

QUESTION

Should behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking) vs. no behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking) be used for all individuals who report fatigue with Friedreich ataxia?

POPULATION:	all individuals who report fatigue with Friedreich ataxia
INTERVENTION:	behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)
COMPARISON:	no behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)
MAIN OUTCOMES:	Reported fatigue; Improved quality of life; Improved energy levels; Improved physical capacity; Improved physical capacity; Improved capacity to participate in daily tasks; Reduced falls;

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Fatigue may be a rather frequent and often under recognized feature in individuals with FRDA (da Silva et al, 2013).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of fatigue. 4/7 indicated that the problem was serious, 3/7 indicated probably serious. 3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 2/7 indicated probably not urgent. 4/7 indicated that the problem was a priority, 3/7 indicated probably a priority. (Aug 2020)
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know		Trivial/small effect on fatigue per se however moderate effects on QoL and activity participation (surrogate marker of fatigue).

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)	Risk difference with behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)
Reported fatigue assessed with: Checklist Individual Strength	292 (4 RCTs) ^{1,2,3,4}	⊕○○○ Very low ^{a,b,c,d,e}	-	<p>91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).</p> <p>53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. There were no significant group differences for CIS-fatigue. (Veenhuizen</p>	

				<p>et al 2019) 86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the CIS20r fatigue subscale. (Blikman et al 2017).</p> <p>59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. MANOVA analyses showed significant time effects for CIS-20-fatigue ($p=0.004$). Effect sizes were moderate for CIS-20-fatigue (partial $\eta^2= 0.17$). One-way repeated-measures ANOVAs showed that there were no significant changes for the outcome measures during the waiting list period. After the intervention, 31% scored under the severely fatigued cut-off score of the CIS-20-fatigue (<35), as opposed to zero participants at inclusion of this study. Furthermore, despite still scoring above the cut-off after the intervention, 15% reached a clinically relevant decline of 8 points on the CIS-20-fatigue. Hence, in total 46% of the group that completed the intervention reached a clinically</p>	
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				relevant result. (Hoogerwerf et al 2017).
Reported fatigue assessed with: Epworth Sleepiness Scale	0 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).
Reported fatigue assessed with: Brief Illness Perception Questionnaire	91 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).

Reported fatigue assessed with: Borg score	255 (1 RCT) ⁵	 Low ^{e,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no between-group differences on the Borg score ($p=0.083$). (Okkersen et al 2018).
Reported fatigue assessed with: Fatigue and daytime sleepiness scale	255 (1 RCT) ⁵	 Low ^{e,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were significant between-group differences on the FDSS scale ($p=0.0002$). (Okkersen et al 2018).
Reported fatigue assessed with: Modified Fatigue Impact Scale	307 (3 RCTs) ^{3,6,7}	 Very low ^{a,c,d,h,i}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed

				<p>at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the MFIS (Blikman et al 2017).</p> <p>139 people with multiple sclerosis were randomised to an MS-specific online mindfulness meditation intervention (n=54) or to a psychoeducational control (n=67) group. Participants were assessed at recruitment, 2 months, and after 6 months. The effects of the mindfulness intervention on primary and secondary outcomes were analysed using an ANCOVA, with condition (mindfulness vs psychoeducation) as the between-subject factor and baseline values for each outcome as covariates. Fatigue score differences at post-intervention were borderline significant ($F(1,111) = 3.674, p = 0.058$) and nonsignificant at the follow-up ($F(1,95) = 0.251, p = 0.617$). (Cavalera et al 2019).</p> <p>82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. Participants in the intervention group reported lower total MFIS scores post-trial compared with controls ($p=0.07$), although this difference did not reach statistical significance. For MFIS subscales, the intervention was associated with significant improvements on the physical subscale</p>	
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				($p=0.008$), but not the cognitive or psychosocial subscale. (Pilutti et al 2014)
Reported fatigue assessed with: Fatigue Severity Scale	2677 (4 RCTs) ^{3,6,8,9}	⊕○○○ Very low ^{a,c,d,i,j}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the FSS (Blikman et al 2017). 40 patients with multiple sclerosis were randomised to an 8-week intervention of a specially adapted Skype distant-delivered mindfulness intervention (n=19), or a waiting list control group (n=21). Questionnaires were completed at baseline, post-intervention and 3-month follow up. Treatment effects on the outcomes were estimated using linear mixed modelling where the outcome variables at the two post-intervention time points were the dependent variable. Fatigue was reduced for the mindfulness group compared to the waiting-list group at both post-intervention and three-month follow-up. (Bogosian et al 2015). 82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. FSS scores

				<p>were significantly lower in the intervention group compared with controls post-trial ($p=0.001$). (Pilutti et al 2014)</p> <p>2469 patients with multiple sclerosis took part in an online survey answering questions relating to health related QOL and their involvement in meditation practices. Bivariate analyses were undertaken to explore the relationship between meditation and each variable. T-tests were used to analyse significant differences in continuous variables between those that did and did not meditate (dichotomous variable), using Levene's test for assessment of equal variance. Analysis of the categorical meditation data was undertaken using cross tabulation with categorical data and one way ANOVA for comparison with continuous data. There was no significant relationship between those who did and did not meditate and FSS scores. (Levin et al 2014)</p>
Reported fatigue assessed with: Fatigue Catastrophizing Scale	59 (1 observational study) ⁴	⊕○○○ Very low ^{a,d,e,k}	-	59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. MANOVA analyses showed significant time effects for the FCS ($p=0.003$). (Hoogerwerf et al 2017).
Improved quality of life assessed with: Myotonic Dystrophy	255 (1 RCT) ⁵	⊕⊕○○ Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months

