BMJ Open

What is the best way to keep walking and moving around for individuals with Machado-Joseph disease? A scoping review through the lens of Aboriginal families with Machado-Joseph disease in the Top End of Australia

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To cite: Carr JJ, Lalara J, Lalara G, *et al*. What is the best way to keep walking and moving around for individuals with Machado-Joseph disease? A scoping review through the lens of Aboriginal families with Machado-Joseph disease in the Top End of Australia. *BMJ Open* 2019;**9**:e032092. doi:10.1136/bmjopen-2019-032092

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-032092).

Received 05 June 2019
Revised 30 July 2019
Accepted 02 August 2019

Check for updates

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ABSTRACT

Objectives Machado-Joseph disease (MJD) is the most common spinocerebellar ataxia worldwide. Prevalence is highest in affected remote Aboriginal communities of the Top End of Australia. Aboriginal families with MJD from Groote Eylandt believe 'staying strong on the inside and outside' works best to keep them walking and moving around, in accordance with six key domains that form the 'Staying Strong' Framework. The aim of this current study was to review the literature to: (1) map the range of interventions/strategies that have been explored to promote walking and moving around (functional mobility) for individuals with MJD and; (2) align these interventions to the 'Staying Strong' Framework described by Aboriginal families with MJD.

Design Scoping review.

Data sources Searches were conducted in July 2018 in MEDLINE, EMBASE, CINAHL, PsychINFO and Cochrane Databases.

Eligibility criteria for selecting studies Peer-reviewed studies that (1) included adolescents/adults with MJD, (2) explored the effects of any intervention on mobility and (3) included a measure of mobility, function and/or ataxia were included in the review.

Results Thirty studies were included. Few studies involved participants with MJD alone (12/30). Most studies explored interventions that aligned with two 'Staying Strong' Framework domains, 'exercising your body' (n=13) and 'searching for good medicine' (n=17). Few studies aligned with the domains having 'something important to do' (n=2) or 'keeping yourself happy' (n=2). No studies aligned with the domains 'going country' or 'families helping each other'.

Conclusions Evidence for interventions to promote mobility that align with the 'Staying Strong' Framework were focused on staying strong on the outside (physically) with little reflection on staying strong on the inside (emotionally, mentally and spiritually). Findings suggest future research is required to investigate the benefits of lifestyle activity programmes that address both physical and psychosocial well-being for families with MJD.

Strengths and limitations of this study

- This is the first review to map interventions trialled for individuals with Machado-Joseph disease (MJD) to enhance walking and moving around and to align findings with the 'Staying Strong' Framework.
- Studies typically focussed on interventions that promote 'staying strong on the outside' (physically), with few targetting 'staying strong on the inside' (emotionally, mentally and spiritually).
- This study is limited by a shortage of high-quality research that includes individuals specifically with MJD.
- This review highlights opportunities for investigating the benefit of lifestyle activity programmes that address both physical and psychosocial well-being for families with MJD.

INTRODUCTION

Machado-Joseph disease (MJD), or spinocerebellar ataxia type 3, is an autosomal-dominant neurodegenerative disease. Individuals with MJD experience progressive cerebellar ataxia and decline in mobility caused by premature cell death in the cerebellum and brainstem.[1] Average life expectancy is 20 years from onset of symptoms, with most individuals wheelchair users within 10 years of symptoms emerging.[2] MJD is the most common spinocerebellar ataxia (SCA) worldwide[3] and is most prevalent in remote Aboriginal communities in the Top End of Australia. For example, prevalenace estimates for the Groote Eylandt Archipelago in Australia are ~743/100 000, compared with ~39/100 000 for the Azores Archipelago in Portugal, where MJD is also common.[4–7]

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Many trials are underway to find a cure for a range of SCAs.[8 9] Other research efforts have focused on physiotherapeutic interventions to address impairments and activity limitations resulting from a range of hereditary ataxias (HAs).[10–13] These interventions have been shown to enhance mobility and potentially delay symptom progression.[14] For people with MJD, current recommended physiotherapeutic interventions are based on findings from studies on other SCAs.[13 15–17] A focus on MJD is required, given the differences in pathophysiology and neurochemistry between SCA types,[9] and to understand what interventions have been previously explored and where gaps lie. This information will provide future direction for targeted interventions for people with MJD to maximise their functional mobility.

Interventions designed to promote mobility for Aboriginal families with MJD from the Top End of Australia, whose culture and lifestyle are uniquely different to those with MJD in other parts of the world, have not been investigated.[18] Importantly, these interventions are unlikely to be effective if they do not incorporate Indigenous views and concepts of physical activity and lifestyle in line with cultural and traditional practices.[18–20]

Aboriginal families with MJD from the Groote Eylandt Archipelago have experienced the impact of MJD on their families for generations.[18] In a recent study,[21] these families shared their perspectives on what is important and what works best to keep walking and moving around.[18] Participants emphasised the importance of 'staying strong on the inside and outside' (physically, mentally, emotionally and spiritually) through 'exercising your body', 'keeping yourself happy', 'going country', 'searching for good medicine', 'families helping each other' and having 'something important to do'.[18] These domains formed the 'Staying Strong' Framework to keep walking and moving around; a framework driven by community and culturally founded needs (table 1).[18] This review set out to explore: (1) What interventions/strategies have been explored to promote walking and moving around for people with MJD (2); How the findings of these explorations align with the perspectives of families with MJD from Groote Eylandt, according to the domains of the 'Staying Strong' Framework.[18]

METHODS AND ANALYSIS

A scoping review was conducted following the five-step approach recommended by Arksey and O'Malley and further developed by Levac *et al*.[22 23] A scoping review was chosen to allow a broad range of topics across a range of study types and designs to be explored, to identify the nature and extent of research evidence available.[24] The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews

Table 1 'Staying Strong' Framework

Domains	Definition
Exercising your body	► Having an active lifestyle and keeping your body moving every day keeps you physically strong (ie, going country, walking, hunting, fishing swimming, dancing, doing housework and yard work, riding a bike, walking on a treadmill). ► Exercising your body helps you cope with the worries and sadness that come with MJD.
Something important to do	► Finding something meaningful to do pushes you to keep your body moving and keep physically strong. ► Having something important to do helps you feel you are contributing to your family and community, sets an example for others and builds self-esteem and happiness.
Keeping yourself happy	► Finding ways to stay happy and positive, and drawing on family and support services when required, helps you keep persevering in life despite having MJD. ► It helps you to keep doing the things you need to do to stay physically strong. ► Feeling low and unhappy can make you feel physically weak.
Searching for good medicine	► Searching for good medicine or food from the natural environment, or useful clinical medicines, is important for staying physically and emotionally strong. ► It is important to find good medicines that help you to manage other illnesses that negatively impact living with MJD (colds, flus, infections and pain). ► For Aboriginal people of Groote Eylandt, finding traditional medicines in the bush or beach is important for staying active and keeping physically and emotionally strong.
Going country	► Going country means getting out and about, to places meaningful to the individual, to do things that matter, with people that matter, to keep yourself both physically and emotionally strong. ► For Aboriginal families of Groote Eylandt, going country involves getting out of the home, visiting their lands, at the bush or beach, often to go hunting or fishing with family.
Families helping each other	► Family support is important for having opportunities to keep physically strong and for physical assistance as the disease progresses. ► Support from families offers important emotional support, keeping you strong inside. ► Family extends to local and trusted service providers.

MJD, Machado-Joseph disease.

