Project title

Clinical and cost-effectiveness of manual therapy for the management of a variety of musculoskeletal and non-musculoskeletal conditions: a systematic review and narrative synthesis

Sutcliffe P, Clar C, Tsertsvadze A, Briscoe S, Court R, Gurung T, Hundt G, Clarke A

Contact
Dr Paul Sutcliffe
Associate Professor and Deputy Director for Warwick Evidence
Health Sciences Research Institute
Warwick Medical School
Coventry
CV4 7AL
Tel: 02476 574505
Fax: 02476 528375
Email: P.A.Sutcliffe@warwick.ac.uk

Contents

List of abbreviations 7
Take home messages 10
Lay Summary 11
Executive summary 14
Objectives 14
Background 14
Methods 15
Search strategy 15
Inclusion criteria 15
Quality assessment 16
Study selection and data extraction 16
Results 16
Clinical effectiveness 16
Search results 16
Clinical outcomes 17
Adverse events 18
Cost-effectiveness and cost-utility 19
Search results 19
Cost outcomes 19
Discussion 20
Clinical effectiveness 20
Cost-effectiveness 21
Dissemination event 22
Research needs / recommendations 22
Conclusions 23
Chapter 1 – Background 25
Objectives 25
Definition and scope 25
Origins and development of manual therapy 28
Main types of manual therapy 29
Hypothesised mechanisms underlying the effects of manual therapy 30
Use of manual therapy and conditions treated 31
Effectiveness and safety 32
Previous work 33

Why this review is important 34
Chapter 2 – Methods 36
Inclusion criteria 36
Types of studies 36
Types of participants 36
Types of interventions 37
Types of outcome measures 38
Search strategy 39
Study selection 39
Data extraction and management 40
Evidence catalogue 40
Overview of new / omitted studies 40
Systematic review of cost-effectiveness studies 41
Assessment of risk of bias 42
Methods of analysis 44
Overview of new / omitted studies 44
Systematic review of cost-effectiveness studies 45
Identification of future areas for primary research 45
Chapter 3 – Clinical effectiveness results 46
Search results 46
Catalogue summary 47
Summary of new and additional studies 53
Conditions / interventions that were ‘inconclusive’, ‘negative’ or not covered in the Bronfort report 57
Musculoskeletal conditions 57
Sciatica and back-related leg-pain 57
Neck pain (cervical manipulation / mobilisation alone) 61
Non-specific mid-back pain 70
Coccydynia 72
Ankle and foot conditions 72
Carpal tunnel syndrome 80
Lateral epicondylitis (tennis elbow) 83
Shoulder conditions 94
Temporomandibular disorders 104
Headache and other conditions 109
Cervicogenic headache 109

Tension-type headache 112
Miscellaneous headaches 118
Fibromyalgia 124
Myofascial pain syndrome 126
Non-musculoskeletal conditions 130
Asthma 130
Attention Deficit / Hyperactivity Disorder (ADHD) / Learning disabilities 135
Cancer care 138
Cerebral palsy in children 140
Cervicogenic dizziness / balance 144
Chronic fatigue syndrome / myalgic encephalomyelitis 147
Chronic pelvic pain 149
Cystic fibrosis 152
Dysfunctional voiding 154
Paediatric nocturnal enuresis 156
Infantile colic 156
Dysmenorrhoea 157
Premenstrual syndrome 157
Menopausal symptoms 157
Gastrointestinal disorders 159
Hypertension 162
Peripheral arterial disease 165
Insomnia 167
Otitis media 169
Parkinson's disease 169
Pneumonia and other respiratory disorders 171
Pregnancy/obstetric care/neonatal care 174
Rehabilitation 178
Systemic sclerosis 185
Conditions / interventions that were 'conclusive' in the Bronfort report 188
Musculoskeletal conditions 188
Back pain 188
Neck pain 189
Whiplash-associated disorder 191
Adhesive capsulitis 192
Hip or knee osteoarthritis 193

Patello-femoral pain syndrome 193
Headache and other conditions 194
Migraine 194
Adverse events 199
Chapter 4 – Comparative cost-effectiveness and cost-utility evaluations of manual therapy interventions 219
Objectives 219
Results 219
Search results 219
Systematic reviews assessing economic evaluations of different treatments including manual therapy 219
Studies evaluating cost-effectiveness and cost-utility of manual therapy 220
Study characteristics 220
Quality of economic evaluations of included studies 221
Cost-effectiveness and cost-utility of included studies 222
Spinal Pain (low back, upper back, and/or neck) 222
Low Back Pain 222
Neck Pain 224
Shoulder Pain 226
Ankle Fracture rehabilitation 226
Summary 226
Chapter 5 – Discussion 227
Outline of what we achieved 227
Summary 227
Clinical effectiveness 227
Cost-effectiveness and cost utility 228
Limitations and strengths 229
Dissemination event 231
Research needs / recommendations 231
Conclusions 234
Acknowledgements 235
Appendix I – Search strategies 236
Appendix II – Comparison of studies included in the Bronfort report and new / additional studies in the current review 254
Appendix III – Quality assessment tables for condition overview 266
Systematic reviews 266

RCTs 271
Controlled cohort studies 275
Qualitative studies 277
Appendix IV – Ongoing studies 278
Appendix V – Additional tables for cost-effectiveness review 283
Section A 283
Section B 287
Section C 290
Appendix VI – Feedback information (flipchart /questionnaires) from group work at University of Warwick Dissemination Event 313
References 316

List of abbreviations

?	Not clear
A & E	Advice and exercise
ADD	Attention deficit disorder
ADHD	Attention deficit / hyperactivity disorder
AIMS	Alberta Infant Motor Scale
AMED	Allied and complementary medicine database economic evaluation databases
ANCOVA	Analysis of Covariance
ARAT	Action Research Arm Test
ASA	Advertising Standards Authority
ASSIA	Applied Social Sciences Index and Abstracts
AT	Alexander Tsertsvadze
BEAM	Back Pain Exercise and Manipulation
BGA	Behavioural graded activity
BMI	Body mass index
BP	Back pain
BPM	Brief pain management
CABG	Coronary artery bypass graft
CAM	Complementary alternative medicine
CAP	Code of Advertising Practice
CASP	Critical Appraisal Skills Program
CBA	Cost-benefit analysis
CC	Christine Clar
CCA	Cost-consequence analysis
CCT	Controlled clinical trials
CDC	Centers for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CGH	Cervicogenic headache
Chiro	Chiropractics
CHQ	Child quality of life
CI	Confidence interval
CINAHL	Current Index to Nursing and Allied Health Literature
CMA	Cost-minimisation analysis
COPD	Chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CTSD	Corticosteroid
CU	Cost-utility
CUA	Cost-utility analysis
DASH questionnaire	Disabilities of Arm, Hand and Shoulder Questionnaire
DI	Daytime urinary incontinence
DSM	Diagnostic and Statistical Manual of Mental Disorders
DYS	Dyssynergic voiding
ESWT	Energy shockwave therapy
EURONHEED	European network of health
FAAM	Foot and Ankle Ability Measure

FABQ	Fear-Avoidance Beliefs Questionnaire
FBDSI	Functional Bowel Disorder Severity Index
FEV	Forced expiratory volume
FVC	Forced vital capacity
GCC	General Chiropractic Council
GI	Gastrointestinal (GI)
GMFCS	Gross Motor Functional Classification System
GP	General practitioner
GRA	Global response assessment
h	Hour
HEP	Home exercise program
HIV	Human immunodeficiency virus
HTA	Health technology assessment
HVLA	High velocity, low amplitude
HVTT	High Velocity Thrust Techniques
ICER	Incremental cost-effectiveness ratio
ICPI	Interstitial cystitis problem index
IMT	Intra-oral myofascial therapy
IS	Incentive spirometry
LBP	Low Back Pain
LE	Lateral epicondylalgia
LEFS	Lower extremity functional scale
LKVCF	Last known value carried forward
LOS	Length of hospital stay
MANTIS	Manual, alternative, and natural therapy
MCID	Minimal clinically important difference
MD	Mean difference
MET	Muscle energy technique
MI	Motricity Index
mins	Minutes
mo	Month(s)
MPT-OA	Manual physical therapy based on an osteopathic approach
MT	Manipulative therapy
MTP	Metatarsophalangeal joint
n	Number
NDI	Neck disability index
NHIS	National Health Interview Survey
NHS	National Health Service
NHS EED	National health service economic evaluation database
NHS HTA	National Health Service Health Technology Assessment
NICE	National Institute of Clinical Excellence
NP	Neck pain
NPQ	Northwick Park Neck Pain Questionnaire
NPRS	Numeric Pain Rating Scale
NR	Not reported
NRS	Numeric Rating Scale
NS	Non-significant
NSAIDs	Non-steroidal anti-inflammatory drugs
NUCCA	National upper cervical chiropractic

	association
OA	Occipito-atlanto
ODI	Oswestry disability index
OLST	One Leg Standing Test
OMT	Osteopathic manual / manipulative treatment
OR	Odds ratio
Ortho	Orthopaedics
PBS	Painful bladder syndrome
PGIC	Patient Global Impression of Change
Physio	Physiotherapy
PL	Placebo
PMR	Progressive muscular relaxation
PPT	Pressure pain threshold
PRTEE	Patient-Rated Tennis Elbow Evaluation
PS	Paul Sutcliffe
PSMT	Paediatric spinal manipulative therapy
PSWD	Pulsed shortwave diathermy
PT	Physical therapy / physiotherapy
pts	Patients
PVR	Post-void residuals
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
ROM	Range of motion
SD	Standard deviation
SF-36	Short Form-36
SFHS	Short form health survey
SFI	Sexual function index
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised mean difference
SMT	Spinal manipulative therapy
SR	Systematic review
TCM	Traditional Chinese medicine
TJM	Thrust joint manipulation
TLP	Thoracic lymphatic pump
TMD	Temporomandibular disorders
TrP	Trigger point
UK	United Kingdom
UTI	Recurrent urinary tract infections
VAD	Vertebral artery dissection
VAS	Visual analogue scale
VBA	Vertebro-basilar artery
VBI	Vertebrobasilar insufficiency
VLBW	Very low birth weight
VUR	Vesicoureteal reflux
wk(s)	Week(s)
WMD	Weighted mean difference
WTP	Willingness to pay
yrs	Years

Take home messages

What was already known on this topic?
• Bronfort and colleagues (2010) evaluated the effectiveness of manual therapies commissioned by the UK General Chiropractic Council (GCC)
Why was this report needed?
• Bronfort and colleagues (2010) referred to limitations in available evidence and a range of issues that needed exploring in a more extensive review • Appraise evidence besides RCTs and systematic reviews, such as controlled cohort studies, non-randomised controlled trials, cost-effectiveness, and qualitative studies • Evaluate areas where Bronfort and colleagues (2010) stated that the available evidence was inconclusive or that manual therapy was not effective
What does this report add?
• Provides a detailed catalogue of 1014 publications and updates the report by Bronfort and colleagues (2010) • Highlights the limited high quality evidence on clinical and cost-effectiveness of manual therapy for the management of a variety of musculoskeletal and non-musculoskeletal conditions • Confirms many of the conclusions by Bronfort and colleagues (2010) about inconclusive evidence, but a few conditions now have moderate positive evidence
What should be done next?
• Need to maintain and update the catalogue • Evaluate the clinical and cost effectiveness of manual therapy interventions for non-musculoskeletal conditions • Explore patients' preferences, attitudes and acceptability issues towards manual therapy • Undertake more high quality, well-conducted prospective controlled studies to draw definitive conclusions regarding the comparative cost-effectiveness of manual therapy interventions
What is the main conclusion?
• The magnitude of benefit and harm of all manual therapy interventions across the many conditions reported cannot be reliably concluded due to the paucity, poor methodological quality and clinical diversity of included studies

Lay Summary

A review to establish the effectiveness and cost effectiveness of manual therapies was conducted by the Health Sciences Research Institute at the University of Warwick for The College of Chiropractors.

