

# The role of non-pharmacological interventions in the management of rheumatoid-arthritis-related fatigue

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## Abstract

Non-pharmacological interventions may be beneficial in the management of rheumatoid arthritis related fatigue. A narrative review was undertaken, with a focus upon research published in the past 6 years. Seven studies were identified, four focusing upon physical activity, two on psychosocial interventions and one that investigated aromatherapy and reflexology. Findings supported previous evidence that physical activity and psychosocial interventions have potential to produce small to moderate reductions in fatigue related to rheumatoid arthritis. Reflexology and aromatherapy interventions also appeared promising. Limitations to the evidence included lack of consistency in fatigue measurement, and minimal data on long-term outcomes and cost effectiveness. The wide range of physical activity interventions prevent specific recommendations. For psychosocial interventions the strongest evidence is for group-based cognitive behavioural approaches. There was lack of consideration given to fatigue mechanisms and intervention design. Due to the complexity of fatigue, future research exploring personalized approaches is warranted.

**Key words:** fatigue, rheumatoid arthritis, physical activity, psychosocial, non-pharmacological

### Rheumatology key messages

- Fatigue related to rheumatoid arthritis may be improved through physical activity and psychological interventions.
- Cognitive behavioural therapy approaches have small to moderate effects on fatigue related to rheumatoid arthritis.
- Research is needed to explore cost-effectiveness and personalized approaches to fatigue management in rheumatoid arthritis.

## Introduction

Fatigue is an important and common issue for people with RA and was identified in research literature over 15 years ago [1]. Despite this, a large number of patients still receive inadequate support. In a survey investigating the impact of fatigue in RA, 51% of respondents ( $n=2029$ ) never or rarely spoke to their general practitioner about fatigue, and 47% never or rarely spoke to their rheumatology healthcare professional. Further to this, the majority of participants (79%) reported that their healthcare professional never measured their level of fatigue [2]. The subjective experience of fatigue can cause distress and

disruption to the daily lives of those with RA and influence their everyday activities and approaches to living [3–5].

People with RA have described fatigue as ‘extreme and persistent tiredness, weakness or exhaustion – mental, physical or both’ [6]. Qualitative exploration of RA fatigue has shown that it is often a frustrating and overwhelming experience that can be frequent, unpredictable and unresolving, and often as severe, or more severe, than pain [3, 4]. To date, however, there is no consensus regarding a definition of RA fatigue. The lack of an agreed definition and the wide range of outcome measures used to determine the presence of RA fatigue have prevented accurate reporting of prevalence, with rates of severe, clinically relevant fatigue varying from 42% to over 80% [7–11].

RA fatigue appears to be a complex and multi-factorial phenomenon and while a conceptual model has been proposed [12], the precise mechanisms and causality remain unclear [13]. Predictors of fatigue in RA are reported to include inflammation (direct and indirect); cognitive behavioural elements (illness beliefs and stress, anxiety

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and depression, under- or overactivity); and personal factors (work, comorbidities, environment, support networks) [14]. The evidence to support these predictors of RA fatigue is, however, equivocal [13] with the presence of comorbidities potentially exacerbating the fatigue experience [15] and further adding to its complexity.

Optimal pharmacological management of RA, with disease modifying anti-rheumatic drugs and biologic therapies, appears to provide only small benefits for fatigue [16, 17]. These benefits may occur indirectly through reduction of inflammation and/or pain [17]. Without amelioration of the cognitive behavioural and personal factors contributing to RA fatigue, even optimal drug management is unlikely to provide large benefit [16]. To address the potentially complex and multifactorial nature of RA fatigue, it is likely best managed as a symptom in its own right using a multidimensional approach that incorporates pharmacological and non-pharmacological approaches [18].

Non-pharmacological interventions may alter the potential causal pathways of RA fatigue [12]. Psychosocial interventions, such as self-management programmes, cognitive-behavioural approaches and lifestyle interventions, or interventions based on physical activity have all been proposed as potentially beneficial [12, 19]. A Cochrane review published in 2013 [19] evaluated the benefits and harm of non-pharmacological interventions for the management of fatigue in people with RA. Inclusion criteria for the review were relatively broad with any randomized controlled trial included as long as it evaluated a non-pharmacological intervention in people with RA where fatigue was included as an outcome. The main stipulation was that fatigue had to be self-reported (subjective) either as a primary or as a secondary outcome. The majority of the 24 included studies investigated physical activity interventions ( $n = 6$ ) or psychosocial interventions ( $n = 13$ ) with meta-analyses demonstrating statistically significant small beneficial effects upon fatigue for both intervention categories. Adverse events were not well reported in the studies, preventing an accurate assessment of potential for harm. In terms of quality, the physical activity evidence was considered to be moderate and the studies investigating psychosocial interventions were considered low quality.