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Table 2 Search terms (MEDLINE)

Concept	Search terms	Limits
What (*interventions*)	program* or promot* or interven* or strateg* or approach* or train* or rehab* or princip* or therap* or support* or motivat*	Nil
Works best (*promote, enhance*)	benefi* or improv* or positiv* or significan* or maint*	Nil
People with MJD (*initially broadened search to HAs to ensure all studies that may have included participants with MJD could be screened*)	cerebellar ataxia/ or exp spinocerebellar ataxias/ or spinocerebellar degenerations/ or friedreich ataxia/ or olivopontocerebellar atrophies/ or 'spinocerebellar ataxia*' or 'machado joseph disease' or 'friedreich's ataxia' or 'inherited olivopontocerebellar atrophy' or 'cerebello-olivary atrophy' or 'spinocerebellar degeneration' or 'genetic degenerative ataxia' or 'cerebellar ataxia' or 'hereditary ataxia' or 'genetic ataxia' or 'inherited ataxia' or 'dentatorubral pallidoluysian atrophy' or 'trinucleotide repeat dis*' or 'inherited neurodegenerative dis*' or 'degenerative ataxia' or 'hereditary neurodegenerative ataxia*' or 'autosomal dominant hereditary ataxia*' or 'autosomal recessive hereditary ataxia*'	Nil
Walking and moving around (*functional mobility*)	exp Movement/ or exp Human Activities/ or exp Locomotion/ or Physical Mobility/ or Motor Activity/ or Stair Climbing/ or walk* or mobil* or function* or move* or moving or activit* or step* or stand* or transfer*	Nil

HAs, hereditary ataxias; MJD, Machado-Joseph disease.

Checklist was followed.[25] This review was not registered with PROSPERO as scoping reviews are not currently accepted.

Relevant studies

A comprehensive search of peer-reviewed published literature was conducted for studies published from 1990 when genetic confirmation of MJD became possible,[26 27] until August 2018. The search was repeated prior to publication to identify studies published up to July 2019. Using MEDLINE, EMBASE, CINAHL, PsychINFO and Cochrane Databases, a combination of medical subject headings terms and keywords with truncations were used (table 2). The search was initially broad to include all HAs, to ensure inclusion of studies with participants with multiple aetiologies including MJD would be identified. Studies were chosen if they (1) included human participants with genetically confirmed MJD either exclusively or within the study sample, (2) included adolescents and/or adults, (3) included at least one measure of mobility, function or ataxia and (4) explored the influence of any intervention/strategy on mobility and/or function using objective measures or from the perspective of the participant. In studies that did not disclose the types of SCA of included participants, authors were contacted to confirm inclusion or exclusion on this basis.

Study selection and quality assessement

Database searches were conducted by one reviewer (JJC) and verified by a second reviewer (JQ). Both reviewers (JJC and JQ) independently screened titles and abstracts and reviewed full-text articles. Additional studies screened for inclusion were identified by handsearching reference lists of included studies, literature reviews that met the eligibility criteria and through citations tracked using Google Scholar.[1 8 9 11 12 14 28–31] The PRISMA flow diagram outlines the results of the search (figure 1).[32] The second search found no new studies that met the inclusion criteria.

Methodological quality assessment of included studies, not typically required of scoping reviews, was employed to identify gaps in the literature and quality of the studies available.[33] Two reviewers (JJC and MS) assessed methodological quality of included studies using the Mixed Method Appraisal Tool (MMAT)[34] and classified them according to the National Health and Medical Research Council (NHMRC) evidence hierarchy.[35] The MMAT was selected as this single tool allowed quality appraisal of the range of study designs relevant to this review (qualitative, randomised controlled (RCTs), non-RCTs and quantitative descriptive studies). Joanna Briggs Institute (JBI) Levels of Evidence for Meaningfulness[36] was used to grade level of evidence for the qualitative study[37] and the expert opinion excerpt.[1] Disagreements were resolved by consensus or referred to a third reviewer (RNB).

Data extraction, collation and analysis

To facilitate analysis and reporting, data were extracted using NVivo V.12[38] following a data extraction guide. Data extracted included study characteristics, participant characteristics, intervention characteristics, outcome measures and study outcomes. Data gathered were charted into tables.[22] Measures of blood chemistry, neuroimaging or measures of upper limb function were not extracted unless included in composite or functional outcome measures, such as the Spinocerebellar Ataxia Functional Index (SCAFI).

All studies found were collated and then mapped according to the domains they aligned to in the 'Staying Strong' Framework (JJC). Studies that aligned to more than one domain were mapped under the domain to which they most strongly aligned (table 3). A descriptive approach was used to analyse the data collected.[39] To

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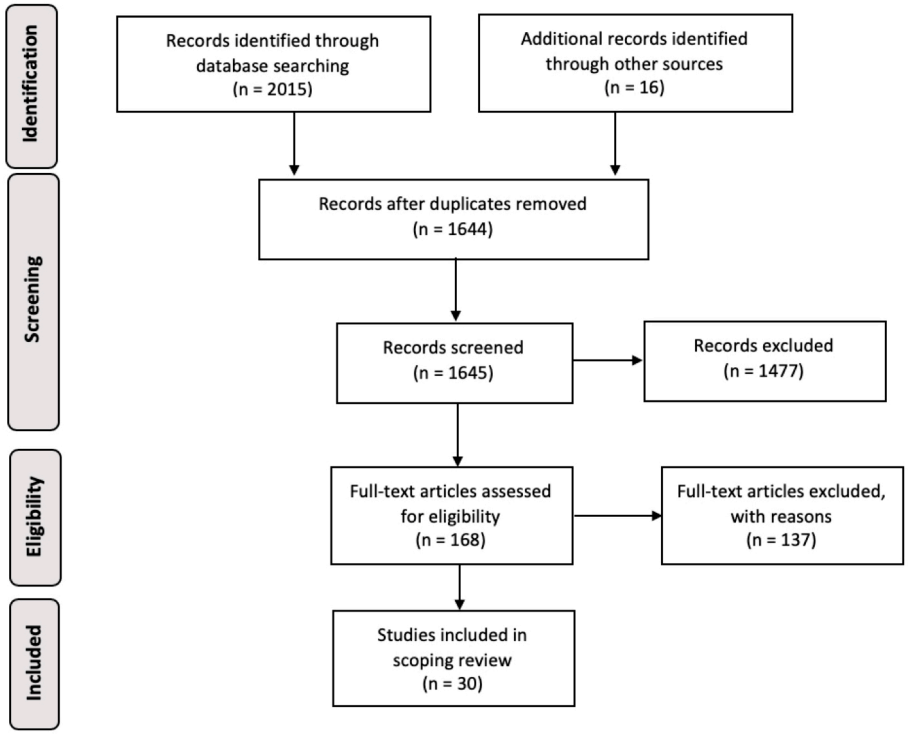

Figure 1 Flow diagram of study selection.

provide an overview, key points that highlight each study's alignment with the different domains were compiled in a separate table (online supplementary table 1). Meta-analysis was not possible due to heterogeneity of outcome measures and interventions in the included studies.

Patient and pubic involvement

There was no patient or public involvement in this study.

RESULTS

A total of 30 studies met the eligibility criteria and included quantitative (experimental (n=27); observational (n=1)) and qualitative (n=1) designs. One expert opinion excerpt (n=1) that was eligible and included was extracted from a literature review that otherwise did not meet the eligibility criteria. Twelve different countries were represented (Brazil (n=6), Germany (n=4), China (n=3), Japan (n=3), Taiwan (n=3), USA (n=3), India (n=2), Italy (n=2), Spain (n=2), Korea, the Netherlands and Scandinavia. Characteristics of the included studies are outlined in table 3.

Study population

Of the 30 studies, 12 studies included MJD participants exclusively. The remaining 18 included participants with both MJD and other HAs. Mobility status was reported as ambulant in 21 studies, able to stand at a minimum in one study, while eight studies did not report mobility status. Study sample sizes ranged from eight to 295 participants, with a total of 850 participants, 429 with MJD (50.5%). Age ranged from 15 to 76 (average across all studies=46.7 years).

Methodological quality

Seven quantitative studies were graded level II (RCTs) according to NHMRC levels of evidence.[30 40–45] The remaining studies were graded III-1 (one study),[46] III-2 (three studies),[47–49] III-3 (one study)[50] and IV (16 studies).[51–66] The qualitative study was graded level 3[37] and the expert opinion excerpt was graded level 5[1] in accordance with the JBI Levels of Evidence for Meaningfulness.[36] MMAT scores for methodological quality are provided in table 4. Quality scores ranged as follows *(n=1),[48] **(n=6),[41 43 51 54 58 64] ***(n=10)[30 37 44 45 49 50 53 57 63 66] and ****(n=12).[40 42 46 47 52 55 56 59–62 65] The expert opinion excerpt was not scored.[1]

Outcome measures

Fifty-three different outcome measures were used to investigate interventions in this review. The SARA scale (14/30 studies) was the measure most commonly used. Outcome measures included measures at the impairment level (ataxia, disease severity and depression), measures at the activity level (function, mobility and balance) and measures of quality of life (QOL). No studies included measures at the participation level. Table 5 presents measures used, as well as outcomes that reached statistical significance.