Despite a noted shortfall in the quality of the evidence, one of the main findings was "moderate (positive)" evidence in favour of spinal manipulation/mobilisation for acute low back pain. The review also found "moderate (positive)" evidence for:

- The use of manipulation and/or mobilisation combined with exercise for neck pain of any duration;
- The use of combined chiropractic care for low back pain;
- The management of acute whiplash-associated disorder with a combination of mobilisation and exercise;
- The use of manual mobilisation combined with exercise for knee osteoarthritis;
- The use of manipulation/mobilisation for hip osteoarthritis;
- The use of manipulation/mobilisation with exercise for plantar fasciitis;
- The use of manipulation/mobilisation combined with exercise therapy in patellofemoral pain syndrome;
- The use of spinal manipulative therapy in migraine.

The Warwick report also concluded that, for patients with neck pain, low back pain, and shoulder pain, osteopathic spinal manipulation, physiotherapy and chiropractic manipulation appeared to be more cost effective than:

- Usual GP care (alone or with exercise);
- Spinal stabilisation;
- GP advice;
- Advice to remain active;
- Brief pain management.

The review is the second major review of the evidence for the effectiveness of manual therapies in recent years. In 2010, Bronfort et al. reviewed more than 100 studies, including recent systematic reviews and randomised controlled trials, in order to evaluate the effectiveness of manual therapies in the treatment of a range of conditions. The current review considered the same studies, as well as identifying other relevant studies, and new research published since the report by Bronfort et al.

For the Warwick review, researchers identified and considered just over 1000 studies. Most of these were randomised controlled trials (where comparable patients were allocated at random to different treatments and the outcomes compared) and systematic reviews. About 1 in 6 of the studies had been published since the Bronfort review was carried out. In addition, the team examined more than 40 publications of cost effectiveness of manual therapies. However, few cost effectiveness evaluations had been done and the design of many of these studies lacked scientific rigour.

The Warwick review updated evidence in a number of areas. For example, Warwick researchers rated the evidence for the use of spinal manipulation/mobilisation for acute low back pain as "moderate

(positive)". But in contrast to the Bronfort et al. review the Warwick review reclassified the evidence for chronic low back pain as only "moderate (positive)".

For treatment of one type of shoulder disorder (manipulation / mobilisation with exercise for rotator cuff disorder) Bronfort et al. rated the evidence as "inconclusive (favourable)", but the Warwick review identified new evidence and was able to reclassify the body of evidence as "moderate (positive)". Likewise, the evidence for the treatment of cervicogenic and miscellaneous headaches changed the conclusions drawn by Bronfort et al. from "inconclusive (unclear)" to "moderate (positive)".

Both Bronfort et al. and Warwick considered the evidence for treating a large range of non-musculoskeletal conditions but despite finding additional evidence in some cases, the Warwick review was unable to change the inconclusive evidence ratings for these conditions including:

- Asthma using osteopathic manual therapy;
- Paediatric nocturnal enuresis using spinal manipulation;
- Infant colic using spinal manipulation;
- Cranial osteopathic manual therapy;
- Dysmenorrhoea using spinal manipulation;
- Premenstrual syndrome using spinal manipulation;
- Stage 1 hypertension using spinal manipulation added to diet;
- Otitis media and pneumonia in elderly adults using osteopathic manual therapy.

The Warwick review also assessed a considerable number of additional non-musculoskeletal conditions not reported by Bronfort et al. However, the new evidence on these non-musculoskeletal conditions was in the majority of cases rated as "inconclusive (favourable or unclear)".

One of the overarching conclusions of the Warwick review is that the available evidence on the effectiveness and cost-effectiveness of various manual therapies—including those delivered by chiropractors—is of such poor quality that it is generally impossible to tell whether these therapies are successful.

Having reviewed the evidence, the researchers have concluded that they cannot rely on the conclusions reached in many studies, because these were so poorly designed. In many cases, studies that would have helped establish the effectiveness or otherwise of various manual therapies are simply non-existent. Chiropractors need to understand the importance of undertaking high-quality research, the review notes.

The Warwick report concludes that its findings provide a platform for further research into the clinical effectiveness, and cost effectiveness, of manual therapy for the management of a variety of musculoskeletal and non-musculoskeletal conditions.

The review identified a range of further research that is now needed:

- High-quality, long-term, large randomised trials reporting on the effectiveness and cost effectiveness of manual therapy, in order to provide clinically relevant and validated efficacy outcomes;

- Where ethically appropriate, trials should include a no-treatment arm to allow researchers to assess and separate factors such as patients' expectations;
- More research into non-musculoskeletal conditions;
- Research into methods that would make it possible to explore patient's attitudes, patient satisfaction and the acceptability of manual therapy to patients;
- Work to improve the consistency of the definitions used in research studies (e.g., types of treatments and outcomes obtained);
- Studies that consider the whole package of care, not just single manipulation or mobilisation interventions.

The Warwick team concludes that if the complexities of this important discipline in health care are to be addressed, further research and good-quality evidence from well-conducted studies will be essential to draw more definitive conclusions and to provide valid recommendations for policy making.

Executive summary

Objectives

1) To catalogue the research evidence on the effects of manual therapy
2) To evaluate and summarise the effects of manual therapy as reported by systematic reviews, randomised controlled trials (RCTs) and comparative effectiveness studies not included in the Bronfort report (2010)
3) To review systematically the cost-effectiveness and cost-utility of manual therapy interventions relative to no treatment, placebo, or other active treatments
4) To capture a stakeholder perspective on the evidence identified at dissemination event at the University of Warwick

Background

Manual therapy is a non-surgical type of conservative management that includes different skilled hands/fingers-on techniques directed to the patient's body (spine and extremities) for the purpose of assessing, diagnosing, and treating a variety of symptoms and conditions.

Manual therapy is used both within the traditional medical context (physiotherapy, orthopaedics, sports medicine) and as part of complementary and alternative medicine (mainly chiropractics and osteopathy). A major difference between the two contexts is that both chiropractic and osteopathy subscribe to a holistic model of health and healthcare where any manual treatment of the musculoskeletal system may have an influence on the rest of the system, whereas orthopeadic / physiotherapeutic manual therapy is based on the traditional biomedical / biopsychosocial model of health and healthcare. One consequence is that while all three professions emphasise the treatment of neuromuscular disorders, both the chiropractic and osteopathic professions will also treat non-neuromuscular conditions to some extent, either using manual treatment or using adjunctive treatment and advice. By contrast, the focus of orthopeadic / physiotherapeutic manual therapy is on neuromuscular conditions only.

Manual therapy constitutes a wide variety of different techniques which may be categorised into four major groups: a) manipulation (thrust manipulation), b) mobilisation (non-thrust manipulation), c) static stretching, and d) muscle energy techniques. The definition and purpose of manual therapy varies across health care professionals.

The current review builds on the "UK evidence report" by Bronfort and colleagues (2010) on the effectiveness of manual therapies commissioned by the UK General Chiropractic Council (GCC). Bronfort and colleagues referred to the limitations of the available evidence and a range of issues that needed exploring in a more extensive review. The current work aimed to:

- Synthesise evidence in addition to the RCTs and systematic reviews captured by the Bronfort report, such as controlled cohort studies, non-randomised controlled clinical trials (CCTs), cost-effectiveness, and qualitative studies
- Synthesise evidence additional to the Bronfort report (RCTs and systematic reviews published since the Bronfort report and additional study types)

- Compare conclusions from the additional studies summarised (new RCTs and systematic reviews and additional study types) to those of the Bronfort report, focusing in particular on areas where the Bronfort report stated that the available evidence was inconclusive or that manual therapy was not effective.
- Identify the limitations of the Bronfort report and gaps in evidence

Methods

Search strategy

A comprehensive literature search was undertaken in 10 major medical, health-related, science and health economic electronic bibliographic databases. In addition, various health service research and guideline producing bodies were consulted via the internet. We utilised the expertise within the group and consulted with national and international experts where necessary. The main search was carried out in August 2011, with some search updates in PubMed up to July 2012.

Inclusion criteria

Types of studies
Systematic reviews, RCTs and CCTs, cohort studies with a comparison group, qualitative studies of patients' views on manual therapy, and cost-effectiveness studies.

For the cost-effectiveness review, studies reporting the assessment of cost-effectiveness and/or cost-utility of manual therapy were eligible for inclusion. The eligible studies had to report cost-effectiveness and/or cost-utility analysis. Full text reports of primary comparative studies (RCTs, CCTs, comparative cohort studies), study protocols (of completed or on-going studies), or systematic reviews were eligible.

Types of participants
Patients of any age and in any setting treated for any musculoskeletal or non-musculoskeletal condition (within indications for chiropractic, osteopathic and orthopaedic manual therapy as defined by the respective professions).

Types of interventions
Studies assessing any manual treatment / therapy were included (alone or in combination). Emphasis was on interventions typically carried out by a manual therapist / chiropractor / osteopath. Comparisons were against any other therapy.

Types of outcome measures
Pain intensity, pain-related disability, analgesic use, function, mobility (e.g. walking distance), and other relevant symptoms, characteristic symptoms or indicators of disease, patient satisfaction, quality of life, activities of daily living, views / themes from qualitative data, adverse events (e.g. strokes, fractures, pain), and mortality.

Outcomes for the cost-effectiveness review: effectiveness outcome measures (e.g., pain, disability, quality of life, utility) and costs; incremental cost-effectiveness ratios (ICERs).

Quality assessment

The following assessment tools were used: AMSTAR (for systematic reviews); Cochrane Risk of Bias (for RCTs); CRD checklist (for controlled cohort studies); CASP (for qualitative studies); Drummond checklist (for cost-effectiveness studies). Based on the quality results, studies were rated as high, medium or low quality and using the same criteria as the Bronfort report (based on consistency between studies, study size, quality etc.) the evidence was rated as 'high quality positive/negative evidence', 'moderate quality positive/negative evidence', or 'inconclusive favourable/non-favourable/unclear evidence'.

Study selection and data extraction

The inclusion/exclusion criteria were applied to the studies identified through the searches by screening the titles/abstracts of the identified records and the full text of any records appearing to fulfil the inclusion criteria. A part (20%) of the full search results were checked in duplicate by two reviewers and good agreement was achieved. For the cost-effectiveness review, the full text of articles appearing to be relevant was checked in duplicate by two independent authors. Agreement was achieved by discussion. Data were extracted using *a priori* developed data extraction forms.

Results

Clinical effectiveness

Search results

The initial database searches yielded 25,539 records. The final version of the evidence catalogue contained 1014 bibliographic records. The majority of relevant studies identified were RCTs and systematic reviews, with only a small number of non-randomised comparative studies. Approximately 17% of studies in the catalogue were published since the searches in the Bronfort report. The majority of studies (approximately 75%) related to treatment of musculoskeletal conditions and approximately 67% of these were concerned with spinal disorders. Studies on back pain were common, followed by studies on neck pain or other disorders. Other identified studies focussed on foot, ankle, knee, or hip disorders or surgery / injury rehabilitation. Studies on shoulder disorders were also common, followed by studies of lateral epicondylitis (tennis elbow). Small numbers of relevant studies were identified on a large range or non-musculoskeletal disorders.