There were a number of limitations of the Cochrane review. Firstly, due to the broad inclusion of fatigue as a primary or secondary outcome the main purpose of the interventions being investigated was rarely management of fatigue. Interventions were therefore not designed specifically to reduce fatigue severity or impact with little or no consideration given to underlying fatigue mechanisms. Only one of the included studies identified fatigue as the primary outcome; another reported fatigue impact as the primary outcome; and a third study included tiredness as one of three primary outcomes. Further to this, the presence of fatigue was not an inclusion criterion for 23/24 of the studies, which is likely to have limited the potential for improvement and resulted in smaller effect sizes. Limiting the review inclusion criteria, however, would potentially

have resulted in an empty and uninformative review. A further limitation of the review was the broad categorization of interventions as physical activity or psychosocial, preventing the identification of optimal parameters and components.

The Cochrane review did, however, indicate that both physical activity and psychosocial interventions have potential for benefit in the management of fatigue in people with RA [19]. Recommendations included the need to design interventions specifically for fatigue management in people with RA. High quality cost effectiveness trials of these interventions with fatigue as the primary outcome were also suggested. Linked to this, the need for a self-reported measure of fatigue validated specifically for people with RA was highlighted and since this time a new outcome measure has been developed [20]. Further systematic reviews, published in 2015 and 2018, investigated the effects of land-based aerobic training upon RA fatigue and reported similar findings and limitations [21, 22].

## Methods

It is now over 6 years since the literature search was carried out to inform the Cochrane review and sufficient time has passed to allow for the publication of a significant body of new evidence. While similar reviews have been undertaken since publication of the Cochrane review they have had a much narrower focus [21, 22]. A narrative review was therefore undertaken to identify key recent research and explore whether the limitations in the evidence base remain. The keyword search employed for the Cochrane review was therefore repeated in February 2019, using the same electronic databases (see [19] for details) and a historical cut-off date of October 2012.

## Findings

The search revealed eight new studies investigating the effect of a non-pharmacological intervention upon fatigue in adults with RA. One of the eight studies was identified as a feasibility study [22] with the full study subsequently reported as a separate publication [23]. There were therefore only seven full trials considered for reporting, with four of these broadly categorized as physical activity [23–26], two as psychosocial [27, 28], and the final study investigating an aromatherapy intervention and a reflexology intervention [29]. These seven studies are summarized in Table 1.

It was promising to note that six of the studies identified fatigue as the primary or joint primary outcome, indicating a focus upon this symptom, with only one study including fatigue as a secondary outcome [23]. It was also reassuring that four of the seven studies screened out participants that were not experiencing significant fatigue [24, 27, 29], with a fifth study identifying 'elevated distress' as an essential inclusion criterion [28]. In relation to the measures used to assess fatigue, there remains a lack of consistency across studies, with the Fatigue Severity Scale [26, 29], visual analogue scale [23, 25], numerical rating scale [27], patient-reported outcome measurement

**TABLE 1** Summary of recent studies investigating non-pharmacological intervention for the management of RA-related fatigue

