarcity of guidance for managing fatigue in long-term conditions is, however, likely to be at least partly explained by the limited available evidence for efficacy of pharmacological and non-

pharmacological interventions. Much of the evidence reported in the included guidelines was rated fairly low quality, a finding that has also been identified elsewhere[46], highlighting the need to develop and test fatigue-management strategies in high quality trials. There is a need to apply learning across long-term conditions, for example, to examine whether interventions that have been found to benefit one long-term condition could also benefit others. This would likely be facilitated by gaining a better understanding of the mechanisms of fatigue in different long-term conditions and any similarities and differences between conditions[83,84], which may also help to inform consideration of whether guidelines on fatigue management need to be disease-specific or could be developed across conditions or categories of conditions.

Strengths and limitations

Limitations of the review include that, owing to limited resources, the review included only guidelines published in English. Although we searched five bibliographic databases and six guideline repositories, limited resources also meant that there are other repositories that we did not search; our searches will therefore not have identified all guidelines for all long-term physical health conditions. In common with other mapping reviews[29], this study does not include a quality appraisal and therefore is not able to comment on the relative quality of individual guidelines.

Review strengths are that searches were conducted in both bibliographic databases and clinical guidelines repositories. Screening and a proportion of data extraction were conducted by two independent reviewers. This review identified a large number of guidelines across a wide range of long-term conditions; given the consistency of the findings across long-term conditions, with few that incorporate recommendations for fatigue, unidentified studies are unlikely to threaten the review's conclusion that this is a neglected area within clinical guidelines.

Conclusions

Despite fatigue being a debilitating symptom for many people with a range of long-term conditions and a common reason for seeking help, clinicians have very little guidance about how best to help people suffering with fatigue.

There is need for greater prioritisation of fatigue research so that practice recommendations can be improved to inform clinicians about better management of a symptom that is very difficult for patients.

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Declaration of interests:

No known conflict of interest.

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Appendices

Appendix A

The following search strategy was used to identify eligible papers:

1. Guideline* or guidance in Title
2. MeSH DESCRIPTOR Fatigue Explode all
3. MeSH DESCRIPTOR long-term conditions Explode all
4. MeSH DESCRIPTOR chronic disease Explode all
5. MeSH DESCRIPTOR chronic illness Explode all
6. Multiple sclerosis
7. Parkinson’s
8. Stroke
9. Polio
10. Epilepsy
11. Rheumatoid arthritis
12. Osteoarthritis
13. Charcot-Marie tooth
14. Systemic lupus erythema
15. Lupus
16. COPD
17. Asthma

18. Heart failure

19. Inflammatory bowel disease

20. Diabetes

21. Thyroid

22. Sickle cell

23. HIV

24. Hepatitis B

25. Hepatitis C

26. Kidney disease

27. Liver disease

28. #1 and #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

Tables

Table 1. Guidelines containing recommendations for managing fatigue

	Condition	Guideline organisation, date and title	Summary of recommendations contained in the guidelines	Level of evidence on which guidance reported to be based and strength of recommendation
			N.B. this information has been condensed and does not provide the full information in the guideline, for which it is necessary to access the source documents.	
	Cardiovascular Conditions			
1.	Chronic Rheumatic Heart Disease	RHDAustralia (ARF/RHD writing group), 2020. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd edition)[49]	• Clinical ○ Worsening fatigue in a pregnant or post-partum woman at higher risk of or diagnosed with RHD should be investigated with an echocardiogram.	GRADE 1C - Strong recommendation but some evidence base of low quality

2.	Heart Failure	Canadian Cardiovascular Society, 2017. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure[50]	Managing options for fatigue as symptom of advanced HF
			• Clinical
			  ○ Consider depression, sleep disordered breathing, or other comorbidities
			• Pharmacological management
			  ○ Optimized CCS HF guideline therapy
			• Behavioural
			  ○ Rehabilitation/physical activity
				Guidance given as 'Practical tips'

