# Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial

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## Summary

**Background** **Evidence suggests that brief physiotherapy programmes are as effective for acute whiplash-associated disorders as more comprehensive programmes; however, whether this also holds true for chronic whiplash-associated disorders is unknown. We aimed to estimate the effectiveness of a comprehensive exercise programme delivered by physiotherapists compared with advice in people with a chronic whiplash-associated disorder.**

**Methods** **PROMISE is a two group, pragmatic randomised controlled trial in patients with chronic (>3 months and <5 years) grade 1 or 2 whiplash-associated disorder. Participants were randomly assigned by a computer-generated randomisation schedule to receive either the comprehensive exercise programme (20 sessions) or advice (one session and telephone support). Sealed opaque envelopes were used to conceal allocation. The primary outcome was pain intensity measured on a 0–10 scale. Outcomes were measured at baseline, 14 weeks, 6 months, and 12 months by a masked assessor. Analysis was by intention to treat, and treatment effects were calculated with linear mixed models. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12609000825257.**

**Findings** **172 participants were allocated to either the comprehensive exercise programme (n=86) or advice group (n=86); 157 (91%) were followed up at 14 weeks, 145 (84%) at 6 months, and 150 (87%) at 12 months. A comprehensive exercise programme was not more effective than advice alone for pain reduction in the participants. At 14 weeks the treatment effect on a 0–10 pain scale was 0·0 (95% CI –0·7 to 0·7), at 6 months 0·2 (–0·5 to 1·0), and at 12 months –0·1 (–0·8 to 0·6). CNS hyperexcitability and symptoms of post-traumatic stress did not modify the effect of treatment. We recorded no serious adverse events.**

**Interpretation** **We have shown that simple advice is equally as effective as a more intense and comprehensive physiotherapy exercise programme. The need to identify effective and affordable strategies to prevent and treat acute through to chronic whiplash associated disorders is an important health priority. Future avenues of research might include improving understanding of the mechanisms responsible for persistent pain and disability, investigating the effectiveness and timing of drugs, and study of content and delivery of education and advice.**

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## Introduction

Whiplash-associated disorders are a large public health problem and are associated with substantial social and economic costs.[1] Findings of systematic reviews of the prognosis of the disorders show that more than half of individuals will continue to report symptoms 6 months after injury,[2] with up to 30% having moderate to severe pain and disability.[1] This group of people with chronic symptoms accounts for a disproportionately large percentage of the burden associated with whiplash-associated disorders because of continuing treatment costs and loss of productivity.[3]

Various treatments have been proposed to manage these chronic disorders; however, up to now very few randomised controlled trials have been done to assess the effectiveness of these interventions.[4] Findings of one of the few high quality randomised controlled trials[5] in this specialty have shown that radiofrequency neurotomy is effective in patients whose pain arose from zygapophyseal joints. However, neurotomies are highly technical procedures, might not provide permanent symptom relief, and even when patients are carefully selected, are effective only in some.[5] Subsequently, clinical practice guidelines recommend the use of conservative treatment approaches such as physiotherapy exercise programmes for chronic whiplash-associated disorders despite the absence of robust evidence supporting this approach.[6] Two trials[7,8] provided some evidence for the effectiveness of physiotherapy exercise programmes; however, the effects of treatments were modest; only 10–20% of patients had a successful outcome, defined as minimum to no pain and disability. On the basis of these findings, our group postulated that a comprehensive exercise programme combining aspects of both specific motor relearning and graded activity might result in greater improvements in pain and disability compared with an exercise programme alone.[9]

Evidence from studies of acute whiplash-associated disorders suggests that extended physiotherapy programmes provide no additional benefit compared with brief physiotherapy interventions. The UK MINT trial[10] showed that six sessions of physiotherapy during 8 weeks provided short-term but not long-term benefits compared with one advice session, and that the comprehensive package of physiotherapy was not cost effective from the UK National Health Service (NHS) perspective. However, whether the MINT results apply to chronic whiplash-associated disorders is unclear. Therefore, we aimed to investigate the effectiveness of a comprehensive exercise programme delivered by physiotherapists compared with one advice session and telephone support for people with a chronic whiplash-associated disorder. We also investigated whether features suggestive of CNS hyperexcitability or psychological distress changed the effect of treatment.

## Methods

### Study design and participants

PROMISE is a two-group, pragmatic randomised controlled trial in which participants were recruited from sites in Sydney and Brisbane, Australia, between Sept 21, 2009, and Feb 27, 2012, with follow-up at 14 weeks, 6 months, and 12 months. Ethics approval was obtained from the University of Sydney (03–2009/11509) and the University of Queensland human research ethics committees (2008002059). All participants gave written informed consent before study entry. The study protocol has been previously published.[9]

Participants were recruited by advertisements in local and metropolitan newspapers, radio, and online media. The Motor Accidents Authority of New South Wales Australia, Motor Accident Insurance Commission Queensland Australia, QBE Insurance, and trial clinics assisted with recruitment by inviting by mail potentially eligible clients to participate. The Motor Accidents Authority and Motor Accident Insurance Commission are statutory authorities that regulate compulsory third party personal injury insurance schemes for motor vehicles registered in the states of New South Wales and Queensland.