Study ID	Aim	RA participants	Intervention	Control arm	Fatigue outcomes	Adverse events
Thomsen <i>et al.</i> 2017 [23]	Efficacy of individually tailored behavioural intervention for reducing sitting time, pain and fatigue and improving quality of life, general self-efficacy, physical function and cardio-metabolic biomarkers	Mean (s.d.) age: 59.3 (12.5) years. Control: 80% women. Intervention: 81% women. Primary analysis based upon $n=74$ intervention and $n=73$ control participants	Three individual motivational counselling sessions from health professionals and individual text messages aiming to increase light intensity physical activity by reducing sedentary behaviour	Instructed to maintain usual lifestyle	Secondary outcome. Visual analogue scale for fatigue and all Multi-dimensional Fatigue Inventory subscales significantly improved at 16 weeks in intervention compared to control arm	Not reported
Katz <i>et al.</i> 2018 [24]	Effect of individualized step-count goals plus a pedometer and step monitoring diary on physical activity and fatigue	Baseline mean (s.d.) age: 54.8 (13.4) years; 88% female; presence of greater than minimal fatigue; $n=96$ recruited, $n=88$ completed week 21 outcomes	Pedometer only: education booklet, pedometer and daily step diary Pedometer +: as per Pedometer only plus individual daily step targets	Education brochure and guided discussion on increasing physical activity in daily life	Joint primary outcome. Patient-reported outcome measurement information system Fatigue Short Form. Both intervention arms significantly improved over time with greater improvements in the Pedometer + arm. No significant group by time effect	One minor event: calf muscle strain that did not prevent study completion
Durcan <i>et al.</i> 2014 [26]	To evaluate the effect of an exercise programme on self-reported sleep quality and fatigue	Adults with RA. $n=40$ intervention [mean (s.d.) age 61 (8) years], $n=38$ control [mean (s.d.) age 59 (12) years]	Twelve week home exercise programme including 30–60 min resistance exercises 3×/week (40–50% one repetition max), daily range of movement exercises, light-moderate intensity walking 5×/week	Standard care plus advice on the benefits of exercise in RA	Joint primary outcome. Fatigue Severity Scale: significant between-group differences in change in fatigue at 12 weeks in favour of the intervention	Not reported
Feldhusen <i>et al.</i> 2016 [25]	To investigate the effects of person-centred physical therapy intervention focused upon health enhancing physical activity and balancing life activities on fatigue and fatigue-related variables	Adults with RA and fatigue >50 on a 0–100 visual analogue scale. Mean (s.d.) age 53.5 (9.7) years, 89% female. $n=70$ recruited; analysis based upon $n=35$ intervention, $n=31$ control	Twelve week intervention – goal was to devise a mutually agreed self-care plan to guide the individual in managing fatigue. Focused upon tailoring health-enhancing physical activity and balancing life activities. Included tailored follow-up meetings and phone calls	Usual care	Primary outcome: general fatigue over the previous week on a visual analogue scale. Compared with control the intervention arm had significantly reduced fatigue between baseline and week 12. Improvements were maintained at 6 months	Not reported
Fenwerda <i>et al.</i> 2017 [28]	Effects of an internet-based tailored cognitive-behavioural intervention for patients with RA with a psychological risk profile of elevated distress	Adults with RA and elevated levels of distress. $n=133$ consented ( $n=62$ intervention; $n=71$ control); 48 male, 85 female. Mean (s.d.) age 56.4 (10) years	Internet-based tailored cognitive-behavioural intervention plus standard care. Initial face to face meeting. All completed at least one of four modules (pain and functional disability, fatigue, negative mood, or social functioning). Weekly or bi-weekly emails from therapists. Duration 9–65 weeks	Standard care	Joint primary outcome. Checklist Individual Strength Fatigue scale. No significant difference between groups over time	Not reported
Hewlett <i>et al.</i> 2019 [27]	To see if usual care plus a group course delivered by rheumatology teams using cognitive behavioural approaches reduced RA fatigue impact more than usual care alone	Adults with RA and fatigue severity $\geq 6/10$ on a numerical rating scale. $n=333$ randomized, $n=152/138$ control and $n=156/175$ included at the primary end point; 246/308 female. Age: intervention, median (IQR) 63.7 (54.2–69.9) years; control, median (IQR) 61.8 (54.4–69.6) years	Reducing Arthritis Fatigue: group course using cognitive behavioural approaches delivered by rheumatology nurses or occupational therapists; 2 h per week for 6 weeks then 1 h consolidation at week 14	Usual care, fatigue self-management booklet	Primary outcome, at 26 weeks, Bristol RA Fatigue (BRAF), fatigue impact numerical rating scale. Significant fatigue reduction in intervention arm compared to control at 26 weeks ( $P = 0.03$ ). Effect size 0.36	Not reported
Gök Metin and Özdemir 2016 [29]	Comparison of aromatherapy massage, reflexology and no intervention on pain and fatigue	Presence of pain and fatigue. Mean (s.d.) age 54.4 (1.2) years (range 21–89 years); 88.2% female; 51/54 included in the analysis ( $n=17/arm$ )	Aromatherapy massage: 30 min, 3×/week for 6 weeks. Reflexology: 40 min, 1×/week for 6 weeks	Usual care, no sham	Joint primary outcome with pain. Fatigue severity score completed at baseline then weekly. Fatigue decreased significantly in both intervention arms over time compared with control arm with reflexology showing the greatest effect	Not reported

information system Fatigue Short Form [24], multidimensional fatigue inventory [23] and Checklist Individual Strength [28] all being used. Although fatigue was identified as a primary outcome for most studies, it was not apparent that all the interventions had been designed specifically to target fatigue reduction.