Health Index total score				<p>Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no significant between-group differences noted in the myotonic dystrophy health index score at 10 months. (Okkersen et al 2018).</p>
Improved quality of life assessed with: Individualised neuromuscular quality of life	255 (1 RCT) ⁵	 Low ^{c,f,g}	-	<p>255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no between-group differences in the INQOL score ($p=0.196$). (Okkersen et al 2018).</p>
Improved quality of life assessed with: Medical Outcomes Study Short Form 36	148 (2 RCTs) ^{10,3}	 Low ^{a,d,i}	-	<p>86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group</p>

				<p>allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the SF-36. (Blikman et al 2017).</p> <p>62 adults with multiple sclerosis were randomised to mindfulness-based stress reduction (MBSR, n=33) group or an education control group (n=29). ANCOVA was performed to compare mean change in outcome measures from baseline to 8 weeks and baseline to 12 months between groups. While MBSR participants generally showed greater improvement in SF-36 compared to control, differences in scores between the groups were not statistically significant at either time point. (Senders et al 2019)</p>
<p>Improved quality of life assessed with: Multiple Sclerosis Impact Scale</p>	<p>122 (2 RCTs)^{6,8}</p>	<p>⊕⊕○○ Low^{a,c,i}</p>	<p>-</p>	<p>40 patients with multiple sclerosis were randomised to an 8-week intervention of a specially adapted Skype distant-delivered mindfulness intervention (n=19), or a waiting list control group (n=21). Questionnaires were completed at baseline, post-intervention and 3-month follow up. Treatment effects on the outcomes were estimated using linear mixed modelling where the outcome variables at the two post-intervention time points were the dependent variable. MSIS psychological and MSIS physical scores were reduced for the mindfulness group compared to the waiting-list group at both post-intervention and 3-month follow-up. (Bogosian et al 2015)</p> <p>82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or</p>

				Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. Lower physical HRQOL scores (i.e. superior HRQOL) were reported by participants in the intervention compared with controls post-trial ($p=0.06$), although this difference did not reach statistical significance. There was not a significant difference between groups on the psychological HRQOL scale post-trial. (Pilutti et al 2014)
Improved quality of life assessed with: Patient-Reported Outcomes Measurement Information System	62 (1 RCT) ¹⁰	⊕○○○ Very low ^{a,i,k}	-	62 adults with multiple sclerosis were randomised to mindfulness-based stress reduction (MBSR, n=33) group or an education control group (n=29). ANCOVA was performed to compare mean change in outcome measures from baseline to 8 weeks and baseline to 12 months between groups. While MBSR participants generally showed greater improvement in PROMIS compared to control, differences in scores between the groups were not statistically significant at either time point. (Senders et al 2019)
Improved quality of life assessed with: Multiple Sclerosis Quality of Life-54	2608 (2 RCTs) ^{7,9}	⊕○○○ Very low ^{a,h,i,j}	-	139 people with multiple sclerosis were randomised to an MS-specific online mindfulness meditation intervention (n=54) or to a psychoeducational control (n=67) group. Participants were assessed at recruitment, 2 months, and after 6 months. The effects of the mindfulness intervention on primary and secondary outcomes were analysed using an ANCOVA, with condition (mindfulness vs psychoeducation) as the between-subject factor and baseline values for each outcome as covariates. QOL, measured with the MSQOL-54, was significantly higher in the mindfulness group at the post-intervention assessment ($F(1,110) = 4.68, p = 0.033$), but no difference was found after 6

				<p>months. (Cavalera et al 2019).</p> <p>2469 patients with multiple sclerosis took part in an online survey answering questions relating to health related QOL and their involvement in meditation practices. Bivariate analyses were undertaken to explore the relationship between meditation and each variable. T-tests were used to analyse significant differences in continuous variables between those that did and did not meditate (dichotomous variable), using Levene's test for assessment of equal variance. Analysis of the categorical meditation data was undertaken using cross tabulation with categorical data and one way ANOVA for comparison with continuous data. Mental health composite (MHC) and physical health composite (PHC) scores were significantly higher in respondents who meditated compared to those who did not ($p = 0.001$ and <0.001, resp.). Similarly the overall quality of life, energy, health distress, emotional well-being, health perception, and cognitive function HRQOL scales were all significantly higher in those who meditated ($p < 0.001$). (Levin et al 2014)</p>	
	<p>Improved quality of life assessed with: Life Satisfaction Questionnaire</p>	<p>59 (1 observational study)⁴</p>	<p>⊕○○○ Very low^{a,d,e,k}</p>	<p>-</p> <p>59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. There were no significant time effects for LiSat-9. (Hoogerwerf et al 2017)</p>	

Improved energy levels - not measured	-	-	-	-	-
Improved physical capacity assessed with: SF-36 Physical Functioning Subscale	91 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).	
Improved physical capacity assessed with: 6 min walk test	308 (2 RCTs) ^{2,5}	⊕⊕○○ Low ^{b,c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. Differences at 10 months in favour of cognitive behavioural therapy were shown for total distance on the 6-min walk test (p=0.0000) (Ouberson et al	