See Online for appendix

Patients were eligible for inclusion if they met all the following criteria: grade 1 or 2 whiplash-associated disorder of at least 3 months' but less than 12 months' duration, feeling at least moderate pain or moderate activity limitation because of pain (modified items seven and eight of Short Form 36 survey[11]), not receiving care for whiplash-associated disorder (excluding drugs), aged between 18 and 65 years, proficient in written and spoken English, and able to attend four assessment sessions at the trial centre. Because of recruitment difficulties, 6 months after the start of the trial the eligibility criterion relating to the duration of symptoms was changed from less than 12 months to less than 5 years.

Exclusion criteria were known or suspected serious spinal disease (eg, metastatic disease of the spine), nerve root compromise (grade 3 whiplash-associated disorder), confirmed fracture or dislocation at time of injury (grade 4 whiplash-associated disorder), spinal surgery in the past 12 months, any coexisting medical disorder that would severely restrict participation in the exercise programme (eg, traumatic brain injury), or any of the contraindications to exercise listed in the American College of Sports Medicine guidelines[12] as assessed with the Physical Activity Readiness Questionnaire.[12]

### Randomisation and masking

A computer-generated randomisation schedule, stratified for recruitment site (Sydney and Brisbane), was produced before the trial start by C-WCL. C-WCL was also in charge of randomly assigning recruited patients and arranging their initial physiotherapy appointment for the Sydney sites, but was not involved in participant recruitment, assessment, or treatment provision. This researcher did participate in analysis and interpretation of trial results, but only after masked results were re-coded to ensure all authors were masked to group allocation. To ensure allocation was concealed, participants were randomly assigned immediately after baseline assessment by opening the next sealed, sequentially numbered, opaque envelope. Participants were deemed to have entered the study at the time that the envelope was opened.

### Procedures

All participants were provided with the patient educational booklet entitled whiplash injury recovery: a self-management guide.[13] The booklet provided information about whiplash-associated disorders, advice on how to manage the symptoms, and outlined a simple exercise programme to help with reduction of associated neck pain. Additionally, participants were randomly allocated to receive advice or a comprehensive exercise programme. In the advice group, participants received a 30 min consultation with a physiotherapist during which they read the educational booklet, practised the exercises with minimum guidance (verbal or physical) from the physiotherapist, and had any questions or concerns clarified (appendix p 21). Participants were then required to implement the advice provided and practise the exercises independently at their own discretion. No additional supervision was provided. Participants had the opportunity to contact the physiotherapist by telephone on two occasions if they needed further verbal clarification of the information covered in the consultation.

In the comprehensive exercise programme group, participants received 20 individually tailored and supervised exercise sessions lasting 1 h for 12 weeks (two physiotherapy sessions per week for 8 weeks; one session per week for 4 weeks; appendix pp 69–101). The comprehensive exercise programme began with 4 weeks of specific cervical spine exercises, consisting of craniocervical flexion training, neck extensor training,

scapular training, posture re-education, and sensorimotor exercises (kinaesthetic sense, balance and eye movement control).[8] Manual therapy techniques (excluding manipulation) could be used by physiotherapists only in the first week (maximum two sessions) to correct any underlying musculoskeletal problems that would otherwise prevent the participant from being able to do the specific motor relearning exercises. Between weeks 4 and 6, participants entered a transition period in which the focus shifted from specific neck motor relearning exercises to integration of this control into functional whole body exercise. By week 7, all participants had started the graded activity programme; an individually designed, submaximum programme aimed to help participants progressively achieve their nominated functional goals. Exercises in this stage consisted of upper and lower limb muscle strength and endurance exercises, specific functional task practice (whole or part practice), and progression of the aerobic, neck flexor, and neck extensor endurance exercises.[7] Additionally, aerobic exercise was prescribed from week 1 to week 12 in a submaximum and progressive way.

Throughout the comprehensive exercise programme, specific cognitive-behavioural therapy strategies were used by the physiotherapists, who had to encourage skill acquisition by modelling, setting progressive goals, and self-monitoring, and to positively reinforce progress.[14] We used these strategies in conjunction with a progressive exercise programme to guide participants to progressively return to their pre-injury work and home activities, become more self-reliant with an improved ability to problem solve, and therefore be able to independently manage their disorder and potential flare-ups. Participants were provided with a 12 week home exercise programme that was to be completed on days they did not attend the treatment clinic. Exercises were outlined in an exercise diary, which was also used to monitor participant's compliance with the exercises.

All treatments were delivered by physiotherapists with experience in the trial treatments. Before the start of the trial, physiotherapists were trained at a 1 day workshop to give both interventions. A second training session was held halfway through the trial to ensure that both interventions continued to be given in accordance with the trial protocol (appendix pp 1–68). Every treating physiotherapist had one treatment and one advice session audited by experts in the specialty to ensure treatment fidelity.

## Outcomes

All outcome measures were obtained by an investigator who was unaware of group allocation at baseline, 14 weeks, 6 months, and 12 months after randomisation. Demographic characteristics such as age, employment, medical history, present drugs, previous investigations and treatment, and information about whiplash-associated disorder symptoms, including accident history, and compensation status were obtained at baseline assessment.