Adverse events

Nine studies reported adverse events, all within pharmacological studies. None were considered serious or life threatening.[30 41 42 44 45 53 55 64 66] One study reported two-drop outs due to side effects, but details of the effects were not specified.[64]

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Table 3 Summary of studies exploring interventions to promote walking and moving around for people with MJD

Staying strong domain: exercising your body

Study characteristics				Participant characteristics			Intervention				Measurement and Outcomes		
Author, year, country	**Design**	**Level of evidence NHMRC**	**Quality MMAT**	**Participants (n=); diagnosis**	**Age (y) *mean (SD)***	**Mobility status**	**Description**	**Duration (week)**	**Frequency (/week)**	**Intensity**	**Outcome measures**	**Assessment timepoints**	**Significant outcomes**
Wang *et al* 2018 China	RCT	II	****	n=9; MJD	Exp: 54 (51–60) Control: 57 (44–61)	Ambulant	Exergames training vs conventional balance +coordination training	4	3	40 min	▶ SARA (I) ▶ Limit of stability test (A) ▶ Spatiotemporal gait parameters (A)	▶ Pre and post	Between groups: not significant Within group (exp group): ▶ Improved SARA gait-posture (p=0.038)*, SARA total (p=0.042)*
Kaut *et al* 2014 Germany	Pseudo RCT	III-1	****	n=31; MJD (n=2) SCA1 SCA2 SCA6	Exp: 61.2 (12.3) Control: 57.3 (12.7)	Ambulant	Stochastic vibration therapy vs sham	8 days	4 sessions total	5×60 s on/60 s off	▶ SARA (I) ▶ SCAFI (A) ▶ INAS (I)	▶ Pre and post	Between groups: not significant Within group (exp group): ▶ Improved SARA gait and posture (p<0.01)*, 8MWT (p=0.02)*
Conte *et al* 2017 Italy	Non-randomised experimental trial	III-2	****	n=13; MJD (#) SCA1 SCA2 SAOA	50.2 (9.5)	Ambulant	Wide BOS walking vs walking between two white lines (width determined by healthy controls)	6×10 m walking trials per session, 1 min rest between trials	2 walking sessions on 2 separate days 1 week interval between days	Gait speed matched to healthy controls	▶ Spatiotemporal gait parameters (A) ▶ Upper body and lower body kinematics (A) ▶ Muscle coactivation (A) ▶ Energy recovery and expenditure (I)	▶ Each session recorded	Between groups: not significant Within group: ▶ Narrow BOS walking: reduced speed*, step length*, hip and knee ROM*, energy recovery*; increased double support,* gait variability,* trunk oscillation,* ankle joint muscle coactivation* ▶ Widened BOS walking—increased dynamic stability*; reduced compensatory mechanisms*, mechanical energy*
Tabbassum *et al* 2013 India	Non-randomised experimental trial	III-2	*	n=20; MJD (#) SCA1 SCA2 SCA3 OPCA	Not reported	Ambulant	Core stability training+balance training vs balance training+relaxation	4	3	1 hour/day	▶ BESTest (A) ▶ MFES (Falls) (A)	▶ Pre and post ▶ 4 weeks post	Between groups (exp group): ▶ BEStest each assessment* ▶ Not significant: MFES
Fonteyn *et al* 2014 The Netherlands	Case series with pretest/post-test outcomes	IV	****	n=10; MJD (n=1) SCA6 SAOA	61.4 (5.7)	Ambulant	Gait adaptability training on treadmill with visual cues on treadmill	5	2	6 gait adaptability exercises for 60 min No handrail used. Difficulty gradually progressed	▶ Obstacle avoidance task success rate (A) ▶ SARA (I) ▶ 10MWT (A) ▶ TUG (A) ▶ BBS (A) ▶ EFAP (A) ▶ ABC (A) ▶ No of falls (A) ▶ Experience of training questionnaire (Q)	▶ 1-week pre ▶ 1-week post	Between groups: NA Within group: ▶ Improved SARA and EFAP obstacle subtask*, increased short-step strategy preference (p=0.003)*, success rates increased (78.5%–94.8%)* ▶ Not significant: BBS, TUG, 10MWT, Obstacle Avoidance Task
Im *et al* 2017 Korea	Case series with pretest/post-test outcomes	IV	****	n=19; MJD (n=3) SCA2 SCA6 Idiopathic MSA-C	53.2 (13.8)	Ambulant	Task specific walking training: part practice (weight shifting, stepping)+whole practice of walking Manual support provided and weaned as required	12	2	1.5 hours each session	▶ ICARS (I) ▶ Spatiotemporal gait parameters (A)	▶ Pre and post ▶ 3 months post	Between groups: NA Within group: ▶ Improved ICARS each assessment*; reduced spatiotemporal gait parameter variability*
Leonardi *et al* 2017 Italy	Case series with pretest/post-test outcomes	IV	****	n=9; MJD (n=2) SCA1 SCA2 FA	35.3 (16.3)	Ambulant	Wearable proprioceptive stabiliser+conventional balance training (limit of stability training+external perturbations practice in protected conditions)	Device wear: 3 Usual balance training: 6	Device wear: 5 Usual balance training: 5	Device wear: 3 (hour) Usual balance training: 40	▶ SARA (I) ▶ 6MWT (A) ▶ Spatiotemporal gait parameters (A)	▶ Pre and post 3 weeks of device wear (T1)+usual training ▶ 3 weeks postdevice discontinuation+usual training only (T2)	Between groups: NA Within group: ▶ Improved SARA*, 9HPT-dominant hand*, PATA*, 6MWT*, spatiotemporal gait parameters (T1)*, length of gait cycle (T2)*
de Oliveira *et al* 2018 Brazil	Case series with pretest/post-test outcomes	IV	**	Stage 1: n=9 Stage 2: n=5 MJD (n=6) SCA1 SCA7	43 (11)	Ambulant	PBWS treadmill training: Stage 1: CV training Stage 2: dynamic balance training	Stage 1:8 Stage 2:10	2 (days)	50 min	▶ CPET (A) ▶ BORG (A) ▶ BBS (A) ▶ DGI (A) ▶ SARA (I) ▶ BARS (I) ▶ Katz ADL (Q) ▶ Treadmill inclination (A)	▶ Prestage 1 (S0) ▶ Prestage 2 (S1) ▶ Poststage 2 (S2)	Between groups: NA Within group: ▶ S1: Improved DGI (p=0.03)*, CPET duration (p<0.01)*, treadmill inclination (p<0.01)* ▶ S2: Improved BBS compared with S1 (p=0.04)* ▶ Not significant: SARA, Katz ADL, BARS, VE peak/VO2 max
de Oliveira *et al* 2015 Brazil	Case series with pretest/post-test outcomes	IV	****	n=11; MJD (n=8) SCA2 SCA7	46.1 (range 28–59) SD not reported	Ambulant	Balance training	4	2–3	1 (hour)	▶ BBS (A)	▶ Pre and post	Between groups: NA Within group: ▶ Improved BBS (p=0.0034)*
Sawant and Gokhale 2015 India	Case series with pretest/post-test outcomes	IV	***	n=3; MJD (n=1) Hereditary SCA	24.6 (3.4)	Ambulant	Occupational therapy+intensive functional physical training (tailored programme meaningful to participant)	12	5 (supervised=3; home/unsupervised=2)	45 min–1 hour	▶ BBS (A) ▶ FIM+FAM (A)	▶ Pre and post	Between groups: NA Within group: ▶ Improved BBS (p=0.05)*, FIM+FAM (p=0.01)*