				2018). 53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. Significant effects in favor of the intervention group were found on the 6MWT ($p=0.00092$) at 11 month follow up. (Veenhuizen et al 2019)
Improved capacity to participate in daily tasks assessed with: Dutch General Self-Efficacy Scale	91 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).
Improved capacity to participate in daily tasks assessed with: DM1-Activ-c scale	255 (1 RCT) ⁵	⊕⊕○○ Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening

				<p>followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. After 10 months, there was an adjusted mean increase in scores on the DM1-Activ-c scale of 1.53 points (95% CI – 0.14 to 3.20) in the cognitive behavioural therapy group compared with an adjusted mean decrease of – 2.02 points (–4.02 to –1.01) in the standard care group. In the predefined primary outcome analysis of DM1-Activ-c, there was a difference between groups of 3.27 points (95% CI 0.93 to 5.62, $p=0.007$) in favour of the intervention group at 10 months. (Okkersen et al 2018).</p>
Improved capacity to participate in daily tasks assessed with: Canadian Occupational Performance Measure	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	<p>53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. After the 4-month treatment period (T1), the intervention group showed significantly higher mean COPM performance scores compared to the control group ($p<0.0001$). This effect was still significant at 11 months ($p=0.049$) follow-up and after correction for possible confounders. (Veenhuizen et al 2019).</p>
Improved capacity to participate in daily tasks assessed with: Activity Card Sort	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	<p>53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. Significant effects in favor of the</p>

				intervention group were found on the ACS ($p= 0.047$) directly post intervention. (Veenhuizen et al 2019)
Improved capacity to participate in daily tasks assessed with: General Self Efficacy Scale	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. There were no significant group differences for GSES. (Veenhuizen et al 2019)
Improved capacity to participate in daily tasks assessed with: Rehabilitation Activities Profile	86 (1 RCT) ³	⊕⊕○○ Low ^{a,c,d}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the RAP (Blikman et al 2017).
Improved capacity to participate in daily tasks assessed with: Impact on Participation and Autonomy	86 (1 RCT) ³	⊕⊕○○ Low ^{a,c,d}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. The IPA (all domains) showed no overall or time-specific intervention effects. The only positive overall effect was for the

				IPA domain social relations, in favour of the control group (difference between groups=0.19; 95% CI: 0.03, 0.35), an outcome also reflected in time-specific effects at T8 and T26. No interval-specific effects were found for the IPA outcomes. (Blikman et al 2017)
Reduced falls - not measured	-	-	-	-

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3. Blikman LJ, van Meeteren J Twisk JW et al. Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: A randomized controlled trial. *Multiple Sclerosis*; 2017.
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5. Okkersen K, Jimenez-Moreno C Wenninger S et al. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. *Lancet Neurology*; 2018.
6. Pilutti L.A., Dlugonski D. Sandroff B.M. Klaren R. Motl R.W. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. *Multiple Sclerosis Journal*; 2014.
7. Cavallera C, Rovaris M Mendozzi L et al. Online meditation training for people with multiple sclerosis: A randomized controlled trial. *Multiple Sclerosis*; 2019.
8. Bogosian A, Chadwick P Windgassen S et al. Distress improves after mindfulness training for progressive MS: A pilot randomised trial. *Multiple Sclerosis*; 2015.
9. Levin A.B., Hadgkiss E.J. Weiland T.J. et al. Can meditation influence quality of life, depression, and disease outcome in multiple sclerosis? Findings from a large international web-based study.. *Behavioural Neurology*; 2014.
10. Senders A, Hanes D Bourdette D Carson K Marshall LM Shinto L. Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial. *Multiple Sclerosis*; 2019.
 - a. Participants with Multiple Sclerosis (no participants with a diagnosis of FRDA).
 - b. Participants had a neuromuscular condition - predominantly mitochondrial myopathy or facioscapulohumeral dystrophy (no participants diagnosed with FRDA).