The primary outcome was the average pain intensity during the preceding week before outcome assessment measured with a 0 (no pain) to 10 (worst possible pain) numerical rating scale.[15] Secondary outcomes were average pain intensity over the past 24 h,[15] self-rated recovery (–5=vastly worse, 0=unchanged, 5=completely recovered),[16] disability measured with the ten item Neck Disability Index (scale range 0–100),[17] and the 13 item Whiplash Disability Questionnaire[18] (scale range 0–130), quality of life measured with the Short Form 36,[11] with summary scores standardised with Australian normative values (population mean=50, SD=10),[19] functional ability measured with the Patient-Specific Functional Scale (scale range 0–10),[20] and cervical spine range of motion measured with an inclinometer.[21] We identified serious adverse events (defined as an event that is life threatening, requires inpatient hospitalisation, or will result in persistent or significant disability or incapacity) and adverse effects (defined as an exacerbation of a pre-existing condition such as neck pain or headache) of treatment with open-ended questioning at the 3 month follow-up assessment.

We obtained measures of CNS hyperexcitability and psychological distress at baseline and at every follow-up assessment to investigate the effect of these factors on treatment effect. To measure neuropathic pain, we used the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) pain scale score,[22] pressure pain threshold measured over the cervical spine (C5 spinous process) and tibialis anterior (bilateral) with a pressure algometer (Somedic AB, Hörby, Sweden),[23] and cold pain threshold measured bilaterally over the cervical spine (level C3 to C7) with a Thermotest system (Somedic AB).[24] To measure psychological distress, we assessed symptoms of post-traumatic stress with the Posttraumatic Stress Diagnostic Scale,[25] and symptoms of catastrophising measured with the Pain Catastrophising Scale.[26]

## Statistical analysis

The sample size of 172 participants was calculated a priori and took into account both the treatment effectiveness and effect modification analyses. This sample size provided 80% power to detect a difference of 1 unit for the effectiveness analyses and 2 units for the effect modification analyses for the primary outcome of pain intensity (estimated SD 2·0, on the basis of previous trials that recruited similar patient cohorts).[7,8] This calculation assumed an $\alpha$ of 0·05 and allowed for up to 10% loss to follow up and 10% treatment non-compliance.

The analyses followed a pre-specified protocol.[9] All data were double-entered and analyses were done on the locked data file. The statistical analyses were done with IBM SPSS Statistics (version 21.0.0.0) by intention to treat. The investigator who did the analyses was masked

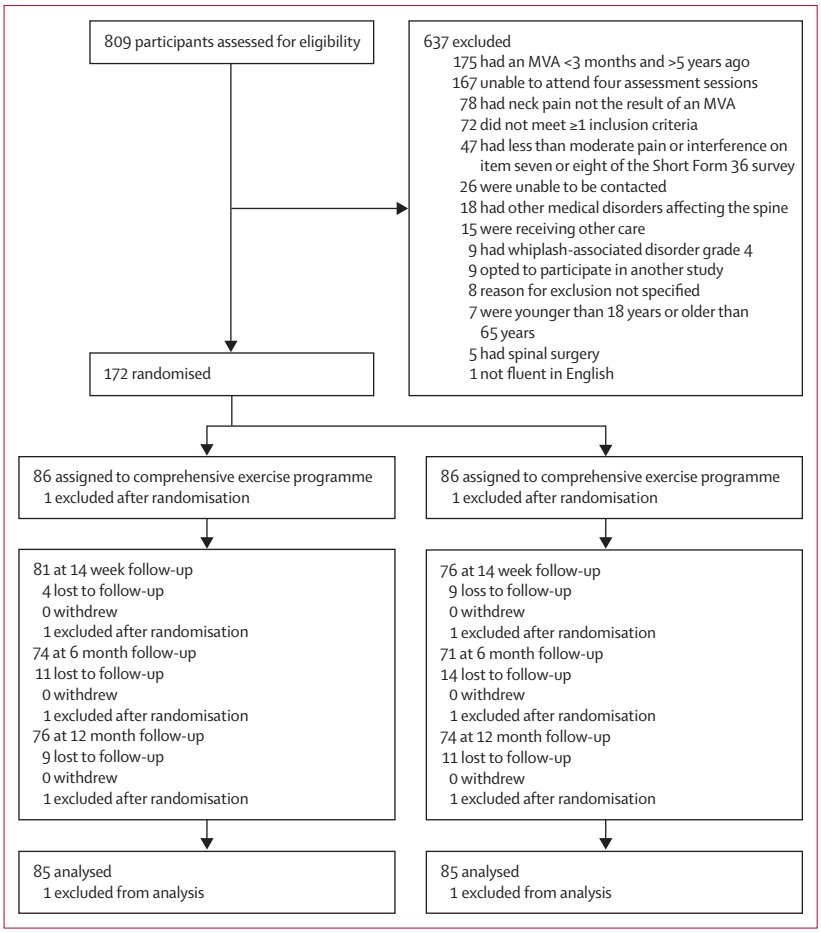


***Figure:*** **Trial profile**
MVA=motor vehicle accident.

to group allocation. All analyses were double checked by a second independent investigator. The mean effects of the intervention on pain, function, disability, global perceived effect, and quality of life were calculated with linear mixed models that incorporated terms for participant, clinician, treatment group, time, and treatment by time interactions. Treatment effect modification was tested by adding the putative effect modifier to the model and a treatment by effect modifier interaction term. We used an independent *t* test to assess whether self-rated recovery differed significantly between groups.