Clinical outcomes

Musculoskeletal

Combined chiropractic treatment (spinal manipulation as part of a chiropractic intervention package) for low back pain was not considered by Bronfort, although moderate (positive) evidence has now been identified. Furthermore, support for the moderate (positive) rating by Bronfort on low back pain (acute) using spinal manipulation / mobilisation was confirmed in the current study. However, the authors of this review rated the overall evidence for low back pain (chronic) as moderate (positive) in contrast to Bronfort, who rated the evidence as high grade (positive). The majority of interventions (mobilisation / massage) for the spinal musculoskeletal conditions (sciatica / radiating leg pain, neck pain, mid back pain, coccydynia, temporomandibular disorders) reported by Bronfort had inconclusive (favourable) ratings, and the level of evidence remained unchanged despite new evidence being identified. Literature on other musculoskeletal conditions / treatments not reported by Bronfort were identified: a) whiplash-associated disorder (subacute) cervical / thoracic manipulation, (chronic) chiropractic cervical manipulation, cranio-sacral therapy; b) temporomandibular disorders (mandibular manipulation); and c) intra-oral myofascial therapy, osteopathic manual therapy (cervical and temporomandibular joint regions) and myofascial pain syndrome (ischaemic compression, integrated neuromuscular inhibition technique). However, the new evidence on these musculoskeletal conditions not reported by Bronfort was in the majority of cases rated as inconclusive (favourable or unclear) or in one case, inconclusive (non-favourable) for myofascial pain syndrome trigger point release. Only whiplash-associated disorder (acute) using mobilisation with exercise was rated moderate (positive) evidence by the current study and Bronfort.

The current review identified new evidence for interventions on upper extremity disorder conditions (shoulder disorders: rotator cuff disorder using manipulation / mobilisation [with exercise]) which changed the evidence ratings reported by Bronfort from inconclusive (favourable) to moderate (positive). Evidence for the majority of upper extremity disorders remained inconclusive (favourable) (carpal tunnel syndrome using mobilisation and trigger point therapy, lateral epicondylitis with manual tender point therapy and mobilisation with exercise). Evidence on lateral epicondylitis with manipulation was rated as inconclusive (non-favourable) and shoulder girdle pain / dysfunction using manipulation / mobilisation (mobilisation with movement) and adhesive capsulitis using high grade mobilisation, was rated as moderate (positive), this was in agreement with Bronfort. Several additional interventions for upper extremity disorders not reported by Bronfort were rated as inconclusive (unclear or favourable) including: a) carpal tunnel syndrome using diversified chiropractic care, neurodynamic technique, soft tissue mobilisation (with or without Graston instrument) and b) shoulder disorders such as adhesive capsulitis (mobilisation with movement, osteopathy – Niel-Asher technique, or manual therapy with exercise) and minor neurogenic shoulder pain (cervical lateral glide mobilisation and / or high velocity low amplitude manipulation with soft tissue release and exercise). Finally, evidence on other interventions for conditions not reported by Bronfort (soft tissue shoulder disorders using myofascial treatments such as ischaemic compression, deep friction massage, therapeutic stretch) was rated as moderate (positive).

The identified evidence on interventions for lower extremity disorders (ankle sprains, ankle fracture rehabilitation, morton's neuroma / metatarsalgia, hallux limitus, plantar fasciitis, hallux abducto valgus, hip osteoarthritis, knee osteoarthritis, patellofemoral pain syndrome) did not change the conclusions drawn by Bronfort. It was noted that interventions for the following conditions did have moderate (positive) supporting evidence: a) plantar fasciitis (manipulation / mobilisation with exercise; b) hip osteoarthritis (manipulation / mobilisation); c) knee osteoarthritis (mobilisation with

exercise); and d) patellofemoral pain syndrome (manipulation / mobilisation with exercise). Evidence on interventions for several conditions not reported by Bronfort (ankle sprains using muscle energy technique, ankle fracture rehabilitation using Kaltenborn-based manual therapy, plantar fasciitis using trigger point therapy) was rated inconclusive (favourable).

The current review did not identify any new evidence in addition to the Bronfort report on cervicogenic headaches involving spinal manipulation, self-mobilising apophyseal glides, friction massage and trigger points. However, new evidence on mobilisation interventions for cervicogenic and miscellaneous headaches changed the conclusions drawn by Bronfort from inconclusive (unclear) to moderate (positive). The evidence for the treatment of migraine headache using spinal manipulation remained moderate (positive) as reported by Bronfort, although there are considerable limitations in the evidence reported. For a range of other related conditions including migraine headache, tension-type headache, balance in elderly people, and fibromyalgia there were no changes to the evidence ratings reported by Bronfort (inconclusive with the exception of cervicogenic dizziness that was rated moderate (positive)).

Non-musculoskeletal

The evidence ratings in the current report for the majority of non-musculoskeletal conditions considered by Bronfort remain unchanged (asthma using osteopathic manual therapy, paediatric nocturnal enuresis using spinal manipulation, infant colic using spinal manipulation, cranial osteopathic manual therapy, dysmenorrhoea using spinal manipulation, premenstrual syndrome using spinal manipulation, stage 1 hypertension using spinal manipulation added to diet, upper cervical using spinal manipulation, instrument assisted spinal manipulation, otitis media and pneumonia in elderly adults using osteopathic manual therapy). However, the new evidence identified on asthma treatment using spinal manipulation has changed Bronfort's rating from moderate (negative) to inconclusive (unclear). Additional evidence was identified concerning several conditions and interventions that were not reported by Bronfort (asthma using cranio-sacral therapy, ADHD, cancer care, cerebral palsy, chronic fatigue syndrome / myalgic encephalomyelitis, chronic pelvic pain - interstitial cystitis / painful bladder syndrome / chronic prostatitis / chronic pelvic pain in women / chronic prostatitis, cystic fibrosis, paediatric dysfunctional voiding, paediatric nocturnal enuresis using Chinese pinching massage, menopausal symptoms, gastrointestinal disorders using reflux disease, duodenal ulcer and irritable bowel syndrome, stage 1 hypertension using osteopathic manual therapy and Gonstead full spine chiropractic care, intermittent claudication, insomnia, Parkinson's disease, COPD in elderly adults, back pain during pregnancy, care during labour / delivery, care of preterm infants, surgery rehabilitation, stroke rehabilitation, systemic sclerosis). However, the new evidence on these non-musculoskeletal conditions not reported by Bronfort was in the majority of cases rated as inconclusive (favourable or unclear). Only in one case there was moderate negative evidence: in some types of cancer such as osteosarcoma, manipulative therapy may have significant adverse effects and is contraindicated.

Adverse events

Seven systematic reviews and seven primary studies were identified concerning adverse events. With manual therapy, mild-to-moderate adverse events of transient nature (e.g., worsening symptoms, increased pain, soreness, headache, dizziness, tiredness, nausea, vomiting) were relatively frequent. For example, evidence from high, medium, and low quality systematic reviews specifically focussing on adverse events suggest that approximately half of the individuals receiving manual therapy

experienced mild-to-moderate adverse event which had resolved within 24-74 hours. In agreement with the Bronfort report, evidence indicated that serious (or major) adverse events after manual therapy were very rare (e.g., cerebrovascular events, disc herniation, vertebral artery dissection, cauda equine syndrome, stroke, dislocation, fracture, transient ischemic attack). Evidence on safety of manual therapies in children or paediatric populations was scarce; the findings from two low quality cohort studies and one survey were consistent with those for adults that transient mild to moderate intensity adverse events in manual treatment were common compared to more serious or major adverse events which were very rare. However, the evidence on adverse events in manual therapy warrants caution due to relative paucity of evidence and poor methodological quality of the included primary studies.

Cost-effectiveness and cost-utility

Search results

Our searches identified 42 relevant publications, representing 28 unique studies (11 systematic review/health technology assessment reports, 16 RCTs, and 1 controlled cohort study), which were included in the review. A total of 11 systematic review/health technology assessments, 5 primary study protocols, and 12 completed primary study reports were identified as eligible for the section of economic evaluation of the review.

Cost outcomes

This section focused on the results reported in 12 primary studies, of which 11 were RCTs and one was an observational prospective cohort study. Briefly, the studies evaluated participants recruited from general primary care practices, chiropractors' or physiotherapists' offices. The study participants in the majority of studies presented with non-specific back and/or neck pain. The mean age of the study population ranged from 37 to 51 years. The economic evaluations included assessments of cost-effectiveness (based on pain intensity and disability measures) and/or cost-utility (QALYs based on quality of life measures) of manual treatment techniques (manipulation, mobilisation) compared to usual general practitioner (GP) care, physiotherapist (PT) advice, pain management, exercise, or PT. Most interventions lasted from 6 to 12 weeks. The costs were evaluated from societal, public payer/primary care, or both perspectives. Given the short follow-up of most studies (12 months), no discounting was considered.

All economical evaluations except for one study were conducted alongside RCTs. In all or most studies the research question was clearly formulated with sufficient information on the test intervention, control group intervention, costs, and comparative effectiveness results including uncertainty around the estimates. For more than half of the studies costs were not individually itemized, and therefore, it was not clear what types of costs were included in the calculations. The valuation methods of costs reported in the studies were judged as adequate.

In studies of low back and shoulder pain, the use of manual therapy interventions (i.e., osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, chiropractic manipulation) resulted in at least numerically greater total costs and improvements in

pain, disability, and QALYs gained compared to alternative treatments such as usual GP care, pain management, spinal stabilisation, GP advice, or exercise. The observed extra costs needed for one unit improvement in low back or shoulder pain/disability score or one QALYs gained were lower than the willingness-to-pay thresholds reported across the studies. Given the estimates of ICERs and corresponding uncertainties, the manual treatments (chiropractic, osteopathic spinal manipulation or combination of manipulation and mobilisation), in addition or alone, were shown to be more cost-effective options at least for short term in the treatment of low back pain and disability compared to usual GP care (ICER: £3,560 per QALY gained), spinal stabilisation (ICER: £1,055 per QALY gained), GP advice (ICER: £318 and £49 per score improved in pain and disability, respectively), advice to remain active (ICER: £3,010 per QALY gained), or brief pain management (ICER: £156 per score improved in disability and ICER: £2,362 per QALY gained). Similarly, the use of manipulation plus mobilisation for treating shoulder pain was more cost-effective compared to GP care with respect to recovery (ICER: £1,812), pain (ICER: £110.25), disability (ICER: £3.15), and general health (ICER: £1,860). The findings from the UK BEAM study indicated that the addition of chiropractic and osteopathic manipulations to exercise and GP care was dominant (less costly and more effective) over the combination of exercise and GP care. In the same study, the addition of manipulation alone (ICER: £4,800) or manipulation plus exercise (ICER: £3,800) to GP care was more cost-effective than GP care alone. According to the UK BEAM study results, the most cost-effective treatment option for patients with low back pain was the addition of manipulation alone to GP care (the willingness-to-pay ≥ £10,000 per QALY gained).