- c. Allocation concealment not reported or allocation not concealed from enrolling investigator.
- d. ≥20% drop out in one study.
- e. Non-randomised, participants acting as own controls in one study.
- f. Participants with myotonic dystrophy (no participants with a diagnosis of FRDA).
- g. Desirability bias - participants in intervention group received more contact with clinicians administering intervention in one study.
- h. Confidence intervals not reported.
- i. Participants aware of allocation in one study.
- j. Responder bias in one study.
- k. Small sample size.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS																		
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know 	<table border="1"> <thead> <tr> <th data-bbox="520 768 684 1247">Outcomes</th> <th data-bbox="684 768 823 1247">No of participants (studies) Follow-up</th> <th data-bbox="823 768 961 1247">Certainty of the evidence (GRADE)</th> <th data-bbox="961 768 1056 1247">Relative effect (95% CI)</th> <th colspan="2" data-bbox="1056 768 1415 1247">Anticipated absolute effects* (95% CI)</th> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <th data-bbox="1056 846 1234 1247">Risk with no behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)</th> <th data-bbox="1234 846 1415 1247">Risk difference with behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)</th> </tr> </thead> <tbody> <tr> <td data-bbox="520 1247 684 1487">Reported fatigue assessed with: Checklist Individual Strength</td> <td data-bbox="684 1247 823 1487">292 (4 RCTs)^{1,2,3,4}</td> <td data-bbox="823 1247 961 1487">⊕○○○ Very low^{a,b,c,d,e}</td> <td data-bbox="961 1247 1056 1487">-</td> <td colspan="2" data-bbox="1056 1247 1415 1487">91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT</td> </tr> </tbody> </table>					Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)						Risk with no behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)	Risk difference with behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking)	Reported fatigue assessed with: Checklist Individual Strength	292 (4 RCTs) ^{1,2,3,4}	⊕○○○ Very low ^{a,b,c,d,e}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT		
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				<p>treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).</p> <p>53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. There were no significant group differences for CIS-fatigue. (Veenhuizen et al 2019) 86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the CIS20r fatigue subscale. (Blikman et al 2017).</p> <p>59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as</p>	
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				<p>a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. MANOVA analyses showed significant time effects for CIS-20-fatigue ($p=0.004$). Effect sizes were moderate for CIS-20-fatigue (partial $\eta^2=0.17$). One-way repeated-measures ANOVAs showed that there were no significant changes for the outcome measures during the waiting list period. After the intervention, 31% scored under the severely fatigued cut-off score of the CIS-20-fatigue (<35), as opposed to zero participants at inclusion of this study. Furthermore, despite still scoring above the cut-off after the intervention, 15% reached a clinically relevant decline of 8 points on the CIS-20-fatigue. Hence, in total 46% of the group that completed the intervention reached a clinically relevant result. (Hoogerwerf et al 2017).</p>	
	<p>Reported fatigue assessed with: Epworth Sleepiness Scale</p>	<p>0 (1 RCT)¹</p>	<p>⊕⊕○○ Low^{a,c}</p>	<p>-</p> <p>91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, $n=44$) or MS-nurse consultations ($n=47$) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).</p>	

Reported fatigue assessed with: Brief Illness Perception Questionnaire	91 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).
Reported fatigue assessed with: Borg score	255 (1 RCT) ⁵	⊕⊕○○ Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no between-group differences on the Borg score ($p=0.083$). (Okkersen et al 2018).
Reported fatigue assessed with: Fatigue and daytime	255 (1 RCT) ⁵	⊕⊕○○ Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months

sleepiness scale				<p>Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were significant between-group differences on the FDSS scale ($p=0.0002$). (Okkersen et al 2018).</p>
Reported fatigue assessed with: Modified Fatigue Impact Scale	307 (3 RCTs) ^{3,6,7}	 <p>Very low^{a,c,d,h,i}</p>	-	<p>86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the MFIS (Blikman et al 2017).</p> <p>139 people with multiple sclerosis were randomised to an MS-specific online mindfulness meditation intervention (n=54) or to a psychoeducational control (n=67) group. Participants were assessed at recruitment, 2 months, and after 6 months. The effects of the mindfulness intervention on primary and secondary outcomes were analysed using an ANCOVA, with condition (mindfulness vs psychoeducation) as the between-subject factor and baseline values for each outcome as covariates. Fatigue score differences at post-intervention were borderline significant ($F(1,111) = 3.674$, $p = 0.058$) and nonsignificant at</p>

				<p>the follow-up ($F(1,95) = 0.251, p = 0.617$). (Cavalera et al 2019).</p> <p>82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. Participants in the intervention group reported lower total MFIS scores post-trial compared with controls ($p=0.07$), although this difference did not reach statistical significance. For MFIS subscales, the intervention was associated with significant improvements on the physical subscale ($p=0.008$), but not the cognitive or psychosocial subscale. (Pilutti et al 2014)</p>	
<p>Reported fatigue assessed with: Fatigue Severity Scale</p>	<p>2677 (4 RCTs)^{3,6,8,9}</p>	<p>⊕○○○ Very low^{a,c,d,i,j}</p>	<p>-</p>	<p>86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the FSS (Blikman et al 2017). 40 patients with multiple sclerosis were randomised to an 8-week intervention of a specially adapted Skype distant-delivered mindfulness intervention (n=19), or a waiting list control group (n=21). Questionnaires were completed at baseline, post-intervention and 3-</p>	

				<p>month follow up. Treatment effects on the outcomes were estimated using linear mixed modelling where the outcome variables at the two post-intervention time points were the dependent variable. Fatigue was reduced for the mindfulness group compared to the waiting-list group at both post-intervention and three-month follow-up. (Bogosian et al 2015).</p> <p>82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. FSS scores were significantly lower in the intervention group compared with controls post-trial ($p=0.001$). (Pilutti et al 2014)</p> <p>2469 patients with multiple sclerosis took part in an online survey answering questions relating to health related QOL and their involvement in meditation practices. Bivariate analyses were undertaken to explore the relationship between meditation and each variable. T-tests were used to analyse significant differences in continuous variables between those that did and did not meditate (dichotomous variable), using Levene's test for assessment of equal variance. Analysis of the categorical meditation data was undertaken using cross tabulation with categorical data and one way ANOVA for comparison with continuous data. There was no significant relationship between those who did and did not meditate and FSS scores. (Levin et al 2014)</p>	
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Reported fatigue assessed with: Fatigue Catastrophizing Scale	59 (1 observational study) ⁴	 Very low ^{a,d,e,k}	-	59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. MANOVA analyses showed significant time effects for the FCS ($p=0.003$). (Hoogerwerf et al 2017).
Improved quality of life assessed with: Myotonic Dystrophy Health Index total score	255 (1 RCT) ⁵	 Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no significant between-group differences noted in the myotonic dystrophy health index score at 10 months. (Okkersen et al 2018).
Improved quality of life assessed with: Individualised neuromuscular quality of life	255 (1 RCT) ⁵	 Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five

				assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. There were no between-group differences in the INQOL score ($p=0.196$). (Okkersen et al 2018).
Improved quality of life assessed with: Medical Outcomes Study Short Form 36	148 (2 RCTs) ^{10,3}	⊕⊕○○ Low ^{a,d,i}	-	<p>86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. No significant overall or time-specific intervention effects were found for the SF-36. (Blikman et al 2017).</p> <p>62 adults with multiple sclerosis were randomised to mindfulness-based stress reduction (MBSR, n=33) group or an education control group (n=29). ANCOVA was performed to compare mean change in outcome measures from baseline to 8 weeks and baseline to 12 months between groups. While MBSR participants generally showed greater improvement in SF-36 compared to control, differences in scores between the groups were not statistically significant at either time point. (Senders et al 2019)</p>
Improved quality of life assessed with: Multiple Sclerosis Impact	122 (2 RCTs) ^{6,8}	⊕⊕○○ Low ^{a,c,i}	-	40 patients with multiple sclerosis were randomised to an 8-week intervention of a specially adapted Skype distant-delivered mindfulness intervention (n=19), or a waiting list control group (n=21). Questionnaires were completed

Scale				<p>at baseline, post-intervention and 3-month follow up. Treatment effects on the outcomes were estimated using linear mixed modelling where the outcome variables at the two post-intervention time points were the dependent variable. MSIS psychological and MSIS physical scores were reduced for the mindfulness group compared to the waiting-list group at both post-intervention and 3-month follow-up. (Bogosian et al 2015)</p> <p>82 patients with multiple sclerosis were randomised 1:1 to an internet-delivered, behavioural intervention or control group for 6 months. The effect of the behavioral intervention on physical activity, symptomatic, and HRQOL outcomes was examined using analysis of covariance (ANCOVA) with condition (Group: Intervention or Control) as the between subjects factor and pre-trial outcome scores for each outcome as the covariate. Lower physical HRQOL scores (i.e. superior HRQOL) were reported by participants in the intervention compared with controls post-trial ($p=0.06$), although this difference did not reach statistical significance. There was not a significant difference between groups on the psychological HRQOL scale post-trial. (Pilutti et al 2014)</p>
Improved quality of life assessed with: Patient-Reported Outcomes Measurement Information System	62 (1 RCT) ¹⁰	 Very low ^{a,i,k}	-	<p>62 adults with multiple sclerosis were randomised to mindfulness-based stress reduction (MBSR, n=33) group or an education control group (n=29). ANCOVA was performed to compare mean change in outcome measures from baseline to 8 weeks and baseline to 12 months between groups. While MBSR participants generally showed greater improvement in PROMIS compared to control, differences in scores between the groups were not statistically significant at either time</p>

				<p>point. (Senders et al 2019)</p>	
	<p>Improved quality of life assessed with: Multiple Sclerosis Quality of Life-54</p>	<p>2608 (2 RCTs)^{7,9}</p>	<p>⊕○○○ Very low^{a,h,i,j}</p>	<p>-</p> <p>139 people with multiple sclerosis were randomised to an MS-specific online mindfulness meditation intervention (n=54) or to a psychoeducational control (n=67) group. Participants were assessed at recruitment, 2 months, and after 6 months. The effects of the mindfulness intervention on primary and secondary outcomes were analysed using an ANCOVA, with condition (mindfulness vs psychoeducation) as the between-subject factor and baseline values for each outcome as covariates. QOL, measured with the MSQOL-54, was significantly higher in the mindfulness group at the post-intervention assessment ($F(1,110) = 4.68, p = 0.033$), but no difference was found after 6 months. (Cavalera et al 2019).</p> <p>2469 patients with multiple sclerosis took part in an online survey answering questions relating to health related QOL and their involvement in meditation practices. Bivariate analyses were undertaken to explore the relationship between meditation and each variable. T-tests were used to analyse significant differences in continuous variables between those that did and did not meditate (dichotomous variable), using Levene's test for assessment of equal variance. Analysis of the categorical meditation data was undertaken using cross tabulation with categorical data and one way ANOVA for comparison with continuous data. Mental health composite (MHC) and physical health composite (PHC) scores were significantly higher in respondents who meditated compared to those who did not ($p = 0.001$ and <0.001, resp.). Similarly the overall quality of life, energy, health distress, emotional well-being, health perception, and cognitive</p>	

				function HRQOL scales were all significantly higher in those who meditated ($p < 0.001$). (Levin et al 2014)
Improved quality of life assessed with: Life Satisfaction Questionnaire	59 (1 observational study) ⁴	⊕○○○ Very low ^{a,d,e,k}	-	59 patients with multiple sclerosis with severe fatigue were administered mindfulness-based cognitive therapy. Measurements were completed at T0 (baseline), T1 (after 10-week waiting period), T2 (post-treatment), T3 (follow up at 3 months post-treatment). A MANOVA was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise post-hoc ANOVA to detect in which time period significant changes occurred. There were no significant time effects for LiSat-9. (Hoogerwerf et al 2017)
Improved energy levels - not measured	-	-	-	-
Improved physical capacity assessed with: SF-36 Physical Functioning Subscale	91 (1 RCT) ¹	⊕⊕○○ Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).