Because PROMISE consisted of participants with longer duration of whiplash-associated disorders than originally pre-specified, we did a post-hoc analysis to assess if the duration of symptoms changed the effect of treatment. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12609000825257.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Recruitment ran between Sept 21, 2009, and Feb 27, 2012, with follow-up completed on Feb 27, 2013. The figure shows the reasons for ineligibility and the flow of participants through the trial. Of the participants who were randomly assigned, 157 participants (91%) were followed up at 14 weeks, 145 (84%) at 6 months, and 150 (87%) at 12 months. Two participants (one from each group) were later excluded when additional information about their health status emerged after randomisation. One participant was diagnosed with metastatic breast cancer and one was diagnosed with an upper motor neuron lesion. Knowledge of these disorders before enrolment into the study would have excluded both people from participation. 25 physiotherapists delivered the trial treatments across 20 private physiotherapy clinics (Sydney: 11 physiotherapists from eight clinics; Brisbane 14 physiotherapists from 12 clinics).

Table 1 shows baseline characteristics. Participants were mainly middle-aged, there were more women than men, and participants had their whiplash-associated disorder symptoms for nearly 2 years. More people were eligible for compensation than were not, with about a third having settled a claim. Participants typically reported moderate pain and disability and lower quality of life than the Australian population norms (table 2).[19]

No serious adverse events were reported. Adverse effects were recorded for five patients who received the comprehensive exercise programme and four who received advice. Adverse effects were headache (n=4), musculoskeletal symptoms (n=3), exacerbation of existing symptoms (n=1), and stiffness (n=1). None of the patients withdrew from the trial because of adverse effects. Compliance with treatment was good for both intervention groups; in the exercise group the median (IQR) number of comprehensive sessions attended by participants was 17 (13–20) of the maximum 20 sessions; in the advice group the median number of advice sessions and phone follow-up sessions was 1 (1–3).

Table 2 shows unadjusted outcomes and table 3 shows treatment effects at every follow-up. To help with interpretation of the size of the treatment effects, we have included the clinically worthwhile effect we specified in the trial protocol.[9] In the primary analyses the comprehensive exercise programme did not provide a benefit over advice. The point estimates of the effects of treatment were close to zero and the 95% CIs did not include a clinically worthwhile effect on pain reduction—eg, the effect at 14 weeks was 0·0 (–0·7 to 0·7) on a 0–10 pain intensity scale, whereas our pre-specified clinically worthwhile effect was 2·0 units.[9]

Most of the secondary analyses were not significant. The exceptions were the results for self-rated recovery at