In relation to the four studies that focused upon physical activity interventions, three had identified fatigue as a primary or joint primary outcome. The home exercise plan investigated by Durcan *et al.* [26] was individualized to target functional limitations that were identified from participant completion of the Health Assessment Questionnaire. There was, however, no reference to fatigue mechanisms in the design or implementation of the intervention at an individual level. The pedometer intervention, with or without step-targets, that was employed by Katz *et al.* [24] aimed to increase participant physical activity. The rationale provided for this approach was based upon their previous research suggesting that physical inactivity was a primary independent predictor of fatigue [30]. Feldthusen *et al.* [25] investigated a person-centred physical therapy intervention that focused on health-enhancing physical activity and balancing life activities. They suggested that this approach could strengthen confidence and resources to control fatigue as well as disease-related symptoms associated with fatigue.

Both psychosocial interventions that were investigated identified fatigue as a primary or joint primary outcome. The intervention described by Hewlett *et al.* [27] was explicitly linked to the management of RA fatigue with cognitive behavioural therapy (CBT) approaches employed to address 'behaviours likely to be related to fatigue and their underpinning thoughts and feelings'. In Ferwerda *et al.* [28] participants completed at least one of four internet-based intervention modules with fatigue being the focus of one module. As a result, not all participants completed the fatigue module and despite fatigue being identified as a joint primary outcome, the overall purpose of the intervention appeared to be reduction of distress. The authors did, however, summarize the content of the fatigue module, which included relevant cognitive and behavioural strategies.

The remaining study [29] investigated an aromatherapy intervention and a reflexology intervention with fatigue as a joint primary outcome. For aromatherapy, the oils were identified including their active ingredients and proposed physiological effects. While some of the proposed effects, such as anti-inflammatory and anti-depressant properties, might affect fatigue, this was not explicit from the information provided. In relation to reflexology, the specific points being stimulated were described, but how these were of relevance to fatigue was not explained.

In relation to the effect of the interventions, three of the four studies that investigated physical activity reported significant improvement in fatigue at the end of the intervention compared with a control arm [23, 25, 26]. Only one study investigated longer-term outcomes with the difference between the physical activity arm, consisting of tailored health enhancing physical activity and balancing life

activities, and the control arm, remaining significant at 6 months [25]. The final physical activity study reported a reduction in fatigue over time in the pedometer and pedometer plus step count arms, but this was not significantly different from the control arm [24]. It should be noted, however, that the target sample size was not reached, which could potentially explain the lack of a significant effect.

For the psychosocial interventions, Hewlett *et al.* [27] reported a significant reduction in fatigue impact at 6 months in the 'Reducing Arthritis Fatigue' intervention arm compared with the control arm. This difference remained significant at the 2-year follow-up time point. The intervention was delivered by trained nurses and occupational therapists and further to the findings from the Cochrane review [19], supports the use of CBT approaches for fatigue management in RA. In contrast, Ferwerda *et al.* [28] identified a non-significant reduction in fatigue over time for their internet-based cognitive behavioural intervention compared with the control arm. It should, however, be noted that only 37/62 participants in the intervention arm completed the internet-based fatigue module. Further to this, although fatigue was identified as one of several primary outcomes, the main purpose of the intervention was to reduce distress levels and hence the intervention did not solely focus upon fatigue.

Finally, Gok Metin and Ozdemir [29] identified significant reduction in fatigue over time for both intervention arms compared with the control arm with the reflexology arm demonstrating greater reduction than the aromatherapy arm. There were, however, some limitations to this study including a lack of assessor blinding, the absence of a long-term follow-up, and no active control arm. Further research is therefore necessary before consideration can be given to recommending aromatherapy or reflexology as an intervention for fatigue in adults with RA.

## Discussion

The findings from these seven studies provide further evidence that physical activity and psychosocial interventions provide small to moderate benefit in relation to self-reported fatigue in adults with RA. Further research is still, however, needed to investigate the effectiveness of psychosocial interventions other than those based upon CBT. Reporting of adverse events remains limited, with only one of the seven studies providing an explicit statement [24]. Future research would also benefit from a more consistent approach to assessment of fatigue. The Bristol RA Fatigue (BRAf) Multidimensional Questionnaire may be the most appropriate outcome as it was designed specifically to capture the multidimensional nature of RA-related fatigue [31]. In addition to the multidimensional questionnaire, there are three numerical rating scales that measure fatigue coping, severity and effect. The BRAf questionnaire and numerical rating scales are free to access, available in 37 languages [20] and have been shown to be valid, reliable and sensitive to change [32].