	Improved physical capacity assessed with: 6 min walk test	308 (2 RCTs) ^{2,5}	 Low ^{b,c,f,g}	-	<p>255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. Differences at 10 months in favour of cognitive behavioural therapy were shown for total distance on the 6-min walk test ($p=0.0009$). (Okkersen et al 2018).</p> <p>53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. Significant effects in favor of the intervention group were found on the 6MWT ($p=0.00092$) at 11 month follow up. (Veenhuizen et al 2019)</p>	
	Improved capacity to participate in daily tasks assessed with: Dutch General Self-Efficacy Scale	91 (1 RCT) ¹	 Low ^{a,c}	-	91 patients with multiple sclerosis were randomised to a 16-week cognitive behavioural therapy (CBT, n=44) or MS-nurse consultations (n=47) to investigate factors that mediate change in fatigue. Questionnaires were completed at baseline, 8, 16, 26 and 52 weeks. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from posttreatment to follow-up was studied separately using	

				assessments at 16, 26 and 52 weeks. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished. (Van den Akker et al 2017).
Improved capacity to participate in daily tasks assessed with: DM1-Activ-c scale	255 (1 RCT) ⁵	⊕⊕○○ Low ^{c,f,g}	-	255 patients with myotonic dystrophy type 1 were randomised to treatment (n=128 to cognitive behavioural therapy + standard care) or to standard care alone (n=127) for 10 months. Patients were to receive 10–14 sessions of cognitive behavioural therapy (no specific duration specified), with most sessions delivered in the first 4–5 months. There were up to five assessment visits: eligibility screening followed by baseline, 5, 10, and 16 months post-randomisation, with the primary outcome measured at 10 months. A mixed-effects regression models with baseline scores as a covariate were used to assess change. After 10 months, there was an adjusted mean increase in scores on the DM1-Activ-c scale of 1.53 points (95% CI – 0.14 to 3.20) in the cognitive behavioural therapy group compared with an adjusted mean decrease of – 2.02 points (–4.02 to –1.01) in the standard care group. In the predefined primary outcome analysis of DM1-Activ-c, there was a difference between groups of 3.27 points (95% CI 0.93 to 5.62, <i>p</i> =0.007) in favour of the intervention group at 10 months. (Okkersen et al 2018).
Improved capacity to participate in daily tasks assessed with: Canadian Occupational	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that

Performance Measure				account for repeated measurements. After the 4-month treatment period (T1), the intervention group showed significantly higher mean COPM performance scores compared to the control group ($p < 0.0001$). This effect was still significant at 11 months ($p = 0.049$) follow-up and after correction for possible confounders. (Veenhuizen et al 2019).
Improved capacity to participate in daily tasks assessed with: Activity Card Sort	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. Significant effects in favor of the intervention group were found on the ACS ($p = 0.047$) directly post intervention. (Veenhuizen et al 2019)
Improved capacity to participate in daily tasks assessed with: General Self Efficacy Scale	53 (1 RCT) ²	⊕○○○ Very low ^{b,c,k}	-	53 patients with neuromuscular disease and chronic fatigue were randomised to Energetic, a 4-month group intervention (n=29), or to usual care (n=24). Participants were followed for 11 months post-intervention. Data were analyzed with linear models that account for repeated measurements. There were no significant group differences for GSES. (Veenhuizen et al 2019)
Improved capacity to participate in daily tasks assessed with: Rehabilitation Activities Profile	86 (1 RCT) ³	⊕⊕○○ Low ^{a,c,d}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect

				of ECM at specific time points. No significant overall or time-specific intervention effects were found for the RAP (Blikman et al 2017).
Improved capacity to participate in daily tasks assessed with: Impact on Participation and Autonomy	86 (1 RCT) ³	⊕⊕○○ Low ^{a,c,d}	-	86 severely fatigued and ambulatory adults with multiple sclerosis were randomised to receive individual energy conservation management (ECM) intervention or information-only (control). Assessments were completed at baseline, 8, 16, 26 and 52 weeks after randomisation. Between-group differences were assessed by adding time and an interaction between group allocation at time to evaluate the effect of ECM at specific time points. The IPA (all domains) showed no overall or time-specific intervention effects. The only positive overall effect was for the IPA domain social relations, in favour of the control group (difference between groups=0.19; 95% CI: 0.03, 0.35), an outcome also reflected in time-specific effects at T8 and T26. No interval-specific effects were found for the IPA outcomes. (Blikman et al 2017)
Reduced falls - not measured	-	-	-	-