| | Comprehensive exercise programme (n=85) | Advice (n=85) |
|---|---|---|
| Age (years) | 42·6 (12·3) | 43·1 (12·7) |
| Female | 48 (57%) | 60 (71%) |
| Duration of symptoms (months) | 20·9 (15·1) | 22·0 (18·2) |
| Position in accident | | |
| Driver | 68 (80%) | 70 (81%) |
| Front passenger | 6 (7%) | 7 (8%) |
| Back seat passenger | 3 (4%) | 4 (5%) |
| Motorbike | 2 (2%) | 1 (1%) |
| Not applicable | 2 (2%) | 2 (2%) |
| Missing | 4 (5%) | 2 (2%) |
| Aware of oncoming accident, yes | 16 (19%) | 24 (28%) |
| Collision impact | | |
| Rear end | 38 (45%) | 35 (41%) |
| Rear and front | 7 (8%) | 10 (12%) |
| Front end | 21 (25%) | 20 (24%) |
| Side | 13 (15%) | 17 (20%) |
| Not applicable | 1 (1%) | 1 (1%) |
| Missing | 5 (6%) | 2 (2%) |
| Stationary at time of impact, yes | 43 (51%) | 45 (52%) |
| Neck pain after accident started | | |
| Immediately | 31 (37%) | 30 (35%) |
| Within 24 h | 44 (52%) | 35 (41%) |
| After 24 h | 9 (11%) | 20 (24%) |
| Missing | 1 (1%) | 0 (0%) |
| Restriction in neck movement | | |
| Not at all | 10 (12%) | 3 (4%) |
| Mildly | 11 (13%) | 15 (18%) |
| Moderately | 33 (39%) | 32 (38%) |
| Severely | 31 (37%) | 33 (39%) |
| Missing | 0 (0%) | 2 (2%) |
| Neck restriction after accident started | | |
| Immediately | 20 (24%) | 22 (26%) |
| Within 24 h | 46 (54%) | 36 (42%) |
| After 24 h | 17 (20%) | 26 (31%) |
| Not applicable | 1 (1%) | 0 (0%) |
| Missing | 1 (1%) | 1 (1%) |
| Loss of consciousness, yes | 5 (6%) | 8 (9%) |
| Admitted to hospital after accident, yes | 15 (18%) | 20 (24%) |
| Investigations, n (%)* | | |
| X-ray | 60 (71%) | 60 (71%) |
| CT | 28 (33%) | 32 (38%) |
| MRI | 24 (28%) | 24 (28%) |
| Previous treatment, yes (%) | | |
| Physiotherapy | 68 (80%) | 70 (82%) |
| Chiropractic | 23 (27%) | 22 (26%) |
| Massage | 37 (44%) | 46 (54%) |
| Acupuncture | 23 (27%) | 29 (34%) |
| Other (eg, osteopathy) | 18 (21%) | 18 (21%) |
| Present drugs for whiplash-associated disorder symptoms | | |
| No drugs | 27 (16%) | 19 (11%) |
| NSAID only | 31 (18%) | 40 (23%) |
| (Continues in next column) | | |
| (Continued from previous column) | | |
| NSAID and codeine | 5 (3%) | 5 (3%) |
| NSAID gel | 2 (1%) | 1 (1%) |
| Paracetamol only | 37 (22%) | 35 (20%) |
| Paracetamol combination | 7 (4%) | 4 (2%) |
| Opioid only | 7 (4%) | 6 (4%) |
| Opioid and paracetamol | 10 (6%) | 20 (12%) |
| Complementary drugs | 7 (4%) | 4 (2%) |
| Anticonvulsant | 0 (0%) | 1 (1%) |
| Benzodiazepine | 3 (2%) | 3 (2%) |
| Selective serotonin-reuptake inhibitors | 1 (1%) | 1 (1%) |
| Tricyclic antidepressant | 0 (0%) | 4 (2%) |
| Antiemetic | 0 (0%) | 1 (1%) |
| Antimigraine agent | 0 (0%) | 1 (1%) |
| Present employment status | | |
| Employed | 59 (69%) | 57 (67%) |
| Self employed | 13 (15%) | 8 (9%) |
| Home duties | 4 (5%) | 2 (2%) |
| Unemployed | 1 (1%) | 7 (8%) |
| Retired | 4 (5%) | 6 (7%) |
| Entitled leave | 1 (1%) | 3 (4%) |
| Student | 3 (4%) | 1 (1%) |
| Missing | 0 (0%) | 1 (1%) |
| Employment hours | | |
| Normal hours | 57 (67%) | 57 (67%) |
| Reduced hours because of whiplash injury | 12 (14%) | 4 (5%) |
| Not working because of whiplash | 7 (8%) | 6 (7%) |
| Not applicable | 8 (9%) | 17 (20%) |
| Missing | 1 (1%) | 1 (1%) |
| Income (AUD$) | | |
| 1–49 999 | 31 (37%) | 43 (51%) |
| 50 000–99 999 | 40 (47%) | 30 (35%) |
| 100 000–149 999 | 9 (11%) | 10 (12%) |
| > 150 000 | 5 (6%) | 2 (2%) |
| Missing | 0 (0%) | 0 (0%) |
| Compensation | | |
| No | 23 (27%) | 22 (26%) |
| Yes, compulsory third party claim | 48 (57%) | 44 (52%) |
| Yes, workers compensation | 10 (12%) | 15 (18%) |
| Yes, other (eg, personal injury claim) | 1 (1%) | 1 (1%) |
| Missing | 3 (4%) | 3 (4%) |
| Compensation settled, yes | 29 (34%) | 24 (28%) |
| Engaged services of a solicitor, yes | 36 (42%) | 34 (40%) |
| Qualification | | |
| Bachelor degree or higher | 42 (49%) | 37 (44%) |
| Diploma or certificate | 29 (34%) | 35 (41%) |
| Secondary level or lower | 14 (17%) | 12 (14%) |
| Missing | 0 (0%) | 1 (1%) |

Data are n (%) or mean (SD). 1·47 AUD$= 1US$ in 2013 (purchasing power parity, OECD). NSAID=non-steroidal anti-inflammatory drug. *Done on the neck at any time since the motor vehicle accident.