Implementation of the evidence in a clinical setting requires careful consideration to ensure that interventions

not only have the potential for benefit but are also acceptable to people with RA and feasible to deliver in practice. While the physical activity intervention delivered by Durcan *et al.* [26] showed a beneficial effect on fatigue post-intervention, there was no investigation of the long-term effect. Given the intensive nature of the intervention, it is likely that people with RA would struggle to adhere to the prescribed home exercise plan in the long term. This view is supported by findings from a systematic review and meta-analysis of land-based aerobic training, which demonstrated a small beneficial effect on RA fatigue at 12 weeks that did not remain significant at 24 weeks [21]. The authors suggested that the lack of sustained effect at 24 weeks was likely to be due to participants discontinuation of the activity following a supervised programme, most of which ended at 12 weeks. Adherence to therapies, including physical activity, has been recognized as a challenge in a wide range of long-term conditions [33]. People with RA are, however, less physically active than the general population with fatigue and physical limitations are frequently identified as barriers [34–37]. When asked about fatigue management in a national RA survey [2], 72% of respondents reported reducing activity levels in response to fatigue, suggesting that physical activity may be counter-intuitive for people already experiencing fatigue. This suggests that interventions need to be designed in collaboration with patients and effective methods to support long-term physical activity engagement established, particularly for those experiencing RA-related fatigue. It is possible that the intervention employed by Thomsen *et al.* [23] to reduce daily sitting time through motivational counselling and SMS reminders would be more acceptable to people experiencing RA-related fatigue than an intensive home exercise programme and as a result more likely to be sustained long term. Further research with long-term follow-up is, however, required to explore these suggestions.

The majority of the psychosocial interventions identified here and in the previous Cochrane review [19] were delivered by clinical psychologists. This creates barriers to delivery in clinical practice due to the limited number of rheumatology teams that include a clinical psychologist [38]. It is, however, promising to note that the motivational counselling in Thomsen *et al.* [23] to reduce sitting time and the cognitive behavioural therapy approach in Hewlett *et al.* [27] to support self-management of fatigue were delivered by rheumatology teams. For both of these studies the health professionals (nurses and occupational therapists) delivering the interventions received prior training from a clinical psychologist. While delivery by health professionals within rheumatology teams shows promise in relation to fatigue outcomes, further research is necessary to explore cost effectiveness. This is particularly important given that the psychosocial interventions that have demonstrated beneficial effects for fatigue have required a time commitment from health professionals and patients. For example, the group intervention delivered by Hewlett *et al.* [27] comprised seven sessions delivered over 14 weeks (total of 13 h contact time); and Thomsen

*et al.* [23] provided three individual counselling sessions with each one lasting up to 90 min (total 4 h 30 min), in addition to SMS reminders.

The findings to date reinforce the Cochrane review conclusions [19] that physical activity and psychosocial interventions have the potential to produce small to moderate benefit for RA-related fatigue. Several disease-specific mechanisms have been proposed to explain these beneficial effects. For example, high-intensity exercise has been shown to restore muscle mass and function in RA [39] with a result that less effort is required to carry out physical tasks. Further to this, regular participation in moderate to high-intensity exercise might improve self-efficacy, well-being and a sense of self-control for people with RA [40, 41]. Education programmes may help people to change behaviours that perpetuate RA fatigue or inhibit its self-management, such as through pacing and lifestyle management, as well as by addressing mood and coping strategies [12, 40]. Interventions that address thoughts and feelings around fatigue may encourage helpful coping strategies, such as emotional expression, reprimatization and work and life balance, and help patients reduce perceived stress and helplessness [19]. It is, however, possible that underpinning mechanisms of action are not only disease-specific, with individual patient-specific factors also being of importance. This suggestion is supported by findings of secondary analysis of data from a range of cross-sectional studies, which indicated that the type of chronic disease explained only 11% of the variance in fatigue severity [42]. The explained variance increased to 55% when factors associated with fatigue were added to the model (specifically, sex, age, motivational and concentration problems, pain, sleep disturbances, physical functioning, reduced activity, and lower self-efficacy concerning fatigue). This suggests that an individualized approach to management that targets the relevant fatigue-related factors may produce larger effects than tightly controlled disease-specific interventions that follow a set protocol. Due to the complexities of manualizing such a personalized approach to management, traditional randomized controlled trials may not be possible or even desirable. In the future, alternative methods of investigation should therefore be considered, such as realist evaluation in which the researcher seeks to identify 'What works for whom, in what circumstances and why?' [43]. Through these methods, it may be possible to identify the interventions that work best for people in different contexts and with differing experiences of fatigue.

While limitations remain in relation to the evidence to support the use of non-pharmacological interventions in the management of RA-related fatigue, it is clear that they have the potential to benefit. In relation to psychosocial interventions, there is evidence that CBT approaches delivered by clinical psychologists or trained rheumatology health professionals can reduce the short- and long-term impact of RA fatigue. Future research investigating the potential for individualized approaches to fatigue management is warranted as well as investigation of a wider range of psychosocial interventions.

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