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2. Veenhuizen Y, Cup EHC Jonker MA et al. Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial. *Neurology*; 2019.
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	<ol style="list-style-type: none"> 6. Pilutti L.A., Dlugonski D. Sandroff B.M. Klaren R. Motl R.W. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. Multiple Sclerosis Journal; 2014. 7. Cavalera C, Rovaris M Mendozzi L et al. Online meditation training for people with multiple sclerosis: A randomized controlled trial. Multiple Sclerosis; 2019. 8. Bogosian A, Chadwick P Windgassen S et al. Distress improves after mindfulness training for progressive MS: A pilot randomised trial. Multiple Sclerosis; 2015. 9. Levin A.B., Hadgkiss E.J. Weiland T.J. et al. Can meditation influence quality of life, depression, and disease outcome in multiple sclerosis? Findings from a large international web-based study.. Behavioural Neurology; 2014. 10. Senders A, Hanes D Bourdette D Carson K Marshall LM Shinto L. Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial. Multiple Sclerosis; 2019. <ol style="list-style-type: none"> a. Participants with Multiple Sclerosis (no participants with a diagnosis of FRDA). b. Participants had a neuromuscular condition - predominantly mitochondrial myopathy or facioscapulohumeral dystrophy (no participants diagnosed with FRDA). c. Allocation concealment not reported or allocation not concealed from enrolling investigator. d. $\geq 20\%$ drop out in one study. e. Non-randomised, participants acting as own controls in one study. f. Participants with myotonic dystrophy (no participants with a diagnosis of FRDA). g. Desirability bias - participants in intervention group received more contact with clinicians administering intervention in one study. h. Confidence intervals not reported. i. Participants aware of allocation in one study. j. Responder bias in one study. k. Small sample size. 	
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>Low to very low certainty of the evidence of effects as per the evidence profile table.</p>	
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																								
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability 	<table border="1"> <thead> <tr> <th data-bbox="518 660 1075 773">Outcomes</th> <th data-bbox="1081 660 1213 773">Importance</th> <th data-bbox="1220 660 1419 773">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td data-bbox="518 777 1075 878">Reported fatigue assessed with: Checklist Individual Strength</td> <td data-bbox="1081 777 1213 878">IMPORTANT^a</td> <td data-bbox="1220 777 1419 878">⊕○○○ VERY LOW^{b,c,d,e,f}</td> </tr> <tr> <td data-bbox="518 883 1075 984">Reported fatigue assessed with: Epworth Sleepiness Scale</td> <td data-bbox="1081 883 1213 984">IMPORTANT^a</td> <td data-bbox="1220 883 1419 984">⊕⊕○○ LOW^{b,d}</td> </tr> <tr> <td data-bbox="518 989 1075 1089">Reported fatigue assessed with: Brief Illness Perception Questionnaire</td> <td data-bbox="1081 989 1213 1089">IMPORTANT^a</td> <td data-bbox="1220 989 1419 1089">⊕⊕○○ LOW^{b,d}</td> </tr> <tr> <td data-bbox="518 1094 1075 1195">Reported fatigue assessed with: Borg score</td> <td data-bbox="1081 1094 1213 1195">IMPORTANT^a</td> <td data-bbox="1220 1094 1419 1195">⊕⊕○○ LOW^{d,g,h}</td> </tr> <tr> <td data-bbox="518 1200 1075 1300">Reported fatigue assessed with: Fatigue and daytime sleepiness scale</td> <td data-bbox="1081 1200 1213 1300">IMPORTANT^a</td> <td data-bbox="1220 1200 1419 1300">⊕⊕○○ LOW^{d,g,h}</td> </tr> <tr> <td data-bbox="518 1305 1075 1406">Reported fatigue assessed with: Modified Fatigue Impact Scale</td> <td data-bbox="1081 1305 1213 1406">IMPORTANT^a</td> <td data-bbox="1220 1305 1419 1406">⊕○○○ VERY LOW^{b,d,e,i,j}</td> </tr> <tr> <td data-bbox="518 1411 1075 1495">Reported fatigue assessed with: Fatigue Severity Scale</td> <td data-bbox="1081 1411 1213 1495">IMPORTANT^a</td> <td data-bbox="1220 1411 1419 1495">⊕○○○</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Reported fatigue assessed with: Checklist Individual Strength	IMPORTANT ^a	⊕○○○ VERY LOW ^{b,c,d,e,f}	Reported fatigue assessed with: Epworth Sleepiness Scale	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d}	Reported fatigue assessed with: Brief Illness Perception Questionnaire	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d}	Reported fatigue assessed with: Borg score	IMPORTANT ^a	⊕⊕○○ LOW ^{d,g,h}	Reported fatigue assessed with: Fatigue and daytime sleepiness scale	IMPORTANT ^a	⊕⊕○○ LOW ^{d,g,h}	Reported fatigue assessed with: Modified Fatigue Impact Scale	IMPORTANT ^a	⊕○○○ VERY LOW ^{b,d,e,i,j}	Reported fatigue assessed with: Fatigue Severity Scale	IMPORTANT ^a	⊕○○○	
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		VERY LOW ^{b,d,e,j,k}
Reported fatigue assessed with: Fatigue Catastrophizing Scale	IMPORTANT ^a	⊕○○○ VERY LOW ^{b,e,f,l}
Improved quality of life assessed with: Myotonic Dystrophy Health Index total score	IMPORTANT ^m	⊕⊕○○ LOW ^{d,g,h}
Improved quality of life assessed with: Individualised neuromuscular quality of life	IMPORTANT ^m	⊕⊕○○ LOW ^{d,g,h}
Improved quality of life assessed with: Medical Outcomes Study Short Form 36	IMPORTANT ^m	⊕⊕○○ LOW ^{b,e,j}
Improved quality of life assessed with: Multiple Sclerosis Impact Scale	IMPORTANT ^m	⊕⊕○○ LOW ^{b,d,j}
Improved quality of life assessed with: Patient-Reported Outcomes Measurement Information System	IMPORTANT ^m	⊕○○○ VERY LOW ^{b,j,l}
Improved quality of life assessed with: Multiple Sclerosis Quality of Life-54	IMPORTANT ^m	⊕○○○ VERY LOW ^{b,i,j,k}
Improved quality of life assessed with: Life Satisfaction Questionnaire	IMPORTANT ^m	⊕○○○ VERY LOW ^{b,e,f,l}
Improved energy levels - not measured	IMPORTANT ⁿ	-
Improved physical capacity assessed with: SF-36 Physical Functioning Subscale	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d}
Improved physical capacity assessed with: 6 min walk test	IMPORTANT ⁿ	⊕⊕○○ LOW ^{c,d,g,h}
Improved capacity to participate in daily tasks assessed with: Dutch General Self-Efficacy Scale	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d}
Improved capacity to participate in daily tasks	IMPORTANT ^a	⊕⊕○○