***Table 1:*** **Baseline characteristics**

For **OECD data** see http://stats.oecd.org/

| | Baseline | | 14 weeks | | 6 months | | 12 months | |
|---|---|---|---|---|---|---|---|---|
| | Comprehensive exercise programme (n=85) | Advice (n=85) | Comprehensive exercise programme (n=81) | Advice (n=76) | Comprehensive exercise programme (n=74) | Advice (n=71) | Comprehensive exercise programme (n=76) | Advice (n=74) |
| **Primary outcome** | | | | | | | | |
| Pain during previous week* | 5·5 (2·1) | 5·9 (1·9) | 3·9 (2·3) | 4·4 (2·5) | 4·4 (2·7) | 4·7 (2·3) | 3·7 (2·6) | 4·4 (2·5) |
| **Secondary outcomes** | | | | | | | | |
| Pain during previous 24 h* | 4·7 (2·0) | 5·5 (2·0) | 3·5 (2·2) | 4·0 (2·5) | 3·9 (2·7) | 4·3 (2·5) | 3·6 (2·6) | 4·1 (2·4) |
| Self-rated recovery† | N/A | N/A | 2·4 (1·6) | 1·2 (2·0) | 2·2 (2·0) | 1·3 (2·0) | 2·2 (2·0) | 1·5 (2·1) |
| Neck Disability Index score(%)‡ | 34·3 (16·3) | 37·7 (15·4) | 27·1 (17·7) | 31·3 (18·8) | 26·8 (18·0) | 31·7 (18·5) | 25·9 (19·6) | 30·0 (18·9) |
| Whiplash Disability Questionnaire score§ | 51·9 (29·3) | 59·7 (27·9) | 39·8 (29·7) | 44·9 (31·3) | 40·6 (31·4) | 45·0 (33·3) | 37·1 (32·1) | 41·6 (32·5) |
| Short Form 36 physical score¶ | 40·6 (7·8) | 39·4 (7·8) | 43·4 (9·0) | 42·6 (9·9) | 44·5 (9·7) | 43·1 (9·5) | 45·1 (9·2) | 42·7 (9·9) |
| Short Form 36 mental score‖ | 42·2 (13·4) | 41·8 (13·3) | 47·0 (12·1) | 43·7 (12·6) | 45·6 (12·3) | 44·5 (9·7) | 46·0 (12·4) | 45·3 (13·0) |
| Functional ability** | 4·0 (1·4) | 3·9 (1·6) | 5·9 (2·4) | 4·8 (2·2) | 6·0 (2·5) | 5·3 (2·5) | 6·3 (2·5) | 5·6 (2·5) |
| Cervical spine flexion (degrees)†† | 44·5 (16·1) | 44·2 (15·8) | 48·0 (16·9) | 48·1 (17·7) | 46·8 (16·3) | 48·9 (16·6) | 46·7 (15·6) | 50·8 (17·1) |
| Cervical spine extension, (degrees)†† | 42·2 (15·4) | 41·5 (17·1) | 46·0 (15·6) | 43·2 (15·4) | 46·5 (15·7) | 44·0 (15·6) | 45·6 (14·2) | 43·8 (14·4) |
| Cervical spine right rotation (degrees)†† | 53·1 (20·3) | 52·5 (20·7) | 58·5 (19·3) | 54·7 (17·4) | 59·8 (19·2) | 56·2 (18·4) | 60·2 (20·5) | 55·7 (16·9) |
| Cervical spine left rotation (degrees)†† | 53·7 (20·0) | 52·2 (18·9) | 58·2 (19·2) | 57·2 (17·4) | 60·0 (18·9) | 54·8 (18·7) | 58·6 (18·1) | 58·2 (17·6) |

Data are unadjusted mean (SD). Self-rated recovery was not measured at baseline.*Numerical pain rating scale scored from 0 (no pain) to 10 (worst pain possible). †Global perceived effect scale scored from −5 (vastly worse), 0 (unchanged), to 5 (completely recovered). ‡Neck Disability Index score: ten items, scored on a 0–50 scale, which is converted to a percentage with 0% (no disability) to 100% (high disability).§Whiplash Disability Questionnaire: 13 items, scored from 0 (no disability) to 130 (high disability).¶Physical component score from the Short Form 36 health survey (Australian population norm standardised mean=50, SD=10). ‖Mental component score from the Short Form 36 health survey (Australian population norm standardised mean=50, SD=10). **Patient-Specific Functional Scale score: average of three scores: 0 (unable to do activity) to 10 (able to do activity at pre-injury level). ††Cervical spine range of motion measured with an inclinometer, average of three measures.

***Table 2:*** **Unadjusted outcomes for each treatment group**

| | Clinically worthwhile effect | 14 weeks | 6 months | 12 months |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Pain during previous week* | 2·0 | 0·0 (−0·7 to 0·7) | 0·2 (−0·5 to 1·0) | −0·1 (−0·8 to 0·6) |
| **Secondary outcomes** | | | | |
| Pain during previous 24 h* | 2·0 | 0·3 (−0·4 to 1·0) | 0·5 (−0·2 to 1·2) | 0·2 (−0·4 to 0·9) |
| Self-rated recovery† | 2·0 | 0·7 (0·3 to 1·1)‡ | 0·9 (0·3 to 1·6)‡ | 0·8 (0·1 to 1·4)‡ |
| Neck Disability Index score(%)§ | 12 | −1·2 (−4·9 to 2·4) | −1·1 (−4·8 to 2·6) | −0·1 (−3·8 to 3·5) |
| Whiplash Disability Questionnaire score¶ | 30 | 2·3 (−4·6 to 9·2) | 3·8 (−3·2 to 10·9) | 3·2 (−3·7 to 10·2) |
| Short Form 36 physical score‖ | 15 | 0·3 (−2·3 to 2·9) | 0·7 (−1·9 to 3·3) | 1·2 (−1·4 to 3·8) |
| Short Form 36 mental score** | 15 | 2·4 (−1·0 to 5·8) | 0·0 (−3·4 to 3·4) | 0·4 (−3·6 to 3·9) |
| Functional ability†† | 1·5 | 1·0 (0·3 to 1·7)* | 0·7 (0·0 to 1·5) | 0·6 (−0·1 to 1·4) |
| Cervical spine flexion (degrees)‡‡ | .. | −1·0 (−6·0 to 3·9) | −3·2 (−8·2 to 1·9) | −4·9 (−9·9 to 0·1) |
| Cervical spine extension, (degrees)‡‡ | .. | 0·7 (−3·4 to 4·9) | 0·9 (−3·2 to 5·1) | 0·1 (−4·1 to 4·2) |
| Cervical spine right rotation (degrees)‡‡ | .. | −0·7 (−5·3 to 3·9) | 2·5 (−2·2 to 7·2) | 0·7 (−4·0 to 5·4) |
| Cervical spine left rotation (degrees)‡‡ | .. | 0·6 (−4·5 to 5·7) | 3·6 (−1·6 to 8·8) | 1·0 (−4·2 to 6·1) |