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Table 3 Continued

Staying strong domain: exercising your body

Study characteristics				Participant characteristics			Intervention				Measurement and Outcomes		
Author, year, country	Design	Level of evidence NHMRC	Quality MMAT	Participants (n=); diagnosis	Age (y) *mean (SD)*	Mobility status	Description	Duration (week)	Frequency (/week)	Intensity	Outcome measures	Assessment timepoints	Significant outcomes
Silva *et al* 2010 Brazil	Case series with pretest/ post-test outcomes	IV	****	n=23; MJD	42.4 (10)	Ambulant	Occupational therapy: training priorities on functional limitations	6 months	Once/week: 0–3 months Once/month: 3–6 months	40 min	▶ FIM (A) ▶ Barthel Index (A) ▶ Hamilton rating scale (Q) ▶ WHOQOL-BREF (Q) ▶ NESSCA (I) ▶ SARA (I)	▶ Pre and post ▶ Mid intervention	Between groups: NA Within group: ▶ Improved Hamilton depression score at 6 months (p<0.0001)* ▶ Not significant: FIM, Barthel Index, WHOQOL-BREF
D'Abreu *et al* 2010 Brazil	Review (expert opinion section)	V (JBI)	NA	n=23; MJD	NA	NA	NA	NA	NA	NA	Recommendations: ▶ Physical therapy assessment +exercise programme. ▶ Falls assessment and assistive device prescription ▶ Trial levodopa for those with dystonia affecting mobility ▶ Exercise improves ability to cope, increases self-esteem, boosts patients' mood and sense of control over their disease. ▶ Source of pain should be identified and managed appropriately (musculoskeletal/neuropathic/secondary to dystonia/ mixed)		

Staying strong domain: searching for good medicine

Study characteristics				Participant characteristics			Intervention				Measurement and outcomes		
Author, year, country	Design	Level of evidence NHMRC	Quality MMAT	Participants (n=); diagnosis	Age (y) *mean (SD)*	Mobility status	Description	Duration (week)	Frequency (/week)	Intensity	Outcome measures	Assessment timepoints	Significant outcomes
Assadi *et al* 2007 USA	RCT	II	***	n=19 MJD (n=2) SCA1 SCA2 SCA17 FA Idiopathic	40.5 (17.3)	Not stated	Buspirone HCl 30 mg twice daily vs placebo Crossover after 4 week washout	Each treatment arm: 12 2 weeks of each arm consisted of titration period.	Twice daily	NA	▶ ICARS (I)	▶ Pre and post each treatment phase	Between groups: not significant
Lei *et al* 2016 China	RCT	II	**	n=34 MJD	Multidose exp: 800 mg: 36.5 (5.4) 1200 mg: 33.9 (7.1) sham: 33.9 (4.5)	Ambulant	Valproic acid low-dose VPA (800 mg/day), high-dose VPA (1200 mg/day) vs placebo	12	Twice daily	NA	▶ SARA (I)	▶ Predose ▶ Week 4 ▶ Week 8 ▶ Week 12	Between groups: ▶ Improved SARA in 1200 mg/day group (–2.05) compared with 800 mg/day (–1.58) and placebo (–0.75) (p=0.021)* ▶ Improved SARA subscores in placebo and VPA groups (800 mg/day and 1200 mg/day) (p<0:05)*
Saute *et al*[~] 2014 Brazil	RCT	II	****	n=60 MJD	Exp: 40.5 (9.6); sham: 40.4 (9.2)	Ambulant	Lithium carbonate vs placebo	48	300 mg once/ day; increased to twice daily until 0.5–0.8 mEQ/L	NA	▶ NESSCA (I) ▶ SARA (I) ▶ 8MWT (A) ▶ SCAFI (A) ▶ CCFS (A) ▶ Barthel Index (A) ▶ WHOQOL-BREF (Q) ▶ BDI (Q) ▶ PGI (Q)	▶ Pre dose ▶ 24 weeks ▶ 48 weeks	Between groups (exp group): ▶ Improved SCAFI (24, 48 week)*; CCFS (48 week)* ▶ Not significant —NESSCA, SARA, 8MWT, 9HPT, BDI, Barthel Index, WHOQOL-BREF, PGI
Schulte *et al* 2001 Germany	RCT	II	**	n=20 MJD	44.7 (11)	Standing (minimum)	Trimethoprim-sulfamethoxazole trimethoprim (160 mg)+sulfamethoxazole (800 mg) 2/52; trimethoprim (80 mg)+sulfamethoxazole (400 mg) remainder of 6 months	Phase 1: 6 months exp or placebo Washout: 4 Phase 2: crossover to alternate preparation.	Twice daily	NA	▶ Posturography (A) ▶ ACRS (I) ▶ SF36 (Q)	▶ Pre ▶ Post 2/52 ▶ Post each 6 months treatment phase	Between groups: not significant
Wessel *et al* 1997 Germany	RCT	II	***	n=18 MJD (n=2) SCA1 idiopathic CA	46.8 SD not reported	Not stated	Physostigmine (30 mg) patch vs sham patch	Each treatment arm: 4 Washout: 1	Patch worn continuously	24 hour/day	▶ ACRS (I) ▶ Posturography (A)	▶ Pre and post each treatment phase	Between groups: not significant
Zesiewicz *et al* 2012 USA	RCT	II	***	n=13 MJD	Exp 47.44 (10.83); Sham: 53.78 (11.18)	Not stated	Varenicline 4 weeks for titration and 4 weeks at 1 mg twice daily	8	Max dose, twice daily	NA	▶ SARA (I) ▶ T25FWT (A) ▶ BDI (Q) ▶ BAI (Q) ▶ CGI (I) ▶ PGI (Q) ▶ SF36 (Q)	▶ Pre and post	Between groups (exp group) ▶ Improved SARA subs scores (gait, stance, rapid alternating movements)*, T25FWT*, BDI (p<0.05)* ▶ Not significant: CGI, PGI, BAI, SF36