3.	Heart Failure	2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[85]	• Clinical ○ Provide palliative and supportive care which can partially remediate symptoms including fatigue	Recommendation 1 [Strong]; Level of Evidence C - Limited Data

4.	Heart Failure	Dutch Royal Society for Physiotherapy 2014. Exercise-based cardiac rehabilitation in patients with chronic heart failure: A Dutch practice guideline [51]	Generic (reducing fatigue is given as a goal of rehabilitation):
			• Behavioural
			  ○ Aerobic endurance or interval training for people in NYHA Classes II-III
			  ○ High-intensity interval training (HIIT) for those in low risk
			  ▪ But caution re HIIT in those with high risk of cardiac overload
			  ○ Strength training for stable CHF
			  ▪ But caution re strength training in those with LVEF<35%
			  ○ Inspiratory muscle training
			  ○ Continuation of physically active lifestyle
			• Psychological
			  ○ Relaxation therapy
				
				Level 1* (Systematic review or at least two independent randomised, double-blind, comparative clinical trial of good quality and sufficient sample size)
				Level 2 (one randomised, double-blind, comparative clinical trial of good quality and sufficient sample size or at least two independent comparative studies)
				Level 4 (expert opinion)
				
				Level 1
				
				Level 4
				Level 2
				Levels 1-2
				
				Levels 2 & 3 (3 - one comparative or non-comparative study)

			Fatigue specific: • Behavioural ○ Severe fatigue would be a sign of excessive strain in which case it is recommended that exercise should be discontinued or intensity decreased • Information ○ Information and advice to promote effective ways of dealing with symptoms, including fatigue (but detail is not included on what the information and advice should be)	Evidence relating to fatigue-specific recommendations not reported.
5.	Heart failure	European Society of Cardiology, 2021. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC[62]	• Pharmacological ○ In treatment of amyloidosis and HF, avoid calcium channel blockers, which may cause fatigue	Unclear
6.	Heart Failure	Scottish Intercollegiate Guidelines Network 2016. Management of chronic heart failure SIGN 147[63]	• Pharmacological ○ In patients taking beta blockers, review/ adjustment of medication if symptoms worsen (tiredness, fatigue, breathlessness)	Recommendation re fatigue given as practical guidance for use of beta blockers
	Diabetes and other Endocrinal, Nutritional and Metabolic Conditions			

7.	Diabetes	International Diabetes Federation and DAR International Alliance, 2021. Diabetes and Ramadan: Practical Guidelines[73]	• Behavioural ○ Break the fast if symptoms of hyperglycaemia (which include fatigue) occur	Unclear re fatigue recommendation
8.	Type 2 Diabetes	Colombian Ministry of Health and Social Welfare 2016. Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults[64]	• Pharmacological ○ Less intensive treatment recommended (target HbA1c between 7% and 8%) for patients >65 years who exhibit fragility, defined as significant fatigue and severe restrictions on mobility or strength, who are at greater risk of falls and institutionalization	GRADE [86]: Weak recommendation in favour, based on expert consensus
9.	Haemochromatosis	American Association for the Study of Liver Diseases 2011. Diagnosis and management of hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases [52]	• Clinical ○ Likely to be ameliorated by phlebotomy	GRADE: Strong recommendation for phlebotomy (not fatigue specific) based on high quality evidence “further research is unlikely to change confidence in the estimate of the clinical effect”
10.	Adrenal Insufficiency	The Endocrine Society 2016. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society clinical practice guideline [53]	• Clinical ○ In patients with Primary AI who are pregnant, monitor at least once per trimester for clinical symptoms and signs of glucocorticoid over- and under-replacement, including fatigue.	GRADE [86]: Ungraded best practice statement
	Digestive Tract Conditions			