assessed with: DM1-Activ-c scale		LOW ^{d,g,h}
Improved capacity to participate in daily tasks assessed with: Canadian Occupational Performance Measure	IMPORTANT ^a	⊕○○○ VERY LOW ^{c,d,l}
Improved capacity to participate in daily tasks assessed with: Activity Card Sort	IMPORTANT ^a	⊕○○○ VERY LOW ^{c,d,l}
Improved capacity to participate in daily tasks assessed with: General Self Efficacy Scale	IMPORTANT ^a	⊕○○○ VERY LOW ^{c,d,l}
Improved capacity to participate in daily tasks assessed with: Rehabilitation Activities Profile	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d,e}
Improved capacity to participate in daily tasks assessed with: Impact on Participation and Autonomy	IMPORTANT ^a	⊕⊕○○ LOW ^{b,d,e}
Reduced falls - not measured	CRITICAL ^o	-

- a. Identified as important (6/6) by people with FA and critical by expert authors on this topic.
- b. Participants with Multiple Sclerosis (no participants with a diagnosis of FRDA).
- c. Participants had a neuromuscular condition - predominantly mitochondrial myopathy or facioscapulohumeral dystrophy (no participants diagnosed with FRDA).
- d. Allocation concealment not reported or allocation not concealed from enrolling investigator.
- e. ≥20% drop out in one study.
- f. Non-randomised, participants acting as own controls in one study.
- g. Participants with myotonic dystrophy (no participants with a diagnosis of FRDA).
- h. Desirability bias - participants in intervention group received more contact with clinicians administering intervention in one study.
- i. Confidence intervals not reported.
- j. Participants aware of allocation in one study.
- k. Responder bias in one study.
- l. Small sample size.
- m. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic.
- n. Identified as important (6/6) by people with FA and important by expert authors on this topic.
- o. Identified as critical (3/6) and important (3/6) by people with FA and critical by expert authors on this topic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 		<p>A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of Behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking) as a management strategy for all individuals who report fatigue.</p> <p>Reflecting on the impact of Behavioural management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, CMT, relaxation, avoiding multitasking) on Reported fatigue, 50% (12/24) clinical experts reported a benefit (large, moderate or small), 8.33% (2/24) reported no effect and, 0% (0/24) reported observing a harm (large, moderate or small). 10 clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on quality of life, 54.16% (13/24) clinical experts reported a benefit, 4.17% (1/24) reported no effect and, 0% (0/24) reported observing a harm. 10 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on energy levels, 50% (12/24) clinical experts reported a benefit, 8.33% (2/24) reported no effect and, 0% (0/24) reported observing a harm. 10 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on physical capacity, 41.67% (10/24) clinical experts reported a benefit, 16.67% (4/24) reported no effect and, 0% (0/24) reported observing a harm. 10 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on capacity to participate in daily tasks, 50% (12/24) clinical experts reported a benefit, 8.33% (2/24) reported no effect and, 0% (0/24) reported observing a harm. 10 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on falls, 45.83% (11/24) clinical experts reported a benefit, 12.5% (3/24) reported no effect and, 0% (0/24) reported observing a harm. 10 expert clinicians could not</p>

		provide any information on this outcome.
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Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No published evidence.	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if behavioural management in people who report fatigue was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>4/4 indicated the intervention was acceptable. (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

We suggest behavioral management (mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, cognitive behavioral therapy, relaxation, avoiding multitasking) may assist in managing fatigue in individuals with Friedreich ataxia.

Justification

There is low-level of evidence indicating benefits in other conditions with similar characteristics to Friedreich ataxia.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who report fatigue.

Research priorities

Exploration of behavioral management techniques in managing fatigue in FRDA.

Reference

da Silva CB, Chevis CF, D'Abreu A, Lopes-Cendes I, Franca MC, Jr. Fatigue is frequent and multifactorial in Friedreich's ataxia. *Parkinsonism Relat Disord.* 2013;19(8):766-7.