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Table 3 Continued

Staying strong domain: searching for good medicine

Study characteristics				Participant characteristics			Intervention				Measurement and outcomes		
Author, year, country	Design	Level of evidence NHMRC	Quality MMAT	Participants (n=); diagnosis	Age (y) *mean (SD)*	Mobility status	Description	Duration (week)	Frequency (/week)	Intensity	Outcome measures	Assessment timepoints	Significant outcomes
Shiga *et al* 2002 Japan	Non-randomised experimental trial	III-2	***	n=74 MJD (#) sporadic OPCA SCA1 SCA6	Exp: 58.83 (1.47) Sham: 56.31 (1.96)	Ambulant	TMS over cerebellum vs sham	21 days	Once daily	▶ 10 pulses ▶ Pulse duration: 0.1 ms ▶ Output adjusted to 100% of maximum output	▶ 10MWT (A) ▶ Walking capacity (A) ▶ Standing capacity (A) ▶ Tandem steps (A)	▶ Pre and post	Between groups (exp group): ▶ Improved 10MWT time (p<0.05)*, 10 m steps (p<0.05)*, tandem steps (p<0.005)*, standing capacities (p<0.05)* Within group (sham group): ▶ Improved 10 m time (p<0.05)*, 10 m steps (p<0.05)*, standing capacities (p<0.05)
Liu *et al* 2005 Taiwan	Interrupted time series without a parallel control	III-3	***	n=6 MJD	27 SD not reported	Ambulant	Lamotrigine	Week 0–1: No meds Week 2–7: LTG (6 weeks) Week 8–9: Withdrawal	25 mg daily	NA	▶ TGI (A) ▶ OLS (A)	▶ Weekly (0–9 week)	Between groups: NA Within groups: ▶ Improved TGI with LTG (p<0.05; week 4, 5, 6, 7)*, OLS scores (p<0.05; week 7)* but not during withdrawal
Arpa *et al* 2015 Spain	Case series with pretest/post-test outcomes	IV	****	n=12 MJD (7) SCA7	51 (13)	Not stated	Human IGF-1 (subcutaneous administration)	2 years	Twice daily	0.05 mg/kg	▶ SARA (I)	▶ Pre ▶ 4 months ▶ 8 months ▶ 12 months ▶ 16 months ▶ 20 months ▶ 24 months	Between groups: NA Within group: ▶ Improved SARA for SCA3 after IGF-1 treatment at 8 months (p=0.0061)*
Giordano *et al* 2013 Germany	Case series with pretest/post-test outcomes	IV	**	n=14 MJD (2) SCA1 SCA6 ADCA POLG SAOA	60 (11.3)	Ambulant	Slow release 4-Aminopyridine	14 days	Once daily	2×10 mg	▶ SARA (I) ▶ EQ-5D (Q) ▶ 8MWT (A) ▶ SCAFI (A)	▶ Pre ▶ 4 hour post 4-AP ▶ 14 days post 4-AP	Between groups: NA Within group: ▶ Improved SCAFI after 4 hours and after 14 days (p=0.01)*, 8MWT after 14 days*, but not after 4 hours (p<0.01)* ▶ Not significant: SARA, 9HPT, EQ-5D
Monte *et al* 2003 Brazil	Case series with pretest/post-test outcomes	IV	**	n=13 MJD	41 (13)	Ambulant	Fluoxetine	6	Once daily	20 mg	▶ EDSS (A) ▶ UPDRS (A)	▶ Pre and post	Between groups: NA Within group: not significant
Sanz-Gallego *et al* 2014 Spain	Case series with pre/post-test outcomes	IV	***	n=26 MJD (n=19) SCA6 SCA7	SCA3: 50.3 (13) Total: 49.3 (14.1)	Ambulant	IGF-1 therapy	12 months	Twice daily	NA	▶ SARA (I) ▶ SF36 (Q)	▶ Pre ▶ 4 months ▶ 8 months ▶ 12 months	Between groups: NA Within group: ▶ Improved SARA (p=0.013), 8 and 12 months) in SCA3* and SCA7 subgroups after 12 months (p values not provided)* ▶ SF36: 18.5% were dissatisfied, 14.8% had poor satisfaction, 37% had fair satisfaction, and 29.6% showed high satisfaction over study durations
Takei *et al* 2004 Japan	Case series with pretest/post-test outcomes	IV	***	n=10 MJD	41.9 (2.4)	Ambulant and non-ambulant	Tandospirone 15 mg/day, increased to 30 mg/day after 1 week	7 Week 0–1: Nil therapy Week 1–4: Tandospirone Week 5: Withdrawal Week 6–7: Follow-up with Tandospirone	Once daily	NA	▶ ARS (I) ▶ TLT (A) ▶ SDS (Q) ▶ Leg pain questionnaire (I)	▶ ARS: Week 0, 4, 5, 7 ▶ SDS: Week 0, 4, 5, 6 ▶ Leg pain questionnaire: Week 0, 4, 5, 6 ▶ TLT: Week 0– 7	Between groups: NA Within group: ▶ Improved ARS (from week 3) and SDS (from week 2) (p<0.05)*; Increased ICARS in withdrawal but decreased significantly to lower than pre-therapy level after restart (p<0.05)* ▶ TLT reduced in 5/7 patients more than 10% ▶ Leg pain alleviated in 5/7 patients (significance level not provided) ▶ Not significant: SDS
Takei *et al* 2010 Japan	Case series with pre-test/post-test outcomes	IV	**	n=39 MJD (n=14) SCA1 SCA2 SCA6 MSA-C MSA-P	52.4 (14.5)	Ambulant	Tandospirone 15 mg/day	4	Once daily	NA	▶ ICARS (I) ▶ TLT (A) ▶ SDS (Q)	▶ Pre and post	Between groups: NA Within group: ▶ Improved ICARS (p=0.005) (MJD)*, TLT (p=0.002) (MJD)* ▶ SDS (significance not reported): 5/14 MJD scored>50 indicating depression; 3/5 improved to<50 after therapy
Tsai *et al* 2017 Taiwan	Case series with pretest/post-test outcomes	IV	****	n=7 MJD (n=6) MSA-C	41.57 (range 21–66) SD not reported	Not stated	Adipose mesenchymal stem cells	Once	Once	NA	▶ SOT—posturography (A) ▶ SARA (I)	▶ 1 month before baseline ▶ 0.5, 1, 3, 6, 9 and 12 months after AD-MSC	Between Groups: NA Within group: ▶ Improved SOT (p<0.05 at 3 and 6 months) (MJD)* ▶ Not significant: SARA
Yang *et al* 2011 China	Case series with pretest/post-test outcomes	IV	***	n=30 MJD (n=5) SCA1 SCA2 SCA6 Unknown FA	43.14 (12.77)	Not stated	Stem cell treatment+balance training	4–6 weeks	Stem cells: 4– 6 times (5–7 day interval) Balance training: Twice daily	Stem cells; 15–30 min Balance training: 30 min/session	▶ BBS (A)	▶ Pre and post	Between groups – NA Within group: ▶ Improved BBS (p=0.0001)*

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Table 3 Continued

Staying strong domain: searching for good medicine

Study characteristics				Participant characteristics			Intervention				Measurement and outcomes		
Author, year, country	Design	Level of evidence NHMRC	Quality MMAT	Participants (n=); diagnosis	Age (y) *mean (SD)*	Mobility status	Description	Duration (week)	Frequency (/week)	Intensity	Outcome measures	Assessment timepoints	Significant outcomes
Berntsson *et al* 2017 Scandinavia	Qualitative	III (JBI)	***	n=4 MJD (n=1) SCA4 SCA FA	56.7 (range 51–72) SD not reported	Not stated	NA—qualitative investigation on patients' experiences with cerebellar ataxia and intrathecal baclofen	NA	NA	NA	Overall theme: Living in the present/taking 1 day at a time. Main categories: 1. Uncertainty about the future 2. Impact on life as a whole 3. Feeling forced to terminate employment 4. Limiting daily activities: helped manage cramps =+ve impact on mobility 5. Intrathecal baclofen therapy: 3/4 recommended baclofen. Other participant not discussed. +ves: improved control of body, improved sleep quality -ves: Increased body weight		

Staying strong domain: keeping yourself happy

Study characteristics				Participant characteristics			Intervention				Measurement and outcomes		
Author, year, country	Design	Level of evidence NHMRC	Quality MMAT	Participants (n=); diagnosis	Age (y) *mean (SD)*	Mobility status	Description	Duration (week)	Frequency (/week)	Intensity	Outcome measures	Assessment timepoints	Outcome
Lo *et al* 2016 Taiwan/USA	Case series with pretest/post-test outcomes	IV	****	n=295 MJD (n=123) SCA1 SCA2 SCA6	SCA3: 51.1 (12.4)	Not stated	No intervention. Evaluated the prevalence and influence of depressive symptoms on people with SCA	NA	NA	NA	▶ SARA 9I) ▶ UHDRS-IV (A) ▶ PHQ-9 (Q) ▶ EQ-5D (Q)	▶ Baseline ▶ 6 months ▶ 12 months ▶ 18 months ▶ 24 months	▶ Depression common in SCAs (26%); significantly higher in SCA3 ▶ Depression associated with SARA but did not significantly progress over time or deteriorate with increased CAG repeats ▶ Depression significantly impacted negatively on functional status and QOL in all SCAs, independent of ataxia progression
Sawant and Gokhale 2015 India (also reported in 'exercising your body')	Case series with pretest/post-test outcomes	IV	***	n=3 MJD (n=1) Hereditary SCA	24.6 (3.4)	Ambulant	Occupational therapy+intensive functional physical training (tailored programme meaningful to participant)	12	5 (supervised=3; home or unsupervised=2)	0.45–1	▶ BBS (A) ▶ FIM+FAM (A)	▶ Prior to intervention ▶ Post intervention	Between groups: NA Within group: ▶ Improved BBS (p=0.05)*, FIM+FAM (p=0.01)*