11.	Inflammatory Bowel Disease	British Society of Gastroenterology, 2019. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults [39]	• Clinical/Pharmacological ○ Ask about symptoms of fatigue ○ Investigate for subclinical disease activity ○ Consider potentially modifiable factors (sleep pattern, medication side effects, anaemia, iron deficiency, electrolyte disturbance, thyroid dysfunction, vitamin D and B12 deficiency, psychological symptoms) ○ Those with disabling fatigue in whom no correctable metabolic deficiency or active disease is found, or where fatigue persists despite addressing these factors, may be directed to non-pharmacological therapies (see Behavioural/Psychological below) • Behavioural ○ Graded exercise • Psychological ○ Supportive psychotherapy, stress management	GRADE Good Practice Recommendations GRADE weak recommendation based on low-quality evidence GRADE weak recommendation based on low-quality evidence
	<u>Gynaecological conditions</u>			
12.	Polycystic Ovary Syndrome	Centre for Research Excellence in Polycystic Ovary Syndrome, European Society of Human Reproduction and Embryology and American Society	• Clinical ○ If women with polycystic ovary syndrome have symptoms of obstructive sleep apnoea and a positive screen, consider referral to specialist centre for further evaluation	Clinical practice point

		of Reproductive Medicine, 2018. International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018[54]		
	Infections			
13.	HIV	British Columbia Centre for Excellence in HIV/AIDS, 2021. Primary care guidelines for the management of HIV/AIDS in adults in British Columbia [55]	• Clinical / Pharmacological ○ Assess morning serum total testosterone level in HIV-positive cisgender men presenting with fatigue as symptom of hypogonadism ○ Testosterone replacement indicated only for symptomatic cisgender men with total testosterone levels <10 mmol/L	Adapted from Strength of Recommendation Taxonomy [87]: B – Moderate quality evidence D – Very low quality evidence
14.	HIV	British HIV Association, 2021. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018 (2021 interim update).[65]	• Pharmacological ○ Patients (particularly those aged >65 years) who experience symptoms of hepatotoxicity (which can include fatigue) from treatment of latent TB infection, should contact their healthcare providers, and if there is a delay in doing so, immediately stop treatment.	Unclear

15.	HIV	National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America 2023. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV [66]	• Pharmacological ○ If criteria for anti-TB drug-induced liver injury are fulfilled (symptoms of which may include fatigue), potentially hepatotoxic drugs should be stopped and patient evaluated ○ Intralesional interferon is not recommended for first line treatment because of potential for adverse effects, which include fatigue	Strong recommendation based on expert opinion Weak recommendation based on expert opinion
16.	HIV	European AIDS Clinical Society 2020. European AIDS Clinical Society Guidelines Version 10.1 [56]	• Clinical ○ In people living with HIV who are frail, screen for, and address modifiable causes of fatigue (reference given to frailty clinical guidelines). ○ If fatigue present as symptom of hypogonadism, refer to endocrinologist / andrologist / gynaecologist	Not reported "All recommendations are evidence-based whenever possible and based on expert opinions in the rare instances where adequate evidence is unavailable. The Guidelines do not provide formal grades of evidence"
17.	Post-polio syndrome	European Federation of Neurological Societies 2011. Post-Polio syndrome [67]	• Pharmacological ○ No definitive therapeutic effect for pyridostigmine, prednisolone, amantadine, modafinil • Behavioural ○ Supervised muscular training, both isokinetic and isometric	EFNS scheme for guidelines [88] Pharmacological – IA (established as not useful based on adequate RCTs/systematic review) Supervised training –IIB and IIIB (established as probably useful based on cohort study,

			• Periods of rest between series of exercises • Environmental ○ Training in a warm climate	suboptimal RCT, other controlled trial) Rest – not reported Environmental – IB (established as probably useful based on adequate RCT/systematic review)
	Liver Conditions			