In the neck pain studies, the use of manual therapy interventions (chiropractic manipulation plus joint mobilisation with low-velocity passive movements) incurred lower total costs compared to alternative treatments such as behavioral graded physical activity program, PT, GP care, or advice plus exercise. Results on cost-effectiveness of manual therapy for reducing neck pain, disability, and QALYs gained compared to other treatments were not consistent across these studies. For example, in one study of patients with subacute neck pain, the behavioral graded physical activity (BGA) was more cost-effective than manual therapy (small amplitude thrust manipulation plus large-amplitude mobilisation) in reducing pain intensity (ICER: £209) and disability (£77.70). However, there was no difference between the two treatments in cost-utility. In another study, the manual therapy (various chiropractic manipulation techniques plus low-velocity articular mobilisation) dominated either PT (ICER: -£19,620 per QALY gained) or GP care (ICER: -£9,769 per QALY gained). The results of one neck pain study on cost-effectiveness of manual therapy (hands-on passive or active movements, mobilisation, soft-tissue/joint spinal manipulation) compared to advice and exercise were inconclusive due to high uncertainty.

Discussion

Clinical effectiveness

The current report catalogued and summarised recent systematic reviews, RCTs and comparative effectiveness studies that were not all included in the Bronfort report (e.g. non-English literature) and compared results and updated conclusions. A large number of studies were included (over 1000 in the evidence catalogue, over 100 in the more detailed summaries). The majority of studies were concerned with musculoskeletal conditions, and the majority of these were about spinal disorders. The

most common study design was the RCT. There were relatively few non-randomised comparative and qualitative studies meeting the current inclusion criteria.

The majority of conditions previously reported to have "inconclusive" or "moderate" evidence ratings by Bronfort remained the same. Only in three cases, evidence ratings changed in a positive direction from inconclusive to moderate evidence ratings (manipulation / mobilisation (with exercise) for rotator cuff disorder, mobilisation for cervicogenic and miscellaneous headache). It was also noted that some evidence ratings by Bronfort changed in the current report in a negative direction from moderate to inconclusive evidence or high to moderate evidence ratings. In addition, evidence was identified on a large number of non-musculoskeletal conditions that had not previously been considered by Bronfort; all this evidence was rated as inconclusive.

Overall, it was difficult to make conclusions or generalisations on all the conditions due limitations in quality of evidence, short follow-up periods reported (<12 months), and high uncertainty in the effectiveness measures. Most reviewed evidence was of low to moderate quality and inconsistent due to substantial methodological and clinical diversity, thereby rendering some between-treatment comparisons inconclusive. The differences in the therapy provider's experience, training, and approaches may have additionally contributed to the inconsistent results.

Cost-effectiveness

Twelve primary studies compared cost-effectiveness and/or cost-utility of manual therapy interventions to other treatment alternatives in reducing non-specific musculoskeletal pain (spinal, shoulder, ankle). All economic evaluations except for one were conducted alongside RCTs. It remains difficult to draw definitive conclusions regarding the comparative cost-effectiveness of manual therapy techniques in patients presenting with spinal pain due to the paucity and clinical heterogeneity of the identified evidence.

Manual therapy techniques such as osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, and chiropractic manipulation in addition to other treatments or alone appeared to be more cost-effective than usual GP care (alone or with exercise), spinal stabilisation, GP advice, advice to remain active, or brief pain management for improving low back/shoulder pain/disability and QALYs gained during one year. Moreover, chiropractic manipulation dominated (i.e., less costly and more effective than alternative treatment) either physiotherapy or GP care in improving neck pain and QALYs gained.

An advantage of this review over others is that it includes only those studies that evaluated costs and effectiveness simultaneously through cost-effectiveness and/or cost-utility analyses by providing ICERs and the associated uncertainty measures.

The main limitation of the cost-effectiveness review stems from the reviewed evidence itself. Namely, the current review found a paucity of evidence of cost-effectiveness/cost-utility evaluations for manual therapy interventions. The review extracted only those outcomes used in the economical evaluations of included studies. The findings of the cost-effectiveness review warrant caution given the following issues a) lack of blinding and its effect on subjective outcomes (pain, disability, recovery) and b) contextual effects (e.g., care giver experience).

Overall, manual therapy techniques such as osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, and chiropractic manipulation in addition to other treatments or alone appeared to be more cost-effective than usual GP care (alone or with exercise), spinal stabilisation, GP advice, advice to remain active, or brief pain management for improving low back/shoulder pain/disability and QALYs gained during one year. Moreover, chiropractic manipulation dominated (i.e., less costly and more effective than alternative treatment) either physiotherapy or GP care in improving neck pain and QALYs gained. The evidence regarding cost-effectiveness of manual therapy (hands-on passive or active movements, mobilisation, soft tissue/joint spinal manipulation) compared to advice plus exercise in reducing neck pain was limited in amount and inconclusive due to high uncertainty.

Dissemination event

The dissemination event held at the University of Warwick in June 2012 involved 23 people (14 male, 9 female) of which 21 were professionals and two were patients. The attendees were given an opportunity to provide the research team with their thoughts about the overall findings. A series of questions were explored with the attendees.

The attendees were in agreement that the findings provided a useful platform or baseline for future research. They were encouraged by the findings as they felt there were now the reasons for developing collaborative research. They recognised that there had been a plethora of evidence published, but concluding anything from it was very difficult due to the limited high quality research. They wanted to see more high quality research being funded, widespread dissemination to clinicians and students being educated on how to undertake high quality research.

It was suggested that trials on specific conditions might be undertaken and further investigations about patients' experiences in terms of satisfaction, acceptability and attitudes towards treatment outcomes. There was discussion about the need for a prospective RCT, possibly between chiropractic versus usual GP care on the clinical and cost-effectiveness of manual therapy on specific conditions. The attendees recognised the value of evaluating the cost-effectiveness of interventions. They also would like to see more evaluation and synthesis of the available trial evidence, as the current review was limited in the amount of detail it could report due to the large number of conditions included.

The attendees would like to be kept up-to-date with the College of Chiropractors overall findings and recommendations. They stated that different undergraduate colleges need to work together and discuss the mechanism to maintain the catalogue. There was a suggestion that greater communication could take place through forums or a Wiki.

Research needs / recommendations

The current research has highlighted the need for long-term large pragmatic head-to-head trials reporting clinically relevant and validated efficacy outcomes along with full economic evaluations. Ideally, future studies should use and report unit cost calculation and costs need to be broken down by each service to allow the judgment as to whether all relevant costs applicable to a given perspective were considered and how the total costs were calculated. If ethically justifiable, future trials need to include sham or no treatment arm to allow the assessment and separation of non-specific effects (e.g.,

patient's expectation) from treatment effects. Furthermore, future research needs to explore which characteristics of manual therapies (e.g., mode of administration, length of treatments, number of sessions, and choice of spinal region/points) are important in terms of their impact on clinically relevant and patient-centered outcomes. Also, strong efforts are needed to improve quality of reporting of primary studies of manual therapies.

The following key research needs and recommendations were highlighted from the report findings:

- There is a need to maintain and update the catalogue;
- The current research provides a strong argument in support of further trials in this area (e.g. funding from NIHR Health Technology Assessment Programme) through research collaboration;
- Provision of more training and education in research for the chiropractic community is needed – this includes training in secondary research;
- Studies need to be developed that involve qualitative research methods to explore patient attitudes, satisfaction and acceptability towards manual therapy treatments, this could also take the form of mixed methods studies exploring both effectiveness and patient views;
- Greater consistency is needed across research groups in this area in terms of definition of participants, interventions, comparators and outcomes;
- More research is needed on non-musculoskeletal conditions;
- High quality, long-term, large, randomised trials reporting effectiveness and cost-effectiveness of manual therapy are needed for more definitive conclusions.

Conclusions

The current report provides a platform for further research into the clinical and cost-effectiveness of manual therapy for the management of a variety of musculoskeletal and non-musculoskeletal conditions. There is need to maintain and update the catalogue. Limited research had been published on many non-musculoskeletal conditions. Raising awareness about the importance of undertaking high quality research is needed among the chiropractic community. The magnitude of benefit and harm of all manual therapy interventions across the many conditions reported cannot be reliably concluded due to the paucity, poor methodological quality and clinical diversity of included studies.

Overall, manual therapy techniques such as osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, and chiropractic manipulation in addition to other treatments or alone appeared to be more cost-effective than usual GP care (alone or with exercise), spinal stabilisation, GP advice, advice to remain active, or brief pain management for improving low back/shoulder pain/disability and QALYs gained during one year. Moreover, chiropractic manipulation dominated (i.e., less costly and more effective than alternative treatment) either physiotherapy or GP care in improving neck pain and QALYs gained. The evidence regarding cost-effectiveness of manual therapy (hands-on passive or active movements, mobilisation, soft tissue/joint spinal manipulation) compared to advice plus exercise in reducing neck pain was limited in amount and inconclusive due to high uncertainty. Further research and good quality evidence from well-conducted studies is needed to draw more definitive conclusions and valid recommendations for policy making.

It is important to consider whether the evidence which is available provides a reliable representation of the likely success of manual therapy as provided in the UK. Given the considerable gaps in the evidence and the inconsistent reporting on techniques and interventions used (and often a lack of

description of techniques used), and the fact that many reported studies failed to consider the generalisability of the findings to the range of settings in which manual therapy is practised in the UK, this is unlikely. There is a need to consider the whole package of care, rather than just single manipulation or mobilisation interventions. A mixed methods approach should be considered for expanding the evidence base and addressing the complexities of this important discipline in health care.

Chapter 1 – Background

Objectives

1) To catalogue the research evidence regarding the effects of manual therapy using comprehensive evidence tables; this will include any forms of manual therapy and any comparators in the treatment of a variety of musculoskeletal and non-musculoskeletal conditions based on systematic reviews, controlled clinical trials (randomised, quasi-randomised or non-randomised), comparative cohort studies, qualitative studies and economic (cost-effectiveness) studies.
2) To summarise any recently published systematic reviews and randomised controlled trials (RCTs) and comparative effectiveness studies not included in the Bronfort report in more detail and compare the results with the results of the UK evidence report on manual therapy (Bronfort and colleagues, 2010).
3) To undertake a systematic review of cost-effectiveness studies.
4) To capture a user perspective on the information documented by considering qualitative data on patient views of manual therapy and through organisations, charities and a workshop / dissemination event at The University of Warwick.

Definition and scope

Manual therapy is a non-surgical type of conservative management that includes different skilled hands/fingers-on techniques directed to the patient's body (spine and extremities) for the purpose of assessing, diagnosing, and treating a variety of symptoms and conditions.[1-4]

Manual therapy techniques are usually applied to joints (e.g., manipulation, mobilisation, joint distraction, traction, or passive/active range of motion) and soft tissues (e.g. massage) and may be used separately or in conjunction in different combinations.[1;3] Very often, manual therapy is used conjointly with other passive (e.g., heat/cold application, diathermy, electro-stimulation for pain, ergonomic analysis, myofascial techniques, muscle energy techniques) or active physical therapy procedures (e.g., exercises, body training, electro-stimulation for strength, coordination training, biofeedback).[4] Furthermore, manual therapy techniques have been used in combination with other traditional (e.g., acupuncture) or conventional treatments (e.g., anaesthesia, surgery).