Symbols: (?), Participant numbers per condition not provided; ^, randomised, double-blind, placebo-controlled—dose-controlled study phase analysed only; +, combined with; *, significance change <0.005.
ABC, Short version of Activities-specific Balance Scale; ACRS, Ataxia clinical rating scale; 4-AP, 4-Aminopyridine; BAI, Beck Anxiety Inventory; BARS, Brief Ataxia Rating Scale; BBS, Berg Balance Scale; BDI, Beck Depression Inventory; BESTest, Balance Evaluation System Test; BORG, Borg rating of perceived exertion scale; BOS, base of support; CCFS, Composite Cerebellar Functional Score; CGI, Clinical Global Impression; COM, Centre of MASS; CPET, Cardiopulmonary Exercise Test; CV, cardiovascular; DGI, Dynamic gait index; EDSS, Extended Disability Status Scale of Kurtzke; EFAP, Emory Functional Ambulation Scale: Obstacle subtask; EQ-5D, EuroQol health related quality of life measure; Exp, experimental group; FA, Friedreich's ataxia; FIM, Functional Independence Measure; FIM+FAM, Functional Independence Measure + Functional Assessment Measure; 25FWT, Timed 25-foot walk test; 9HPT, 9-hole peg test; 9HPT, 9-hole peg test; ICARS, International Cooperative Ataxia Rating Scale; IGF-1, Insulin-like growth factor; INAS, Inventory of Non-Ataxia Symptoms; JBI, Joanna Briggs Institute Levels of Evidence for Meaningfulness; Katz ADL, Katz index of independence in activities of daily living; LTG, Lamotrigine; mEQ/L, milliequivalents per litre; MFES, Modified Falls Efficacy Scale; mg, milligrams; MJD, Machado-Joseph disease; MMAT, Mixed Methods Appraisal Tool; MSA-C, multisystems atrophy-cerebellar ataxia predominates; MSA-P, multisystems atrophy-Parkinson's type; 6MWT, 6-minute walk test; 8MWT, 8-minute walk test; 10MWT, Timed 10m walk test; NESSCA, Neurological Examination Score for SCA; NHMRC, National Health and Medical Research Council; OLS, one leg standing; OPCA, olivopontocerebellar atrophy; PBWS, partial body weight support; PGI, Patient Global Impression; PHQ-9, Patient health questionnaire; QOL, quality of life; RCT, randomised controlled trials; ROM, Range of movement; S, Significant difference within groups; SAOA, sporadic adult-onset ataxia of unknown origin; SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; SCAFI, SCA Functional Index: Incudes 9HPT, 8MWT, PATA syllables within 10 sec test (PATA); SDS, Self-rating depression scale; SF36, short form 36 health survey; SOT, sensory organisation test; TGI, Tandem Gait Index; TLT, total length travelled; TMS, Transcutaneous Magnetic Stimulation; TUG, Timed Up and Go Test; UHDRS-IV, Unified Huntington's Disease Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; WHOQOL-BREF, World Health Organisation Quality of Life Questionnaire.

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Table 4 Quality assessment of included studies using the Mixed Methods Appraisal Tool (MMAT)*

	Qualitative				Quantitative RCT				Quantitative non-random				Quantitative descriptive					
Author(s)†	Sources of data	Process for analysis	Context	Researchers' influence	Randomisation	Blinding	Outcome data	Dropout rate	Selection bias	Appropriate measurements	Compared groups	Outcome data	Source strategy	Methods of analysis	Context	Reflexivity	Total	Score
Arpa *et al* 2015									1	1	1	1					4/4	100
Assadi *et al* 2007					0	1	1	1									3/4	75
Berntsson *et al* 2017	0	1	1	1													3/4	75
Conte *et al* 2017									1	1	1	1					4/4	100
de Oliveira *et al* 2015									1	1	1	1					4/4	100
de Oliveira *et al* 2018									1	0	1	0					2/4	50
Fonteyn *et al* 2014									1	1	1	1					4/4	100
Giordano *et al* 2013									0	1	0	1					2/4	50
Im *et al* 2017									1	1	1	1					4/4	100
Kaut *et al* 2014					1	1	1	1									4/4	100
Lei *et al* 2016					0	0	1	1									2/4	50
Leonardi *et al* 2017									1	1	1	1					4/4	100
Liu *et al* 2005									0	1	1	1					3/4	75
Lo *et al* 2016													1	1	1	1	4/4	100
Monte *et al* 2003									0	1	0	1					2/4	50
Sanz-Gallego *et al* 2014									1	1	1	0					3/4	75
Saute *et al* 2014					1	1	1	1									4/4	100
Sawant and Gokhale 2015									0	1	1	1					3/4	75
Schulte *et al* 2001					0	0	1	1									2/4	50
Shiga *et al* 2002									0	1	1	1					3/4	75
Silva *et al* 2010									1	1	1	1					4/4	100
Tabbassum *et al* 2013									0	1	0	0					1/4	25
Takei *et al* 2004									0	1	1	1					3/4	75
Takei *et al* 2010									0	1	1	0					2/4	50
Tsai *et al* 2017									1	1	1	1					4/4	100
Wang *et al* 2018					1	1	1	1									4/4	100
Wessel *et al* 1997					0	1	1	1									3/4	75
Yang *et al* 2011									1	0	1	1					3/4	75
Zesiewicz *et al* 2012					1	1	1	0									3/4	75

*A mixed-methods studies column was not included as no mixed-method studies were reviewed.
†D'Abreu *et al* 2010 was not scored (expert opinion excerpt).
1, criterion met; 0, criteria not met or unable to determine; RCT, randomised controlled trials.

Study setting

Of the 27 experimental studies, 12 were conducted under supervision of a health professional in the outpatient setting,[40 46–49 52 56 59 60 62 63] two of which included an additional unsupervised home programme.[52 63] In the remaining 15 studies, participants self-administered medications in their homes.[30 42–45 49–51 53 54 64 65] The qualitative[37] and longitudinal observational studies[61] were conducted face to face in an outpatient Neurology clinic. Study setting was not relevant to the expert opinion excerpt.[1] Assessments were carried out in the inpatient setting in three studies,[41 55 57] outpatient setting for 12 studies,[30 42–45 49–51 53 54 64 65] both in two studies,[41 57] while all follow-up took place in the outpatient setting.

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Table 5 Summary of outcome measures and results+

		Wang *et al*	Kaut *et al*	Conte *et al*	Tabbassum *et al*	Fonteyn *et al*	Im *et al*	Leonardi *et al*	de Oliveira *et al* 2018	de Oliveira *et al* 2015	Sawant and Gokhale 2015	Silva *et al*	D'Abreu *et al*	Assadi *et al*	Lei *et al*	Saute *et al*˜	Schulte *et al*	Wessel *et al*	Zesiewicz *et al*	Shiga *et al*	Liu *et al*	Arpa *et al*	Giordano *et al*	Monte *et al*	Sanz-Gallego *et al*	Takei *et al*	Takei *et al*	Tsai *et al*	Yang *et al*	Berntsson *et al*	Lo *et al*
Impairment	ACRS																NS	NS													
	BARS								NR																						
	ICARS						*							NS											*	*				
	INAS		NS																												
	Leg pain questionnaire																								NR						
	NESSCA											NS				NS															
	SARA	*	*			*		*	NS			NS			*	NS			*BG			*	NS	*			NS			X
Activity	6MWT							*																							
	8MWT															NS							*								
	ABC					NS																									
	Barthel Index											NS				NS															
	BBS					NS			*	*	*																		*		
	BEStest				*BG	NS																									
	BORG								NS																						
	CCFS															*BG															
	CGI*																		NS												
	CPET								*ˆ																						
	DGI								*																						
	EDSS																							NS							
	EFAP					*																									
	Energy recovery/expenditure			*																											
	FIM/FIM-AM										*	NS																			
	Kinematic recordings			*																											
	ˆLimit of stability test	NR																													
	MFES (Falls)	NS																													