18.	Cholestatic Liver Diseases	European Association for the Study of the Liver 2009. EASL clinical practice guidelines: Management of cholestatic liver diseases [40]	• Clinical
			  ○ Exclude associated disease or medication use characterised by fatigue
			  ○ Liver transplantation is not appropriate for treatment of fatigue in the absence of other indications
			• Pharmacological
			  ○ Consider minimising factors likely to exacerbate autonomic dysfunction such as excessive anti-hypertensive medication
			• Behavioural
			  ○ Consider minimising factors likely to exacerbate sleep disturbance such as caffeine in evenings
				Adapted from GRADE [86]:
				Weak recommendation based on expert opinion
				Strong recommendation based on expert opinion
				Weak recommendation based on expert opinion
				Weak recommendation based on expert opinion

			• Psychological ○ Consider psychological support to assist with development of coping strategies	Weak recommendation based on low quality evidence
	Musculoskeletal Conditions			

19.	Fibromyalgia	European League Against Rheumatism 2017. EULAR revised recommendations for the management of fibromyalgia [41]	• Pharmacological ○ Amitriptyline (at low dose) ○ Pregabalin ○ Monoamine oxidase inhibitors ○ Duloxetine and milnacipran ○ Selective serotonin reuptake inhibitor ○ Sodium oxybate • Behavioural ○ Meditative movement therapies (qigong, yoga, tai chi) • Psychological ○ Biofeedback • Multicomponent ○ Combined behavioural/psychological with exercise	Based on systematic reviews (with or without meta-analysis): Weak recommendation for Weak recommendation for Weak recommendation against Weak recommendation for Weak recommendation against Strong recommendation against Weak recommendation for Weak recommendation against Weak recommendation for
			• Complementary ○ Acupuncture ○ S-Adenosyl methionine	Weak recommendation for Weak recommendation against
20.	Rheumatoid Arthritis	Royal Dutch Society for Physical Therapy, 2018. KNGF guideline Rheumatoid arthritis[71]	• Behavioural ○ Provide information about the importance of exercise and a healthy lifestyle ○ Supervise and encourage the patient during exercise if there are RA-specific barriers such as fatigue ○ Any form of exercise therapy, unsupervised at least 50% of the time	Based on literature review but otherwise unclear Based on literature review but otherwise unclear Implementation deemed acceptable and feasible,

			○ Any form of fully supervised exercise therapy	although estimated effects uncertain, based on low quality evidence Effectiveness and quality of evidence re fatigue could not be determined
			○ Any form of fully supervised exercise therapy for patients with serious disease progression	Implementation deemed acceptable and feasible, although no estimated effects available
			○ Frequency of exercise therapy	Unknown – no studies
			○ Intensity of exercise therapy	Unknown – no studies
			○ Type of exercise therapy	Unknown – no studies
			○ Duration of exercise therapy	Unknown – no studies
			○ Hand exercises	Unknown – no studies
			○ Exercise therapy on land versus in water	Unknown – no studies

21.	Sjogren's Syndrome	Sjögren's Syndrome Foundation 2017. Treatment Guidelines for Rheumatologic Manifestations of Sjögren's Syndrome: Use of Biologic Agents, Management of Fatigue, and Inflammatory Musculoskeletal Pain [42]	• Pharmacological ○ Dehydroepiandrosterone is not recommended ○ Hydroxychloroquine may be considered in selected situations ○ Neither etanercept nor infliximab is recommended • Behavioural ○ Education about self-care measures should include advice about exercise	Modified GRADE [86]: Strong recommendation against, based on two well-designed RCTs. Weak recommendation for, based on experience in patients with systemic lupus, one uncontrolled, retrospective study and one RCT in Sjögren's Syndrome. Strong recommendation against, based on insufficient data and experience Strong recommendation for based on one small RCT plus evidence from other musculoskeletal conditions
22.	Systemic Lupus Erythematosus	British Society for Rheumatology 2018. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults[57]	• Clinical ○ Complications of lupus, including chronic fatigue, should be managed according to national and international guidelines • Pharmacological ○ For patients with normal renal and liver function, hydroxychloroquine, can be used up to 6.5 mg/kg/day	Not reported SIGN[89] A1++ At least one high-quality meta-analysis