Manual therapy is used both within the traditional medical context (physiotherapy, orthopaedics, sports medicine) and as part of complementary and alternative medicine (mainly chiropractics and osteopathy). The internationally agreed definitions of the three professional healthcare groups (manual therapists in physiotherapy, chiropractors, osteopaths) are as follows:

- International Federation of Manipulative Physical Therapists (IFOMT): *"Orthopaedic Manual Therapy is a specialised area of physiotherapy / Physical Therapy for the management of NMS conditions, based on clinical reasoning, using highly specific treatment approaches including manual techniques and therapeutic exercises. Orthopaedic Manual Therapy also encompasses, and is driven by, the available scientific and clinical evidence and the biopsychosocial framework of each individual patient"* (http://www.ifompt.com/site/ifompt/files/pdf/IFOMT_Education_Standards_and_International_Monitoring_20080611.pdf)

- World Federation of Chiropractic: *"A health profession concerned with the diagnosis, treatment and prevention of mechanical disorders of the musculoskeletal system, and the effects of these disorders on the function of the nervous system and general health. There is an emphasis on manual treatments including spinal adjustment and other joint and soft-tissue manipulation."* (http://www.wfc.org/website/index.php?option=com_content&view=article&id=90&Itemid=110&lang=en)
- World Osteopathic Health Organisation (WOHO): *"Osteopathy is an established recognised system of healthcare which relies on manual contact for diagnosis and treatment. It respects the relationship of body, mind and spirit in health and disease; it lays emphasis on the structural and functional integrity of the body and the body's intrinsic tendency for self-healing. Osteopathic treatment is viewed as a facilitative influence to encourage this self-regulatory process. Pain and disability experienced by patients are viewed as resulting from a reciprocal relationship between the musculoskeletal and visceral components of a disease or strain."* (http://www.efo.eu/Osteop-Practice-Europe.pdf)

A comparison of the features of the three professions is shown in Table 1.

Table 1. Comparison of the three main professions using manual therapy

	Chiropractic[5]	**Manual therapy (physiotherapy)**[6]	**Osteopathy**[7]
Underpinning philosophy	• Health model based on Innate intelligence (brain and CNS), vitalism, alterations in the spinal column (subluxations) alter neural function and cause disease • Holistic model • "Straights" versus "mixers" (the latter (majority) embrace mainstream views and conventional medical techniques)	• Clinical reasoning • Biomedical / biopsychosocial model • Based on physiotherapy / orthopaedics	• Holistic approach – unity of the body, stimulation of self-healing • Relationship between structure and function, somatic component of disease
Main methods	Techniques include: • Spinal manipulation (e.g. diversified technique of full spine manipulation, Activator-assisted manipulation) • Manipulation of other joints • Traction, mobilisation • Soft tissue techniques • Adjunctive treatment (e.g. physical treatments, acupuncture, exercise, advice etc.)	Techniques include: • Manipulation • Mobilisation • Rehabilitative exercises • Soft tissue techniques (massage, trigger point therapy etc.) • Other adjunctive treatments	Techniques include: • Strain/counterstrain • Muscle energy techniques • Manipulation • Mobilisation • Visceral techniques • Myofascial therapy • Cranio-sacral therapy • Massage • Exercise / advice

	Chiropractic[5]	**Manual therapy (physiotherapy)**[6]	**Osteopathy**[7]
Main conditions treated	Mainly neuromuscular conditions but may also be consulted for other conditions	Neuromuscular conditions (spine and extremities)	Mainly neuromuscular conditions but may also be consulted for other conditions
Qualifications and governing body (UK)			
Regulatory body	The General Chiropractic Council (GCC)	Health Professions Council (HPC)	The General Osteopathic Council (GOsC)
Professional Organisation	British Chiropractic Association	Chartered Society of Physiotherapy / Musculoskeletal Association of Chartered Physiotherapists (MACP) (manipulative therapy)	British Osteopathic Association
Qualification	Recognised 4 year university degree programme (course recognised by the GCC)	Recognised university course (Bachelor degree with honours plus postgraduate qualification in manual therapy)	Recognised 4 year university degree programme (course (recognised by the GOsC); accelerated course for medical doctors / physiotherapists

A major difference between the three professions is that both chiropractic and osteopathy subscribe to a holistic model of health and healthcare where any manual treatment of the musculoskeletal system may have an influence on the rest of the system, whereas orthopeadic / physiotherapeutic manual therapy is based within traditional medicine and the traditional biomedical / biopsychosocial model of health and healthcare. One consequence is that while all three professions emphasise the treatment of neuromuscular disorders, both the chiropractic and osteopathic professions will also treat non-neuromuscular conditions to some extent, either using manual treatment or using adjunctive treatment and advice. By contrast, the focus of orthopeadic / physiotherapeutic manual therapy is on neuromuscular conditions only.

The definition and purpose of manual therapy varies across health care professionals. For example, manual therapy within the field of physical therapy is defined as: "a medical discipline in which practitioners apply their hands skilfully in both diagnostic and therapeutic management of painful neuro-musculo-skeletal disorders and various diseases."[8] Kaltenborn defines manual therapy as "evaluation and treatment of joints and their surrounding structures to relieve pain, increase or decrease mobility, and prevent recurrence of pain."[9] Within the orthopaedic field, manual therapy is defined as "selected passive or active assistive techniques such as stretching, mobilisation, manipulation, and muscle energy-related methods used for the purposes of modulation of pain, reducing or eliminating soft tissue inflammation, improving contractile and non-contractile tissue repair, extensibility, and/or stability, and increasing range of motion (ROM) for facilitation of movement and return to function."[10]

Given the inconsistencies in the terminology and definitions of manual therapy across health care professionals, the American Academy of Orthopaedic Manual Physical Therapists developed a consensus-based set of standardised terminology and definitions.[11;12] The proposed set of guidelines is designed to facilitate uniform reporting/description of any given manual application or technique

through the following domains: a) rate of force of application, b) location in range of available movement, c) direction of force, d) target of force, e) relative structural movement, and f) patient position.[10]

Chiropractors apply manual therapy regularly to treat back pain and other musculoskeletal or non-musculoskeletal disorders. Although the beneficial effects of manual therapies when applied to musculoskeletal disorders and pain may be based on biologically plausible mechanisms, there is no sound underlying biological pathway which would explain how these effects would operate with respect to non- musculoskeletal disorders (e.g., infant colic, asthma, hypertension, chronic obstructive lung disease, otitis media).[13-16] Within the chiropractic field, manual therapy is defined as "procedures by which the hands directly contact the body to treat the articulations and/or soft tissues."[17] Chiropractors often use manipulation (i.e., adjustment) technique with high velocity thrust, when joints are rapidly adjusted and sometimes accompanied with popping sounds. Today, chiropractic is licensed and practiced in many countries throughout the world with the most of the training in this field taking place in the USA.[7;15]

As joint techniques are integral to chiropractics, osteopathy and orthopaedic / physiotherapeutic manual therapy, in this review, we exclude interventions that do not include joint techniques, e.g. just use massage, but we include studies using soft tissue techniques as an adjunctive treatment.

Origins and development of manual therapy

Manual therapy techniques have been used since antiquity, with records of manual therapy in Thai artwork dating back 4000 years and ancient records from Egypt, Persia, China, Japan and Tibet describing the use of manual procedures to treat disease.[5;7] Manual therapy has been widely practiced for centuries in many parts of the world to treat different musculoskeletal conditions including spinal disorders.[18] According to historical references, both Galen (131-202 CE) and Avicenna (980-1037 CE) described in their works manipulative techniques introduced by Hippocrates (460-385 BCE).[18] Until the end of the 19th century, manipulative techniques were the domain of bone setters. [18] Things changed in the early 20th century, when manual therapy became the mainstay of osteopathy and chiropractic, which were founded at the end of the 19th century in the USA by Andrew Taylor Still and Daniel David Palmer, respectively.[13;14;16;18] Physical therapy which evolved in parallel to osteopathy and chiropractic in the USA during the early 20th century, has been assimilating manual therapy techniques from physicians and osteopaths and eventually became a part of the medical profession. In contrast, chiropractic has enjoyed independent existence and still remains autonomous from conventional medicine.[18] In the UK, complementary and alternative medicine (CAM), which is part of conventional treatment, gained a high level of popularity in the general population.[19] Three-quarters of fund folding general practitioners (GPs) supported that complementary medicine be funded by the National Health Service (NHS), particularly osteopathy, acupuncture, chiropractic, and homoeopathy.[20] Similarly, the British Medical Association published a paper titled "Complementary Medicine: new approaches to good practice."[21]

Manual therapy techniques practiced by today's physiotherapy (or physical therapy) professionals belong mainly to several schools/directions of thought that were initiated by James Cyriax, Stanley Paris, Freddy Kaltenborn, Robin McKenzie, Brian Mulligan, Geoffrey Maitland, and John Mennell.[18;22]

Nowadays, in the Western World, manual therapy techniques including traditional approaches (e.g., acupressure, bone setting) are used by different health professionals such as physiotherapists, orthopaedics, physical therapists, massage/manual therapists, chiropractors, clinicians, osteopaths, or bone setters.[2] Moreover, a wide variety of manipulative techniques have been adopted and integrated into general medical practice and different medical specialties (e.g., neurology, orthopaedics, rehabilitation, rheumatology, and sports medicine).[8]

Main types of manual therapy

Manual therapy (as practiced within the physical therapy field but also in chiropractics and osteopathy) constitutes a wide variety of different techniques which may be categorised into four major groups: a) manipulation (thrust manipulation), b) mobilisation (non-thrust manipulation), c) static stretching, and d) muscle energy techniques.[10] Chiropractors apply manipulation and mobilisation as well as chiropractic adjustments. Generally, approaches of manipulation and mobilisation are differentiated based on the fact that manipulation, unlike mobilisation, uses thrusting technique.[8] There are two forms of manipulation, targeted specific and generalised. Mobilisation forms include joint, nerve, and soft-tissue/massage/myofascial release techniques (e.g., gliding, sliding, percussion, compression, kneading, friction, stretching).[10]

There are distinctions in how manipulation and mobilisation techniques are viewed in Europe and the USA. For example, in Europe, manipulation is described as "high velocity, low amplitude thrust" (HVLA), whereas in the USA, manipulation is used as a general term, which may refer to any hands-on therapeutic procedure. In the USA, the term "mobilisation" refers to a soft tissue treatment, which may include other techniques like myofascial release and muscle energy. In Europe, the same term refers to articular mobilisation without thrust.[8] Several other definitions for manipulation, mobilisation, and other techniques can be found in the literature.[10;17;23-26]

The following are several selected examples of these definitions:

Manipulation

- "An accurately localised or globally applied single, quick, and decisive movement of small amplitude, following a careful positioning of the patient."[10]
- "High velocity, low amplitude thrust at the limit of the range of play of the joint."[8]
- "A manual procedure that involves a directed thrust to move a joint past the physiological range of motion, without exceeding the anatomical limit."[17]
- "A passive manual manoeuver during which the three-joint complex may be carried beyond the normal voluntary physiological range of movement into the paraphysiological space without exceeding the boundaries of anatomical integrity. The essential characteristic is a thrust – a brief, sudden, and carefully administered "impulsion" that is given at the end of the normal passive range of movement."[26]

Mobilisation

- "Passive technique designed to restore full painless joint function by rhythmic, repetitive passive movements, well within the patient's tolerance, in voluntary and/or accessory ranges."[10]
- "Non-thrusting and soft-tissue technique."[8]
- "Movement applied singularly and repetitively within or at the physiological range of joint motion, without imparting a thrust or impulse, with the goal of restoring joint mobility."[17]

- "Mobilisation is a non-thrust, manual therapy. It involves passive movement of a joint within its physiological range of motion. This is approximately equivalent of the normal range of motion a joint can be taken through by intrinsic musculature. Active range of motion is motion which patients can accomplish by themselves. Mobilisation is passive movement within the physiologic joint space administered by a clinician for the purpose of increasing overall range of joint motion."[26]

Static stretching

- "Application of a tensile force to tissue in an effort to increase the extensibility of length and ROM of the targeted tissue."[10]

Muscle energy technique

- "A manually assisted method of stretching/mobilisation where the patient actively uses his or her muscles, on request, while maintaining a targeted preposition against a distinctly executed counterforce."[10]

Adjustment

- "Any chiropractic therapeutic procedure that utilises controlled force, leverage, direction, amplitude, and velocity which is directed at specific joints or anatomical regions."[17]

Hypothesised mechanisms underlying the effects of manual therapy

The mechanisms underlying effects of manual therapy are unclear. It is thought that manual therapy impacts primary afferent neurons from paraspinal tissues, the motor control system, and pain processing. Thus, it is hypothesised that the effects of manual therapy operate through biomechanical and/or neurophysiological pathways.[10] According to the biomechanical hypothesis, manual therapy displaces and deforms the tissues, altering orientation or position of anatomic structures, unbuckling some structures, releasing entrapped structures or disrupting adhesions. Biomechanical changes due to manual therapy lead to increased range of motion and reduced positional fault. According to the neurophysiological hypothesis, manual therapy may have an effect on spinal cord and affect central and peripheral nervous system leading to changes in pain perception, pain reduction, and lowered pain threshold.