Data are point estimates and 95% CIs. The treatment effects for self-rated recovery are from an unpaired *t* test. The second column contains the clinically worthwhile effect pre-specified in the trial protocol. For outcomes for which a high score is preferred (eg, range of motion), a positive effect favours exercise, for outcomes for which a low score is preferred, a negative effect favours exercise. Range of movement is variable and no values for clinically worthwhile effect exist.*Numerical pain rating scale scored from 0 (no pain) to 10 (worst pain possible). †Global perceived effect scale scored from −5 (vastly worse), 0 (unchanged), to 5 (completely recovered). ‡Significant, p=<0·05. §Neck Disability Index score: ten items, scored on a 0–50 scale, which is converted to a percentage with 0% (no disability) to 100% (high disability). ¶Whiplash Disability Questionnaire: 13 items, scored from 0 (no disability) to 130 (high disability). ‖Physical component score from the Short Form 36 health survey (Australian population norm standardised mean=50, SD=10). **Mental component score from the Short Form 36 health survey (Australian population norm standardised mean=50, SD=10). ††Patient-Specific Functional Scale score: average of three scores, 0 (unable to perform activity) to 10 (able to perform activity at pre-injury level). ‡‡Cervical spine range of motion measured with an inclinometer, average of three measures.

***Table 3:*** **Treatment effects at 14 weeks, 6 months, and 12 months**

all timepoints and functional ability at 14 weeks, when some point estimates of treatment effect were significant but did not reach the threshold we had set for being clinically worthwhile.[9]

Table 4 shows the results of the treatment effect modification analyses. None of the variables changed the effect of treatment analyses for the primary outcome (pain intensity) at 14 weeks. Because tests of effect

modification include an interaction term in the analysis, they are frequently underpowered in clinical trials[27] and hence provide imprecise estimates. To assess this issue we calculated the additional treatment benefit for a 1 SD increase in the putative effect modifier. In all cases the point estimate and 95% CI did not include a clinically worthwhile effect on pain—ie, 2 points on a 0–10 scale. In a post-hoc analysis, the duration of symptoms did not moderate the effect of treatment on the primary outcome at 14 weeks. We did post-hoc sensitivity analyses to assess the effect of missing data on the primary outcome by replacing missing data with the best or worst possible scores on the numerical rating scale (ie, 0 or 10). These additional analyses did not change the interpretation of the results (appendix p 102).

| | Estimate (95% CI) | p value | Effect for 1 SD increase |
|---|---|---|---|
| Neuropathic pain score* | 0·04 (−0·08 to 0·16) | 0·480 | 0·24 (−0·48 to 0·96) |
| Post-traumatic stress symptom score† | −0·03 (−0·08 to 0·03) | 0·288 | −0·36 (−0·96 to 0·36) |
| Pressure pain threshold (peripheral)‡ | 0·00 (0·00 to 0·00) | 0·769 | N/A |
| Pressure pain threshold (neck)§ | 0·00 (0·00 to 0·00) | 0·228 | N/A |
| Cold pain threshold (neck)¶ | 0·01 (−0·08 to 0·10) | 0·776 | 0·10 (−0·64 to 0·80) |
| Catastrophising score‖ | −0·01 (−0·06 to 0·05) | 0·732 | −0·13 (−0·78 to 0·65) |
| Duration of whiplash-associated disorder** | −0·02 (−0·06 to 0·02) | 0·259 | −0·34 (−0·78 to 0·65) |

Estimates of treatment effect modification from the linear mixed models analysis at 14 weeks. The second column is the point estimate and 95% CI for the treatment by time interaction term. The third column quantifies the size of the interaction for a 1 SD increase in the putative effect modifier. *Self-report version of Leeds Assessment of Neuropathic pain Symptoms and Signs scale. †Post-traumatic stress Diagnostic Scale score. ‡Mean of three pressure pain threshold tests over right and left tibialis anterior. §Mean of three pressure pain threshold tests over lower cervical spine. ¶Mean of six cold pain threshold tests. ‖Pain Catastrophising Scale total score sum of 13 items. **Duration of whiplash-associated disorder symptoms (post-hoc analysis).

*Table 4:* **Treatment effect modification on primary outcome at 14 weeks**

## Discussion

An intensive 12 week comprehensive exercise programme delivered by physiotherapists for people with chronic whiplash-associated disorders did not provide additional benefit over advice for the primary outcome of average pain intensity in the preceding week. We noted a significant, although clinically unimportant, benefit for two of the secondary outcome measures (self-reported recovery and functional ability). We did not find any evidence to support the hypothesis that differential responses to treatment arise in individuals with chronic whiplash-associated disorders.

The PROMISE trial was prospectively registered, followed a pre-specified protocol, and incorporated design features known to minimise bias such as assessor blinding, concealed allocation, and an intention-to-treat analysis. The trial achieved high rates of follow-up and the participants were compliant with the interventions that were provided. The participants were generally representative of people with chronic whiplash-associated disorders, and the study cohort was similar to those in previous studies done in this specialty (panel).[7,8,36] Although trial physiotherapists delivered both interventions, the risk of contamination between groups was minimised because the therapists were well trained to deliver the trial interventions, the audit of treatment sessions, and the significantly different duration of direct participant to therapist contact between groups. The conclusions are based on precise estimates of treatment effectiveness and the interpretation of results was unaffected by the sensitivity analyses. Accordingly, we believe that the trial provides a credible assessment of the two study treatments with important implications for clinical practice and for the management of people with chronic whiplash-associated disorders. The results of this study will also be of interest to insurers and those associated with the development of future health policies.