	Neurological Conditions			
23.	Multiple Sclerosis	National Institute for Health and Care Excellence (NICE) Multiple sclerosis in adults: management 2022 ng220 [68]	• Clinical ○ Assess fatigue, including potential causes other than MS ○	Informal consensus
			• Pharmacological ○ Consider: ▪ Amantadine ▪ Modafinil ▪ Selective serotonin reuptake inhibitor ○ Do not use vitamin B12 injections ○ Do not offer hyperbaric oxygen	Amantadine – very low quality evidence Modafinil - consensus based on clinical experience and low quality evidence SSRI – very low quality evidence Vit B12 – no evidence for use Hyperbaric oxygen – lack of evidence, clinical experience and high cost
			• Information • Explain potential precipitants of fatigue in MS	Clinical experience
			• Behavioural ○ Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise ○ Consider vestibular rehabilitation	Mostly low or very low quality evidence

			○ Advise that aerobic, balance and stretching exercises including yoga may be helpful ○ Encourage to keep exercising after treatment programmes end ○ Help continue to exercise, e.g. referral to exercise referral schemes ○ Offer treatment based on person preference and ability to continue the activity after end of treatment programme	
			• Nutritional ○ Explain there is no evidence for specific diet to help fatigue but follow healthy diet for general health	Lack of available evidence on specific diets
			• Multicomponent ○ Consider a combination of supervised aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with moderately impaired mobility ○ Offer discussion about self-management that could include goals, energy conservation, lifestyle factors, use of stress management approaches such as mindfulness and cognitive behavioural techniques	Evidence ranged from very low to high quality Self-mgt discussion – insufficient evidence to recommend formal programmes but recommendation based on clinical experience
24.	Neurological diseases -	European Society for Clinical Nutrition and Metabolism 2017.	• Clinical	

	amyotrophic lateral sclerosis (ALS), Parkinson's disease, stroke and multiple sclerosis (MS)	ESPEN guideline clinical nutrition in neurology [58]	○ Early detection and treatment of problems that could lead to malnutrition in MS as it can compound fatigue • Behavioural ○ In people with ALS with muscular fatigue and long-lasting meals, advise to fractionate meals • Nutritional ○ Consider oral nutrition supplementation for prevention of malnutrition in MS ○ In people with ALS with muscular fatigue and long-lasting meals, advise to enrich meals and recommend nutritional supplementation if weight loss progresses No fatigue-specific recommendations for Parkinson's disease or stroke	Good Practice Point - Strong consensus Good Practice Point - Strong consensus Strong consensus based on Grade B evidence - a body of evidence including high quality systematic reviews of cohort or case-control studies or well conducted cohort or case-control studies Good Practice Point - Strong consensus
25.	Stroke	Heart and Stroke Foundation 2019. Canadian stroke best practice recommendations: Mood, cognition and fatigue following stroke [44]	• Clinical ○ Care should be by health professionals knowledgeable in fatigue and its management ○ Periodically screen for post-stroke fatigue ○ In those with post-stroke fatigue, screen for co-morbidities and medications associated with fatigue	Level C - consensus and/or supported by limited research evidence Level C Level B - Evidence from single RCT or consistent findings from ≥2 well-designed non-randomized and/or non-controlled trials, and large observational studies

			• Pharmacological
			  ○ Some limited evidence that modafinil may be considered
			  ○ Insufficient evidence to recommend antidepressant treatment for post-stroke fatigue
			• Information
			  ○ Provide basic information about potential experience of post-stroke fatigue
			• Psychological
			  ○ Cognitive behavioural therapy may be considered
			  ○ Mindfulness-based stress reduction may be considered
			  ○ Encourage patients to communicate energy status and rest needs to others
			• Behavioural
			  ○ Counselling on graduated exercise schedules is recommended
			  ○ Counselling on energy conservation strategies is recommended
			  ○ Counselling on sleep hygiene is recommended
			  ○ Provide education on pacing activity and rest
				Level C
				Level B
				Level C
				Level B
				Level B
				Level C
				Level C
				Level C
				Level B
				Level C