The mechanisms of chiropractic effects are thought to operate through "innate intelligence" and 'vertebral subluxations', the concepts originally introduced by Daniel David Palmer (1845-1913) and then developed by his son Bartlett Joshua Palmer (1881-1961).[13] Palmer believed that the flow of nerve vibrations from the brain to the spinal cord through openings between the vertebrae governed all body functions. He claimed that most diseases were caused by displaced vertebrae (vertebral subluxations) through their pinching nerves in the intervertebral spaces and altering the normal flow of nerve impulses to organs. Therefore, he suggested, diseases could be cured by correcting vertebral displacements. The theory of subluxation ignored autonomic cranial and sacral nerves which do not pass through intervertebral spaces.

Today, chiropractic practice is still based on the theory of subluxation, and yet, the existence of chiropractic vertebral subluxion (i.e., asymptomatic vertebral misalignment) has not been proven and

the validity of claims regarding the beneficial effects of correcting "vertebral subluxations" remains largely untested.[13-16]

Use of manual therapy and conditions treated

Spinal manipulation and mobilisation are commonly used treatment modalities for back pain, particularly by physical therapists, osteopaths, and chiropractors. Back pain is an important health problem with serious societal and economic consequences for the developed world. It is estimated that in the USA 80% of people will experience back problems at some point during their lifetime.[27] Back pain is also very prevalent in UK, affecting estimated 16.5 million people annually.[28]

The use of chiropractic, osteopathic, and other forms of services delivering various types of manual therapies has been steadily increasing in the Western World.[15] For example, in the United States, 1 of 3 persons with low back pain is treated by a chiropractor.[14]

One UK-based study conducted in 1997 surveyed the prevalence of back pain and the use of chiropractic/osteopathy services in a randomly selected sample of adults aged 18-64 years living in four counties of England.[29] The overall prevalence of back pain in the surveyed population was 15.6% and it increased with age – 8.5%, 15.5%, and 23.4% for the age groups of 18-33, 34-49, and 50-64 years, respectively. About 5% of all the respondents reported to have consulted with practitioners of osteopathy and/or chiropractic during the past three months. In contrast, of the respondents with back pain, 13.4% consulted with osteopathy and/or chiropractic practitioners. According to a multivariable regression analysis, significant predictors of osteopathy/chiropractic consultations were the presence of back pain (OR= 5.11, 95% CI: 4.05, 6.44), non-manual social class (OR= 2.10, 95% CI: 1.58, 2.78), not smoking (OR= 1.50, 95% CI: 1.12, 2.03), and exercising 30 minutes at least once a week (OR= 1.48, 95% CI: 1.16, 1.90). [29]

In a survey of 2598 patients in the USA who received outpatient physical therapy for musculoskeletal impairments, the annual rate of use of manipulation and mobilisation for lumbar impairments were 3.7% and 27.2%, respectively. The corresponding rates for patients with cervical impairments were 1.8% and 41.9%, respectively.[4]

One descriptive review summarised surveys reporting rates of use of CAM therapies for management of low back pain and other conditions (e.g., osteoarthritis, cancer, multiple sclerosis, HIV, asthma, mental disorders, diabetes, special need children, peripheral neuropathy, surgical patients).[30] Results of this review showed that chiropractic was used by 6% to 12% of the surveyed population, majority of whom complained of back pain and not organic disease or visceral dysfunction. The reviewed studies reported that in addition to back pain, chiropractic services were also used for specific conditions such as osteoarthritis (21%), multiple sclerosis (25%), HIV (19%), peripheral neuropathy (21%), and surgical patients (23%). On average, the rates of use of chiropractic care were lower for conditions such as breast cancer (4%-10%), depression (<1%), psychiatric disorders (11%), and special need children (4%-6%). On average, the reviewed studies indicated that chiropractic care offered lower costs for similar results compared to conventional medicine.[30]

The Centers for Disease Control and Prevention (CDC) used data from National Health Interview Survey (NHIS) and reported estimates of CAM use among U.S. adults and children for the period of

2002-2007.[31] According to the survey findings, in 2007, almost 4 out of 10 adults (38.3%) had used some type of CAM in the past 12 months, of which the most commonly used CAMs were nonvitamin/nonmineral/natural products (18%), deep breathing exercises (13%), meditation (9%), chiropractic or osteopathic manipulation (9%), massage (8%), and yoga (6%). In 2007, most often treated musculoskeletal problems amongst adults were back pain or problems (17%), neck pain or problems (6%), joint pain or stiffness or other joint condition (5%), arthritis (3%), and other musculoskeletal conditions (2%).[31]

Effectiveness and safety

Comparative effectiveness research of manual therapy techniques is complicated by several factors: 1) controversies regarding the aetiology of musculoskeletal pain, 2) the force, amplitude, direction, duration, and frequency of manual therapy techniques vary with the practitioner's educational background, clinical experience, and the patient's clinical profile, 3) musculoskeletal conditions may improve over time, 4) operation of non-treatment specific effects in effectiveness studies (e.g., lack of blinding, patient-caregiver interaction), 5) differences in definitions of the outcome measures, 6) teasing out the effects of manual therapy from those of other treatments if administered in combination, and 7) poor reporting of primary research reports (e.g., lack of detailed description of specific techniques and procedures used, participant inclusion/exclusion criteria, distribution of participant baseline characteristics between study treatment groups).[2;3]

Evidence of low methodological quality of trials of back/neck pain additionally complicates the interpretation of the comparative effectiveness research results.[32-34]

The past research has shown short-term benefit of spinal manual therapy (i.e., manipulation, mobilisation) especially in reducing back pain.[34-43] In recent years, the use of manipulation and/or mobilisation has been recommended in clinical practice guidelines in the USA, Great Britain, and the Netherlands.[4] There is little and mostly inconclusive evidence from randomised trials on the effectiveness of manual therapy including chiropractic manipulation for non-musculoskeletal conditions, specifically for patients with dysmenorrhoea, hypertension, chronic obstructive lung disease, asthma, infantile colic, premenstrual syndrome, otitis media, nocturnal enuresis.[14;15;40]

The annual incidence of major harms or complications associated with the use of manipulative procedures is usually low. In general, manipulations using thrust techniques carry a greater risk of major complications than the non-thrusting, low-velocity, low-amplitude soft-tissue approaches.[8] In a recent systematic review, Ernst reviewed and reported evidence on adverse events of spinal manipulation published between 2001 and 2006.[44] He identified 32 case reports, 6 case series (controlled or uncontrolled), three case-control studies, and three surveys. Results from four retrospective case series indicated that spinal manipulation was associated with an increased risk of vascular events and non-vascular complications. Two prospective case series reported mild to moderate adverse events of transient nature in 30% to 61% of patients who had received spinal manipulation. Results from the three case-control studies indicated that participants receiving spinal manipulation were at higher risk of vertebral artery dissection.[44] More recent review by Ernst reported 26 published cases of death following chiropractic treatment that occurred since 1934.[45] The age of about half of the victims was below 40 years and the majority of all fatalities were associated with

vascular complications leading to thrombosis and cerebral infarction. The time interval between chiropractic treatment and death ranged from 1 hour to 58 days.[45]

Carnes and colleagues conducted another comparative systematic review of harms reported (up to March 2008) and published in prospective studies of manual therapy.[46] This review compared the risk of adverse events (defined as major, moderate, and minor) between manual therapy and other alternatives from 8 cohort studies (22898 participants) and 31 RCTs (5060 participants). None of the studies documented the occurrence of death, cerebrovascular accidents, or stroke. The meta-analyses of randomised trials suggested an increased risk of mild (short-term and mild intensity) to moderate adverse events (medium to long term; moderate intensity) in manual therapy versus general practitioner care (pooled RR=1.91, 95% CI: 1.39, 2.64). The risk of mild to moderate adverse events in manual therapy groups was similar to that in exercise (pooled RR=1.04, 95% CI: 0.83, 1.31) or placebo groups (pooled RR=1.84, 95% CI: 0.93, 3.62). The risk of mild to moderate adverse events was significantly lower in manual therapy versus drug therapy (pooled RR=0.05, 95% CI: 0.0, 0.20). None of the RCTs documented any major adverse event. The incidence of major adverse events after manual therapy as reported in the cohort studies was 0.007%. In the cohort studies, the pooled incidence of mild to moderate adverse events after manual therapy was 41.00% (95% CI: 17.00, 68.00).

A recent case-control study of 818 cases with vertebro-basilar artery (VBA) stroke and 3164 matched controls found that a chiropractic visit in the month before the index date was associated with an increased risk for VBA stroke in patients under 45 years of age (OR=3.13, 95% CI: 1,48, 6.63).[47] The same study found also an increased risk for VBA stroke in patients who had visited a primary care physician in the month before the index date (under 45 years of age: OR=3.57; 45 years or older: OR=2.67).[47] Hurwitz and colleagues reported 6 month follow-up safety results from a randomised trial comparing manipulation and mobilisation for cervical spine in patients with neck pain and found a higher incidence of any adverse events (mostly minor and transient) in patients randomised to manipulation versus mobilisation (adjusted OR: 1.44, 95% CI: 0.85, 2.43).[48]

Several other reviews on safety of chiropractic[49;50] and spinal manipulation and/or mobilisation[51-53] have also been published.

Previous work

The current review builds on the "UK evidence report" by Bronfort and colleagues (2010)[40] on the effectiveness of manual therapies commissioned by the UK General Chiropractic Council (GCC). The purpose of the Bronfort report was to establish the evidence for what chiropractors can advertise in line with the CAP code (Code of Advertising Practice) and guidance of the ASA (Advertising Standards Authority). Bronfort and colleagues aimed to identify 'medium to high level evidence' from RCTs. There is an ongoing situation concerning 600 complaints about websites that have allegedly breached ASA guidelines. The quality of evidence and what constitutes health benefits, are all part of ongoing discussion. The profession, through the College of Chiropractors, funded the University of Warwick to undertake a comprehensive systematic review of evidence other than RCTs of the effectiveness of chiropractics, since the Bronfort report only focused on RCTs and systematic reviews (e.g. 49 recent relevant systematic reviews, 16 evidence-based clinical guidelines and 46 RCTs not yet summarised in systematic reviews).