We acknowledge the potential for bias in PROMISE because we were unable to mask participants, and the nature of the intervention meant that we also could not mask the treatment providers. As far as we are aware, the only trial of whiplash-associated disorders that has masked patients and treatment providers and reported that the treatment was efficient, is by Lord and

### Panel: Research in context

#### Systematic review

We searched for randomised controlled trials that addressed our study question and for recent systematic reviews of treatment of chronic whiplash-associated disorders to provide evidence for other treatment options. We searched PubMed and PEDro from inception to Sept 15, 2013, using the search term "chronic whiplash". We identified three randomised controlled trials[7,8,28] and eight systematic reviews[4,29,30–35] comparing a physiotherapy exercise programme with advice in people with a chronic whiplash-associated disorder. The three trials were high quality, and scored 7–8 out of 10 on the 0–10 PEDro scale. Therefore, we pooled these findings with our outcomes for disability in the short term (the only common outcome). The additional benefit of exercise over advice was −3·3 (95% CI −5·5 to −1·1) on a 0–100 scale. Of the eight reviews we identified, three[29,33,34] provided information about chronic whiplash-associated disorders. The evidence from two reviews was low quality[33,34] because 27 of the 45 reviewed studies were not randomised controlled trials; the third review was of higher quality.[29] The randomised controlled trials in the reviews provided evidence that exercise was effective in pain reduction, although whether gains were maintained in the long term and whether radiofrequency neurotomy provided substantial, though not permanent pain relief, were unclear. We noted conflicting evidence for the effectiveness of psychological treatments and a general suggestion that further assessment of a multidisciplinary approach is warranted.

#### Interpretation

Data from our meta-analysis of the four available trials suggest that an exercise programme does not provide clinically important additional benefits to advice for people with chronic whiplash-associated disorders. Additionally, findings of the present study show that a long programme of exercise, combining two different types of exercise, does not provide additional benefit over advice. Furthermore, our results do not support the hypothesis that people with chronic whiplash-associated disorders respond differently to exercise treatment. Radiofrequency neurotomy is effective for patients who have pain arising from the zygapophyseal joints, but the procedure needs to be repeated when the nerves recover. Both the test to establish patient suitability (diagnostic nerve blocks) and radiofrequency neurotomy are technically complex and even when patients are carefully selected, the procedure is only effective in some patients.[5]

colleagues,[5] who investigated radiofrequency neurotomy. The subjective nature of whiplash-associated disorders means that in some societies the injury is associated with suspicion of malingering and fraudulent insurance claims. We cannot say that all participants enrolled in PROMISE were genuine whiplash-associated disorder cases; however, in the jurisdictions where the trial took place, no secondary gain from participation in a trial like PROMISE exists. Cases of malingering seems unlikely because participants reported consistent findings across subjective and objective measures and the cohort enrolled was similar to previous studies done in this specialty.[7,8,36]

The effectiveness of an individually tailored, multimodal treatment approach for whiplash-associated disorders is being challenged. In keeping with the results of the present study, data from previous research suggest that a more comprehensive package of care, designed to address the heterogeneous nature of whiplash-associated disorders, has minimum to no additional benefit over treatments that can be delivered in a small number of sessions such as usual care or advice.[10,36,37] Findings of recent studies done in both acute[10,37] and chronic[36] populations have shown only minimum treatment effects for tailored treatment approaches in the short term, but not at long-term follow-up. The complexity of such disorders, including the presence of central nociceptive hyper-excitability and post-traumatic stress symptoms, might be the reason why these treatment programmes are not showing large improvements in outcomes.

Findings of the latest Global Burden of Disease study[38] showed musculoskeletal disorders are one of the leading causes of disability and chronic pain.[38] The need to identify effective and affordable strategies to prevent and treat these disorders has been highlighted as an important health priority; a concern that is especially true for those with chronic whiplash-associated disorders because most have tried and failed previous treatments and their continuing symptoms mean they would be unlikely to pursue more of the same approaches. The development of new treatments would be advanced with identification of specific patho-anatomical diagnoses and an improved understanding of the mechanisms responsible for the development of persistent pain and disability. The effectiveness and timing of various drugs for the management of nociceptive pain and CNS hyperexcitability, a specialty largely ignored up to now, need to be investigated. Alleviation or lessening of pain might provide an environment in which neuromuscular and functional rehabilitation have a more beneficial effect.[39] Last, how to successfully deliver simple advice needs to be established. Education and advice is as effective as more costly interventions,[29] but how to deliver these interventions to patients in the most effective manner needs to be better understood.[29]

**Contributors**

ZAM, CGM, C-WCL, TR, GJ, JL and MS participated in the conception and design of the study and revision of the report for intellectual content. ZAM, CGM, MS, GJ, C-WCL, JL, and LC acquired, analysed, and interpreted data, and drafted the report. TR trained treatment providers. ZAM and CGM did statistical analysis. CGM, MS, GJ, C-WCL, JL, LC, and TR obtained funding, administrative, technical, or material support, and supervision.

**Declaration of interests**

We declare that we have no competing interests.

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