Continued

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Table 5 Continued

		Wang *et al*	Kaut *et al*	Conte *et al*	Tabbassum *et al*	Fonteyn *et al*	Im *et al*	Leonardi *et al*	de Oliveira *et al* 2018	de Oliveira *et al* 2015	Sawant and Gokhale 2015	Silva *et al*	D'Abreu *et al*	Assadi *et al*	Lei *et al*	Saute *et al*^	Schulte *et al*	Wessel *et al*	Zesiewicz *et al*	Shiga *et al*	Liu *et al*	Arpa *et al*	Giordano *et al*	Monte *et al*	Sanz-Gallego *et al*	Takei *et al*	Takei *et al*	Tsai *et al*	Yang *et al*	Berntsson *et al*	Lo *et al*
	Muscle coactivation (EMG)			*																										
	Obstacle avoidance success					*																								
	OLS																				*									
	No of falls					NS																								
	Posturography															NS										*				
	SCAFI	*													*BG						*									
	Spatiotemporal gait parameters	NR		*			*	*																						
	Standing capacity																		*BG											
	25FWT																		*BG											
	10MWT					NS													*BG											
	TGI/tandem steps																		*BG	SS										
	Total length travelled																									*	*			
	Treadmill inclination (%)								*																					
	TUG					NS																								
	UHDRS-IV																													X
	UPDRS																						NS							
	Walking capacity																			NS										
QOL#	BAI																		NS											
	BDI															NS			*BG											
	EQ-5D																					NS								X
	Experience of training Q					NR																								
	Hamilton rating scale											*																		
	KATZ ADL								NS																					
	PGI global impression															NS			NS											
	PHQ-9																													X
	SDS																								NR	NR				
	SF36										NS	NS						NR												
	WHOQOL-Bref										X	NS																		

Symbols: *, significant difference within groups or significant difference presingle and postsingle group; *BG, significant difference between groups; *^, significant difference in CEPT duration. No significant change in VE peak or VO2 max; ^, activity and impairment measure; #, includes measures for depression, well-being and overall health; +, Note: only outcome measures clinically relevant to function and mobility shown (ie imaging results for brain glucose metabolism and brain metabolite ratios have been excluded); X, relationship between variables assessed only. Nil intervention. See table 3 for findings.

ABC, Short version of Activities-specific Balance Scale; ACRS, Ataxia Clinical Rating Scale; BAI, Beck Anxiety Inventory; BARS, Brief Ataxia Rating Scale; BBS, Berg Balance Scale; BDI, Beck Depression Inventory; BES test, Balance Evaluation System Test; BORG, Borg Rating of Perceived Exertion Scale; CCFS, Composite Cerebellar Functional Score; CGI, Clinical Global Impression; CPET, Cardiopulmonary Exercise Test; DGI, Dynamic Gait Index; EDSS, Extended Disability Status Scale of Kurtzke; EFAP, Emory Functional Ambulation Scale: Obstacle subtask; EQ-5D, EuroQol health related quality of life measure; FIM/FIM-AM, Functional Independence Measure + Functional Assessment Measure; 25FWT, 25-foot walk test; ICARS, International Cooperative Ataxia Rating Scale; INAS, Inventory of Non-Ataxia Symptoms; KATZ ADL, Katz index of independence in activities of daily living; MFES (Falls), Modified Falls Efficacy Scale; 6MWT, 6-min walk test; 8MWT, 8 metre walk test; 10MWT, Timed 10 min walk test; NESSCA, Neurological Examination Score for SCA; OLS, one leg standing; PGI, Patient Global Impression; PHQ-9, Patient health questionnaire; Q, questionnaire; QOL, quality of life; SARA, Scale for Assessment and Rating of Ataxia; SCAFI, SCA Functional Index: Incudes 9HPT, 8MWT, PATA syllables within 10s test (PATA); SDS, Self-rating Depression Scale; SF-36, Short form 36 health survey; TUG, Timed Up and Go Test; UHDRS-IV, Unified Huntington's Disease Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; WHOQOL-BREF, World Health Organisation Quality of Life Questionnaire.

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Interventions

A range of interventions have been explored, both pharmacological and non-pharmacological. Overall, no pharmacological interventions are currently recommended for use by indivudals with MJD. Non-pharmacological, exercise-based interventions, have had a positive impact on walking and moving around. Intervention types have been described under each of their corresponding domains in the 'Staying Strong' Framework (see table 3 and online supplementary table 1). In relation to the International Classification of Functioning, Disability and Health framework,[67] no interventions in this review targeted the participation level, but focussed predominantly on the body functions and structures level and activity level.

Exercising your body

Thirteen studies discussed interventions which aligned with 'exercising your body'.[1 40 46–48 52 56–60 62 63] Exercise in general was reported to be beneficial in one study.[1] Specific interventions could be separated into three types of training: (1) walking training, (2) task specific training and (3) balance training. All studies related to 'exercising your body' reported significant findings, although only three of the 13 studies had a control group. Interventions varied in type, duration and frequency. Intervention sessions occurred on average for 51 min duration, 2.7 times a week for 8 weeks. Dosages such as repetitions completed per session or intensity, in terms of effort per session, were not reported. Rest periods were reported in one study.[47]

Walking practice

Four studies investigated interventions that aligned to walking practice[47 56 58 59] including training on a treadmill,[56 58] over ground walking[59] and walking with a wide base of support.[47] All significantly improved either balance,[47 58] ataxia[56 59] and/or walking ability.[47 56 59]

Task-specific training

Two studies investigated task-specific training through ADL training alone[52] or in combination with strength, balance, coordination, walking and cycling training.[63] ADL training alone significantly improved depression scores,[52] but when combined with other task-specific training, balance and function also improved significantly after 12 weeks.[63]

Balance practice

Six studies explored interventions to challenge balance: balance training alone[62] or in conjunction with 'exergames'[40]; a wearable proprioceptive stabiliser[60]; core stability training[48]; stochastic vibration therapy[46] and task-specific training.[63] Significant improvements (both between and within groups) in balance,[48 62] ataxia severity[40 46 60] and walking[46 60] were found. One study combined stem cell therapy with balance training (see below in 'searching for good medicine').[57]

Searching for good medicine

Seventeen studies evaluated interventions that aligned with 'searching for good medicine'. Fourteen different pharmacological interventions were explored, one in combination with balance training,[57] as well as one non-pharmacological intervention (transcutaneous magnetic stimulation (TMS)). No studies evaluated traditional medicine or complementary medicine use.[68] One study (expert opinion) recommended medications to minimise the sequalae of impairments as a result of MJD (ie, levodopa for dystonia, pain relief for pain).[1] While some therapies demonstrated potential to reduce ataxia (valproic acid,[41] lithium carbonate,[42] varenicline)[45] and improve function (lithium carbonate,[42] TMS),[49] efficacy had not been demonstrated. None of the interventions were recommended for use by individuals with MJD[9] (table 3).

Keeping yourself happy

Two studies aligned with 'keeping yourself happy'.[37 61] Depression was found to have a significant negative impact on functional status and QOL, independent of ataxia, with suicidal ideation more common in MJD than in SCA1, SCA2 or SCA6.[61] Participants living with ataxia shared the devastating impact of the disease on their social life, mood, parental roles, ADLs and employment, but recommended living in the present and taking 1 day at a time.[37] Exercise was reported to help individuals with MJD cope and gain a sense of control over their disease.[1] However, only one study explored individualised interventions designed to promote both physical and psychosocial well-being.[52] Nine studies included measures of QOL or depression to evaluate their intervention[42 43 45 52–54 58 64 66] but only two studies[53 54] demonstrated significant improvements in those measures (table 5).[53 54] The remainder reported either non-significant findings or did not report significance levels.

Something important to do

Two studies aligned with having 'something important to do'. Support from employers was important to maintain work roles.[37] Loss of meaningful employment, lack of support from employers or changes to roles as a parent or provider had a negative impact on mood and identity.[37] Only one study evaluated an intervention tailored to the goals/needs of the participant.[52] Depression scores improved, but measures of function and QOL failed to reach significance.[52] No other included studies explored goal orientated or task-specific training or training based on individual goals/priorities/interests.

Going country

No studies aligned with 'going country'. All studies were conducted either in a hospital or research facility with the exception of two studies that included an unsupervised home programme.[52 63] No studies were found that explored 'going country', community participation, community engagement, vocational rehabilitation, outdoor mobility, sport and/or recreation in relation to mobility for individuals with MJD.

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Families helping each other

No studies aligned with 'families helping each other'. No studies considered the influence of family support, interventions or rehabilitation with family, or the role of families in supporting mobility and function for individuals with MJD.