1. Evidence considered "**supporting**"
    - Spinal manipulation/mobilisation is effective in adults for acute, subacute, and chronic low back pain; for migraine and cervicogenic headache; cervicogenic dizziness; and a number of upper and lower extremity joint conditions.
    - Thoracic spinal manipulation/mobilisation is effective for acute/subacute neck pain, and, when combined with exercise, cervical spinal/manipulation is effective for acute whiplash-associated disorders and for chronic neck pain.
    - Massage in adults was concluded to be an effective treatment option for chronic low back pain and chronic neck pain.

2. Evidence considered "**inconclusive**"
    - The evidence is inconclusive for cervical manipulation/mobilisation alone for neck pain of any duration, and for any type of manipulation/mobilisation for mid back pain, sciatica, tension-type headache, coccydynia, temporomandibular joint disorders, fibromyalgia, premenstrual syndrome, and pneumonia in older adults.
    - In children, spinal manipulation/mobilisation for otitis media and enuresis.
    - Massage for knee osteoarthritis, fibromyalgia, myofascial pain syndrome, migraine headache, and premenstrual syndrome.

3. Evidence considered "**not effective**"
    - Spinal manipulation for asthma and dysmenorrhoea when compared to sham manipulation, or for stage 1 hypertension when added to an antihypertensive diet.
    - In children, spinal manipulation/mobilisation for infantile colic and for improving lung function in asthma when compared to sham manipulation.

Since the publication of the Bronfort report, a range of additional relevant systematic reviews and RCTs have been published (see for example[54-69]).

Why this review is important

In their report, Bronfort and colleagues referred to the limitations of the available evidence (in terms of study quality and availability), but they also highlighted a range of issues that can be tackled in a more extensive review. The report only included systematic reviews and RCTs published in English, and the authors acknowledge that considering other study designs and including non-English language literature may yield important evidence. Another major limitation of the report was the lack of critical appraisal of the systematic reviews and clinical guidelines included in the report. Also, the information on the included systematic reviews and additional RCTs – both in terms of study characteristics and study results – was not reported very systematically and was not tabulated, making it difficult to gain a quick overview of the available evidence and the comparisons assessed.

Therefore, the current work aims to:

- Synthesise evidence besides RCTs and systematic reviews captured by the Bronfort report, such as controlled cohort studies, CCTs, cost-effectiveness, and qualitative studies (this will only be possible in detail in selected areas but an overview will be provided in the evidence catalogue)

- Compare conclusions from the additional studies summarised (new RCTs and systematic reviews and additional study types) to those of the Bronfort report, focusing in particular on areas where the Bronfort report stated that the available evidence was inconclusive or that manual therapy was not effective
- Identify limitations (e.g. some systematic reviews and RCTs were not captured, methodology and reporting) of the Bronfort report and gaps in evidence

In particular, systematic overviews examining evidence in detail were done in the following areas:

- Clinical effectiveness of manual therapies for selected non-musculoskeletal conditions
- Cost-effectiveness studies for manual therapies

This was achieved by the following means:

- First, all available evidence was catalogued. The catalogue included systematic reviews and RCTs, including any new ones published since the publication of the Bronfort report, as well as evidence from relevant cohort studies, cost-effectiveness studies and qualitative studies. The purpose of cataloguing the research was to provide the College of Chiropractors with a database of research they can refer to – there is no analytic part to this, other than a relatively brief overall summary (based on "vote counting") comparing the results to those of Bronfort and colleagues. The catalogue includes brief descriptions of study characteristics and results and aims to be a useful resource for anyone requiring an overview of available studies on different manual therapy techniques used for treating different conditions (providing a database that can be filtered by condition, treatment, study type etc.)
- Secondly, any new relevant systematic reviews or RCTs published since the completion of the Bronfort report were summarised systematically, as were any relevant systematic reviews and RCTs omitted from the Bronfort report
- Thirdly, a systematic reviews of cost-effectiveness was conducted

Chapter 2 – Methods

Inclusion criteria

Types of studies

The following types of studies were considered:

- Systematic reviews
- RCTs and CCTs
- Cohort studies with a comparison group
- Qualitative studies of patients' views on manual therapy
- Cost-effectiveness studies

The following inclusion and exclusion criteria applied:

Inclusions:

- Primary studies comparing interventions (clinical studies or cohort studies) were only included if participants were followed up for a minimum of 12 weeks
- Primary interventions studies (clinical studies or cohort studies) were only included if they included a minimum of 20 participants
- In the case of studies reporting adverse events, other primary study types were also considered (non-comparative studies, case series) if they included at least 20 participants
- Systematic reviews were only included as "new evidence" if they were published after 1995
- For the cost-effectiveness review, primary comparative studies (randomised, non- randomised controlled trials, comparative cohort studies), study protocols (of completed or ongoing studies), or systematic reviews were included if they reported a cost-effectiveness and/or cost-utility analysis

Exclusions:

- Cross-sectional studies with a comparison group
- Conference abstracts

Studies are listed by study type.

Types of participants

Both the evidence catalogue and the more detailed overviews summarised studies of patients of any age and in any setting treated for any musculoskeletal or non-musculoskeletal condition (within indications for chiropractic, osteopathic and orthopaedic manual therapy as defined by the respective professions).

Exclusions:

- Studies in healthy participants (e.g. physiological studies, studies in athletes to improve performance)

- Studies of the use of manipulation / traction in acute injuries for realigning bones (fractures) or reducing dislocated bones (manual therapy for other types of injuries such as ankle sprains, whiplash will be included)
- Studies of manual therapy for congenital conditions (e.g. club foot, congenital torticollis)

Studies are presented by type of condition.

Types of interventions

Both the evidence catalogue and the systematic reviews include studies assessing any manual treatment / therapy (including e.g. spinal and extremity joint manipulation or mobilisation, massage and various soft tissue techniques). Emphasis was on interventions typically carried out by a manual therapist / chiropractor / osteopath. Comparisons are against any other therapy.

The following inclusion and exclusion criteria applied:

Inclusions:
- Studies including massage in a general "manual therapy package" were included, but studies using only massage techniques were excluded. However, studies of transverse / deep friction massage were included as this technique includes elements of mobilisation and manipulation. Systematic reviews of massage were checked for these techniques
- In the case of RCTs, additional treatments (e.g. pain medication, exercise, TENS, elastic tape) were only allowed if used equally in the different comparison groups. For cohort studies, this parameter was not as easily controllable, but any co-interventions should be listed in detail and any imbalances were noted. Studies just mentioning e.g. “physiotherapy” or “conservative treatment” as one of the interventions were checked with respect involvement of manual therapy
- Studies of traction were included if they involved a manual element, rather than using instruments exclusively
- Studies of the hand-held Activator and Integrator instruments were included

Exclusions:
- Manual therapy interventions involving any invasive techniques (e.g. anaesthesia)
- Manual treatment following or in association with surgery (i.e. studies where manipulation is part of the "surgical package"; studies of manipulation in post-surgery rehabilitation were considered)
- Canalith repositioning manoeuvre for benign paroxysmal vertigo
- Passive motion / mobilisation (e.g. in cerebral palsy or after surgery)
- Systematic reviews of some other intervention including manual therapy as one of a variety of possible comparators
- Prevention studies (e.g. injury prevention in athletes)
- Studies where manual therapy is used in all comparison groups (i.e. where the comparison is not against manual therapy)
- Studies of mechanical aids (e.g. braces, shoe orthotics)

Interventions were grouped according to intervention categories depending on studies identified (e.g. standard chiropractic treatment, standard osteopathic treatment, massage (by subtypes), other types of manual therapy).

Duration and frequency of the treatment were also taken into account, as was therapist experience and training. Interventions were also classified regarding their complexity, i.e. the number of co-interventions (e.g. manual therapy alone or with additional massage, exercise etc.).

Types of outcome measures

The following outcomes were considered (depending on condition):

Musculoskeletal conditions:
- Pain intensity
- Pain-related disability
- Analgesic use
- Function
- Mobility (e.g. walking distance)
- Other relevant symptoms

Non-musculoskeletal conditions:
- Characteristic symptoms or indicators of disease

General:
- Patient satisfaction
- Quality of life
- Activities of daily living
- Views / themes from qualitative data
- Adverse events (conceivably related to the treatment, e.g. strokes, fractures, pain)
- Mortality

Where not explicitly used as an intervention, pain medication use was also taken into account.

Based on the data identified, outcomes were subdivided into short term and longer term outcomes.

Outcome measures focused on patient relevant outcomes. Studies reporting only biomechanical and physiological outcomes (e.g. range of motion, heart rate variability) and / or laboratory parameters were excluded. Ideally, outcomes had to be measured using standard validated instruments.

For the cost-effectiveness review, effectiveness outcome measures (e.g., pain, disability, quality of life, utility), costs, and ICERs were reported. Studies reporting only costs without effectiveness (e.g., cost- minimisation), and studies reporting other types of economic analyses (e.g., cost-benefit, cost-consequence) were excluded.

Search strategy

We used a varied range of sources and search techniques to identify relevant literature. A comprehensive literature search was undertaken in the major medical, health-related, science and health economic electronic bibliographic databases. We paralleled the comprehensive searches undertaken by Bronfort et al. (2010)[40] through a clearly defined search strategy using the databases: MEDLINE (Ovid), EMBASE, Mantis, Index to Chiropractic Literature, CINAHL, the specialised databases Cochrane Airways Group trial register, Cochrane Complementary Medicine Field register, and Cochrane Rehabilitation Field register (via CENTRAL). We supplemented these searches by using the following other databases: Science Citation Index, AMED, CDSR, NHS DARE, NHS HTA, NHS EED, CENTRAL (full search), and ASSIA, Social Science Citation Index.

The detailed electronic search strategy is provided in Appendix I. Search terms were restricted to terms related to manual therapy and broader terms like 'physiotherapy' were not included as initial tests suggested that the volume of literature identified using such an extended search strategy would not be manageable. To keep the search as open as possible, no condition terms were included.

There was no language restriction in the searches but due to time constraints, only relevant studies published in the main languages spoken by the review team were included (English, French, German, Spanish).

The main search was carried out in August 2011. Some additional PubMed searches for more up to date studies since the first search (up to July 2012) and of reference lists of relevant reviews were carried out, however, due to time constraints these were not exhaustive.

Study selection

The study selection process comprised the following steps:

1. Collection of references from the electronic and additional searches in a Reference Manager database, enabling studies to be retrieved in each of the identified categories by either keyword or text word searches.
2. Duplicate elimination.
3. After a test run with 50 references, one reviewer (CC) screened titles and abstracts of the identified bibliographic records by comparing them against the inclusion criteria for the evidence catalogue outlined above. Around 20% of the references was checked in duplicate (by AT) and agreement between the reviewers was calculated using the kappa statistic. The second reviewer (AT) also checked any studies selected for possible inclusion by the first reviewer and any records where a decision based on title and abstract screening was difficult.
4. For the evidence catalogue, due to the large number of studies potentially eligible for inclusion, full text records could not be retrieved for all potentially relevant studies, so the approach had to be pragmatic. As far as possible, decisions on inclusion or exclusion were made based on the abstracts of the records. Where no abstract was available or where the abstract was unclear, the full text was retrieved as far as possible, but decisions for exclusion were also made based on other indicators (e.g. the title, the reference or the keywords indicating that the record was e.g. a conference abstract or a commentary). This also means that the catalogue still contains records of uncertain relevance.

5. For the cost effectiveness review, to determine the final selection for inclusion, the two reviewers independently compared the retrieved full text articles against the inclusion criteria outlined above and against the minimum quality criteria outlined below. The decisions were coded and recorded in an Excel database. Studies excluded at the full text screening stage were listed in a table of excluded studies along with reasons for exclusion.
6. Any disagreements at stages (3) to (5) were resolved by consensus or by referring to a third reviewer (PS).