26.	Stroke		• Clinical	

		Intercollegiate Stroke Working Party; 2023 National clinical guideline for stroke for the UK and Ireland [45]	○ Assess and review for factors that may precipitate/exacerbate fatigue (e.g. depression, anxiety, sleep disorders, pain) ○ Consider the impact of post-stroke fatigue and tailor scheduling and length of assessment and rehabilitation accordingly, and provide access to alternative solutions where necessary	Based on a combination of systematic reviews, primary studies, best practice guidelines and expert consensus
			• Pharmacological ○ Fluoxetine should not be used to prevent post-stroke fatigue	Clear evidence from high quality systematic reviews and RCTs
			○ Modafinil should only be provided in the context of a clinical trial	One small high-quality RCT
			• Information/education ○ Provide information and education on how to prevent and manage fatigue and sources of support	Based on a combination of systematic reviews, primary studies, best practice guidelines and expert consensus
			• Behavioural - Consider for the following approaches: ○ using a diary to record activities and fatigue ○ Pacing and prioritising activities ○ Rest ○ Setting small goals ○ Changing diet and/or exercise (tailored to individual)	As above

			• Psychological - Consider for the following approaches: ○ building acceptance and adjustment ○ relaxation and meditation ○ coping methods	As above
			• Complementary ○ Acupuncture should only be provided in the context of a clinical trial	Systematic review but included studies were small with risk of bias
27.	Stroke	Stroke Foundation (2023). Clinical Guidelines for Stroke Management [69]	• Clinical ○ Schedule therapy sessions when patient most alert ○ Consider potential modifying factors for fatigue e.g. avoiding sedating drugs and alcohol, sleep-related sleep disorders, depression • Information/education ○ Provide information and education about fatigue and potential management strategies (details of strategies not provided). • Behavioural ○ Possible interventions could include exercise, improving sleep hygiene • Psychological ○ Possible interventions could include cognitive behavioural therapy	Consensus Consensus Consensus Consensus but insufficient evidence to guide practice Consensus but insufficient evidence to guide practice
	Respiratory Conditions			

28.	Chronic Obstructive Pulmonary Disease	Global Initiative for Chronic Obstructive Lung Disease 2023. Global Strategy for the Prevention, Diagnosis and Management of Chronic Obstructive Pulmonary Disease 2023 Report [70]	• Behavioural
			  ○ Pulmonary rehabilitation
			  ○ Self-management education
			• Nutritional
			  ○ Nutritional support
			• Psychological
			  ○ Mind-body interventions
				For all - Evidence Level B (RCTs with important limitations or limited body of evidence)

29.	Chronic Obstructive Pulmonary Disease	Lung Foundation Australia, 2022. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2022[61]	• Clinical ○ Given the negative impact of exacerbations on symptoms such as fatigue, decide whether performing airway clearance techniques is appropriate, and if so, choose the most appropriate technique during exacerbations. Choice of techniques should be guided by a physiotherapist	Level of evidence not specified
			• Behavioural ○ Non-pharmacological strategies (such as pulmonary rehabilitation and regular exercise) should be provided to all patients	Strong recommendation based on Level I evidence obtained from a systematic review of all relevant randomised controlled trials.
30.	Hoarseness	American Academy of Otolaryngology—Head and Neck Surgery Foundation, 2018. Clinical Practice Guideline: Hoarseness (Dysphonia) (Update)[72]	• Behavioural ○ Rest your voice briefly to prevent voice fatigue, straining, and overuse	Recommendation of high confidence based on Grade C evidence - observational studies, small-sample RCTs, expert opinion, and a