DISCUSSION

The purpose of this review was to map the range of interventions/strategies trialled for people with MJD to enhance walking and moving around and to align those interventions with the 'Staying Strong' Framework developed by individuals and families with MJD from the Groote Eylandt Archipeligo. Studies were typically of low quality and focused on what is largely staying strong on the outside: 'exercising your body' (walking training, balance training or task-specific training) and 'searching for good medicine' (various oral medicines, injectable medicines and non-pharmacological medicines). Few studies explored the impact on mobility of having 'something important to do' (ie, goal orientated, or task specific training based on individual goals/priorities/interests) or strategies for 'keeping yourself happy'. No studies in this review considered the impact on mobility of 'going country' (community participation, outdoor mobility, sport/recreation) or 'families helping each other' (the impact or relationship of family support on functional mobility). This review thereby highlights an opportunity for meaningful, individualised, person-centred interventions to promote physical and psychosocial function, consistent with the views of families with MJD in Australia,[18] and those living with ataxia in other parts of the world.[69 70]

Exercising your body

Overall, exercise or physical activity interventions were found to have positive effects on mobility for individuals with MJD and to be generally safe, inexpensive and in current use. The most effective interventions and the optimal dosage could not be determined, due to heterogeneity of outcome measures and study designs. However, studies that engaged participants in at least 50 min training, at least 2–3 times each week, for approximately 4 weeks, demonstrated improvement. This finding is consistent with ataxia research more broadly, that has shown higher intensity rehabilitation to be more effective (60 min, 2 days per week) than less intensive training.[11] Interestingly, no studies evaluated incidental physical activity or participants' level of activity outside of the intervention, unlike studies in other progressive conditions including Huntington's disease (HD), multiple sclerosis and Parkinson's disease (PD) literature.[71 72] Programmes and interventions that promote participation and an active lifestyle have well known benefits on mobility and well-being for individuals living with neurological disorders.[73] Yet the amount of exercise suggested to bring benefit for people with MJD and other ataxias[11] suggests that lifestyle-orientated programmes that extend well beyond a 4-week intervention are required.[74]

Searching for good medicine

Consistent with perspectives of families with MJD from the Groote Eylandt Archipelago,[18] this review highlights the continued search for good medicine for individuals with MJD. The impact of traditional medicines or nutritional supplements on functional mobility for those with MJD has not been studied as it has in HD and PD.[75 76] Furthermore, none of the many medications that were evaluated are currently indicated for MJD with most studies assessing drug safety with small samples. Notwithstanding, in this review, individuals with MJD were better represented in pharmacological studies than in studies on physiotherapeutic interventions. While large sample size recruitment is an inevitable challenge in rare disease research,[16] sample homogeneity within studies will be important moving forward to generate strong clinical recommendations for those with MJD.[9] Consistent with other ataxias, current recommendations for pharmacological management for those with MJD relate largely to managing the sequalae of disease, such as spasticity, sleeping difficulties and incontinence.[1 9]

Going country

In this study and across all SCAs, research to explore community-based interventions in the context of an individual's environment or lifestyle is lacking, despite known benefits of engagement in sport, recreation and leisure activities for those with disabilities.[77] Dance and participation in sport are some activities that have been evaluated for those with other neurodegenerative conditions.[78 79] While *going country* may be culturally and contextually specific to Aboriginal families with MJD in the Top End of Australia, individuals with ataxia in other parts of the world share similar views, relevant to their own context.[80] Participation in outdoor sports, self-developed exercises, team sports or community-based exercise classes, while beneficial physically, have also been found to promote self-esteem and well-being.[70] Outdoor activities have helped individuals with ataxia manage depression and focus on living life to the fullest.[70] Individuals with MJD generally remain ambulant up to 10 years following onset of symptoms,[4] leaving opportunities for engagement in sport and recreational activities outside of a facility and in the community. Impairment focused intervention programmes restricted to indoor clinical facilities may overlook functional benefits that could be gained through participation in interventions that are fun, enjoyable and meaningful to the person.[70 81] Research to evaluate the benefits of such interventions on mobility is warranted, for those with MJD and HAs more broadly.

Something important to do and keeping yourself happy

Disappointingly, having 'something important to do' and 'keeping yourself happy' were discussed minimally in the literature. The impact of depression on QOL for people

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with SCAs is alarming, particularly the significantly higher rates of suicidal ideation for those with MJD.[61] While a number of studies in this review included measures of depression and QOL,[42 43 45 52–54 58 64 66] interventions tested appeared to have little impact on either. The sensitivity of the measures used over the generally short intervention period should be taken into consideration.[82] On the other hand, this may highlight a need for more individualised interventions that target both physical and psychosocial well-being more effectively. The importance of self-selected meaningful exercise has been echoed by individuals with other degenerative ataxias, finding self-chosen activities that offer physical challenge and personally meaningful rewards, provide a sense of achievement, satisfaction and motivation to carry on.[70] While evaluation of the efficacy of individualised interventions does present challenges,[83] programmes such as ParkFIT for PD in the Netherlands[84 85] and Engage-HD for people with HD in the UK[71] have provided examples on how these challenges can be overcome.[73]

Families helping each other

It is perhaps surprising, considering MJD is an autosomal-dominant disease, that no studies discussed the inclusion of family members as study participants. The devastating impact families face with autosomal-dominant neurodegenerative diseases is well known.[86–88] While family support, peer socialisation and support through physical activity is a facilitator for engagement in physical activity for people with neurodegenerative diseases,[89] no studies in this review discussed these factors. Furthermore, no studies evaluated group-based interventions, although the involvement of peers or family members in physiotherapeutic interventions can enhance motivation, social support and long-term participation in physical activity.[90] There is no doubt that the role of families is worthy of further investigation.

Outcome measures

Consensus and validation of outcome measures for individuals with MJD is required, with consideration given to outcomes in terms of all the domains of the 'Staying Strong' Framework. Reaching agreement on recommended outcome measures for people with MJD will be an important step for future clinical trials and development of clinical guidelines for management of MJD over the course of the disease. Guidelines for people with inherited ataxias have been developed,[91] as have guidelines for those with Friedreich's ataxia,[92] but the particular issues individuals and their families with MJD face require specific attention.

Limitations

There were few studies that contained participants exclusively with MJD, so it is difficult to draw conclusions specifically for people with MJD. However, the findings do highlight the dearth of evidence relating to walking and moving around for individuals with MJD. While there may be interventions trialled that have had a positive impact on functional mobility, they are yet to be evaluated. Additional studies may exist that focus on domains such as having 'something important to do', 'keeping yourself happy' and 'families helping each other', but these may not have been found on initial searches if they did not include a functional mobility-related keyword. However, search strategies in this review were used to identify interventions that promoted functional mobility through staying strong both on the inside and outside.

CONCLUSION

This scoping review mapped studies that investigated the range of interventions to keep people with MJD walking and moving around. Findings were compared with 'what works best' according to families with MJD from the Groote Eylandt Archipelago. Interventions which aligned with their 'Staying Strong' Framework[18] were largely limited to staying strong on the outside (physically), with little reflection on staying strong on the inside (emotionally, mentally and spiritually). The findings of this review suggest future research is required to investigate the benefit of lifestyle activity programmes that address both physical and psychosocial well-being for families with MJD. Detailed reporting on the physical and psychosocial aspects of these interventions, and on the development and delivery of these programmes will help guide programme implementation for health service providers and clinicians working alongside families with MJD. The 'Staying Strong' Framework presented community and culturally founded needs that provided a way to identify significant gaps in the literature and highlight where those needs have not been met. Considerably more effort in culturally informed research is required.

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Acknowledgements The authors would like to acknowledge and thank Aboriginal families with MJD from the Groote Eylandt Archipelago and in Ngukurr who developed the 'Staying Strong' Framework and welcomed the researchers to their country.

Contributors Authors JJC, RNB, AL, ARC designed the study. JJC, JQ, MS and RNB were involved in study selection, quality assessment and data extraction. JJC, JL, GL and RNB collaborated on data analysis and interpretation. The manuscript was drafted by JJC, RNB, AL and ARC. All authors approved the final version of the manuscript.

Funding The authors would like to thank the MJD Foundation, Anindilyakwa Land Council and Lowitja Institute Aboriginal and Torres Strait Islander Health CRC (Lowitja Institute CRC) (grant ID: 017-SF-005) (https://www.lowitja.org.au) for funding this work.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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