				preponderance of benefit over harm

Figures

Figure 1. PRISMA flow diagram

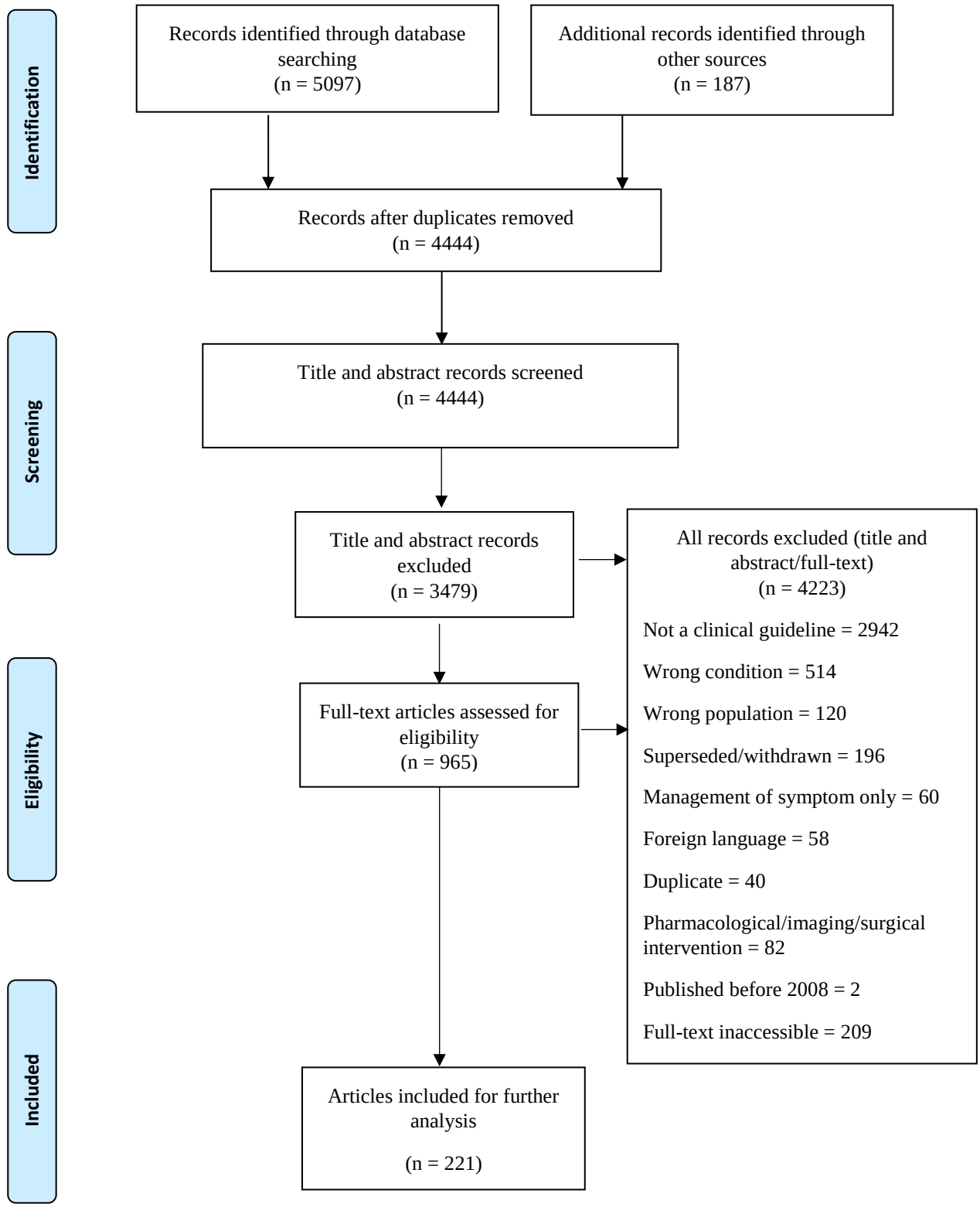

Figure 1. PRISMA flow diagram

Figure 2. Number of guidelines identified by condition, with and without recommendations for managing fatigue