Studies for the systematic review and the update on new studies and studies omitted by the Bronfort report were selected from the list of studies included in the evidence catalogue based on the additional inclusion criteria specified and the data available (to specify key conditions etc.).

Data extraction and management

Evidence catalogue

The evidence catalogue was compiled from records judged to be potentially eligible after screening titles and abstracts of the results of the main search. The data were then examined in detail (as far as possible) and extracted into an a priori developed Excel spread sheet. Data extraction was not exhaustive and was restricted to key information. This comprised basic information on study type, study participants (narrow and broader condition categories, number of participants, basic indicators of sex / age), study intervention (details of the intervention and the comparison, duration and dose). Any abstract included in the record was used to provide a summary of the study description and results. Additionally, a keyword section (as provided by the original database from which the record was retrieved) was included. The summary of number and population group of participants and duration and dose of the intervention was only done as far as was possible based on the study abstracts and thus the data can only be partially provided.

Due to time constraints, the catalogue was not systematically supplemented with additional eligible primary studies identified through included systematic reviews. Similarly the most recently identified relevant studies published in 2012 were included in the main report but not in the catalogue.

A filtering function was included for each column, so that data can be retrieved as required by the user (e.g. studies from a specific date range, studies by specific authors, specific study types, conditions or interventions etc.). References included in the Bronfort report were marked in orange. Any relevant studies included in the Bronfort report but not in the evidence catalogue were added. And records judged not to be eligible after initial inclusion in the catalogue and more detailed scrutiny were moved to a separate spreadsheet of the database with reasons for exclusion.

Overview of new / omitted studies

To obtain an overview of new studies and potentially relevant studies omitted by the Bronfort report, first, all systematic reviews and RCTs included in the Bronfort report were tabulated, by condition as classified in the report. Then the evidence catalogue was filtered by the relevant condition and any studies not already included in the Bronfort report were checked for their relevance and listed (with

systematic reviews, RCTs and other study types listed in separate columns) if they were judged to be relevant additional studies. For most conditions, the Bronfort report listed both included systematic reviews and any RCTs included in the reviews, plus any additional RCT evidence found. However, for back and neck pain, RCTs included in the included reviews were not listed, and so for our comparative table, the last relevant systematic review included by Bronfort was checked for its included studies and the date of the latest search, and the selection focussed on studies published after the latest search of the latest review. This process was followed for all conditions, and conditions not included in the Bronfort report were added. Studies were only included in the table after obtaining and checking their full text publication. When summarising systematic reviews on broader topics than the one considered in this review (e.g. of complementary therapies or physiotherapy in general), only sections of relevance to the current review were considered.

For the summary of new and additional studies, the focus was on conditions and interventions where the evidence had been judged to be inconclusive or negative by in the Bronfort report, or on conditions that the Bronfort report had not reported on. For these cases, a more detailed tabulation of study characteristics, inclusion criteria, methodology and results was done. Study quality was assessed by study type according to the quality criteria outlined below. Studies were grouped by condition and study type. In a few cases, new studies published in 2012 were identified after the respective section was completed. A brief summary of the study was added to the relevant section but no formal data extraction or quality assessment was carried out.

For conditions and interventions judged to have moderate or high quality positive evidence in the Bronfort report, no exhaustive summary of all new / additional systematic reviews and primary studies was carried out. However, the most recent and relevant systematic reviews concerning these conditions / interventions were summarised. These were selected based on year of publication (2010 to 2012), perceived quality (e.g. Cochrane review, adequate description of methodology and quality assessment of included studies), and comprehensiveness (in terms of the spectrum of the condition and available manual therapies). A formal quality assessment was not carried out.

Systematic review of cost-effectiveness studies

Data were extracted by one reviewer using *a priori* developed data extraction forms. The extracted data were then entered into evidence tables. The extracted data included: a) study characteristics (e.g., author name, year of publication, country, design, sample size, follow-up duration), b) types of participants (e.g., study condition, inclusion/exclusion criteria, age, gender), c) types of interventions including comparators (e.g., manual therapy, exercise, usual general practitioner care, soft-tissue massage), d) treatment dose (number of sessions) and duration, e) statistical analysis (e.g., bootstrap techniques, number of replications, parametric tests, levels of statistical significance), f) type of economic evaluation (i.e., cost-effectiveness, cost-utility analysis), g) perspective (e.g., societal, health care payer, patient), h) study currency, i) costs (direct health care, direct non-health care, indirect), j) discounting, and k) outcomes (mean differences in costs, effectiveness/utility measures, ICERs, uncertainty measures, the ceiling willingness-to-pay ratios, probabilities from cost-effectiveness acceptability curves).

Assessment of risk of bias

Quality assessment was done for the cost-effectiveness review and the summary of new and additional evidence but, due to the large number of records, was not possible for the evidence catalogue.

Study quality was assessed according to study type. Quality assessment was done by the reviewer responsible for the respective section (AT for cost-effectiveness, CC and AT for the overview of new and additional studies). The opinion of a third person (PS) was sought when there was any disagreement regarding the quality of a study.

The checklists used for each study type are shown below. There are three possible responses to the items of each checklist: 'yes', 'no', and 'unclear'. In some cases, a rating of 'partially met' is also possible (e.g. in the AMSTAR tool if only a list of included studies is provided). For rating study quality, the number of items in each scale were roughly divided by three and studies were rated as 'high quality' (low risk of bias) if more than two thirds of the quality criteria were met, studies were rated 'medium quality' (moderate risk of bias) if more than one third and up to two thirds of quality criteria were met, and studies were rated 'low quality' (high risk of bias) if a third or fewer of the quality criteria were met (for details see below). In cases where partial ratings were possible, two criteria partially met counted for one criterion completely met.

Systematic reviews were assessed using the AMSTAR tool[70-72]:

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Rating (by criteria fulfilled, i.e. 'yes' response): 9 to 11 high quality, 5 to 8 medium quality, 0 to 4 low quality.

RCTs were assessed using the Cochrane Risk of Bias tool[73]:

1. Adequate sequence generation
2. Adequate allocation concealment
3. Blinding (especially outcome assessment)
4. Incomplete outcome data addressed
5. Free of selective reporting
6. Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)

Rating (by criteria fulfilled, i.e. 'yes' response): 5 to 6 high quality, 3 to 4 medium quality, 0 to 2 low quality.

Controlled cohort studies were assessed based on the CRD checklist (2001, with their original item on dose-response removed as this did not seem relevant to the current review)[74]:

1. Is there sufficient description of the groups and the distribution of prognostic factors?
2. Are the groups assembled at a similar point in their disease progression?
3. Is the intervention/treatment reliably ascertained?
4. Were the groups comparable on all important confounding factors?
5. Was there adequate adjustment for the effects of these confounding variables?
6. Was outcome assessment blind to exposure status?
7. Was follow-up long enough for the outcomes to occur?
8. Was an adequate proportion of the cohort followed up?
9. Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Rating (by criteria fulfilled, i.e. 'yes' response): 7 to 9 high quality, 4 to 6 medium quality, 0 to 3 low quality.

Qualitative studies were assessed based on CASP qualitative appraisal tool[75]:

1. Was there a clear statement of the aims of the research?
2. Is a qualitative methodology appropriate?
3. Was the research design appropriate to address the aims of the research?
4. Was the recruitment strategy appropriate to the aims of the research?
5. Were the data collected in a way that addressed the research issue?
6. Has the relationship between researcher and participants been adequately considered?
7. Have ethical issues been taken into consideration?
8. Was the data analysis sufficiently rigorous?
9. Is there a clear statement of findings?
10. Have the contributions and implications of the research been discussed?

Rating (by criteria fulfilled, i.e. 'yes' response): 8 to 10 high quality, 5 to 7 medium quality, 0 to 4 low quality.

Economic modelling studies were assessed using the Drummond checklist[76]:

1. Are the decision problem, the relevant settings, and audiences (i.e., decision-makers) clearly specified?
2. Does the overall analytical approach incorporate the relevant perspectives (e.g., health service or societal) and relevant objective functions (e.g., maximizing health gain)?
3. Are the data used to populate the model relevant to the target audiences (i.e., decision-makers) and settings?
4. Where data from different sources are pooled, is this done in a way that the uncertainty relating to their precision and possible heterogeneity is adequately reflected?
5. If data from other settings are used, have these been assessed for relevance in the settings of interest?
6. Is uncertainty (i.e., parameter uncertainty and heterogeneity) adequately reflected in the model?
7. Are results reported in a way that allows the assessment of the appropriateness of each parameter input and each assumption in the target settings?

Rating (by criteria fulfilled, i.e. 'yes' response): 6 to 7 high quality, 4 to 5 medium quality, 0 to 3 low quality.

Methods of analysis

Data were summarised in text and tables as outlined above.

Overview of new / omitted studies

For the overview of new and additional studies, evidence summaries were carried out in analogy to those reported in the Bronfort report[40] and it was indicated, whether the additional evidence changed the judgement made in the Bronfort report.

The categories used in the Bronfort report were as follows:

High quality evidence

- Consistent results from well-designed, well conducted studies in representative populations which assess the effects on health outcomes
- The evidence is based on at least two consistent higher-quality (low risk of bias) randomised trials

Moderate quality evidence

The available evidence is sufficient to determine the effectiveness relative to health outcomes, but confidence in the estimate is constrained by such factors as:

- Number, size, or quality of individual studies
- Inconsistency of findings across individual studies
- Limited generalisability of findings to routine practice
- Lack of coherence in the chain of evidence

The evidence is based on at least one higher-quality randomised trial (low risk of bias) with sufficient statistical power, two or more higher-quality (low risk of bias) randomised trials with some inconsistency; at least two consistent, lower-quality randomised trials (moderate risk of bias).

Inconclusive (low quality) evidence

The available evidence is insufficient to determine effectiveness relative to health outcomes. Evidence is insufficient because of:

- The limited number or power of studies
- Important flaws in study design or methods (only high risk of bias studies available)
- Unexplained inconsistency between higher-quality trials
- Gaps in the chain of evidence
- Findings not generalisable to routine practice
- Lack of information on important health outcomes

A determination was made whether the inconclusive evidence appeared favourable or non-favourable or if a direction could even be established (unclear evidence).

In the summary, factors such as study quality, type of manual therapy, comparator treatment, dose and duration of treatment, and severity and chronicity of symptoms were considered.

The eligible primary studies were too heterogeneous in terms of therapies and co-interventions used, conditions treated, and study design to allow meta-analysis.

Systematic review of cost-effectiveness studies

The results were organised by condition and within each condition, by type of manual therapy. The cost-effectiveness and/or cost-utility results were summarised in text and tables. Systematic reviews were not included in evidence synthesis but rather were briefly summarised in terms of included eligible studies. Protocols of ongoing studies were briefly summarised. Study, participant, intervention, outcome characteristics, and results were tabulated in evidence and summary tables. If a study failed to report the ICERs for interventions, the reviewers attempted to calculate them only if data allowed. All costs were converted to the United Kingdom Pounds (GBP) using the exchange rates applicable to the end (the month of December) of the year for which the cost estimates in each study were reported (www.xe.com).

Identification of future areas for primary research

Based on our findings, we compiled a list of areas where research is needed in future. In addition, to help inform future research in this field and to obtain patient perspectives on the acceptability and attitudes of treatments in this broad area of study, a workshop/dissemination event was held at Warwick University.

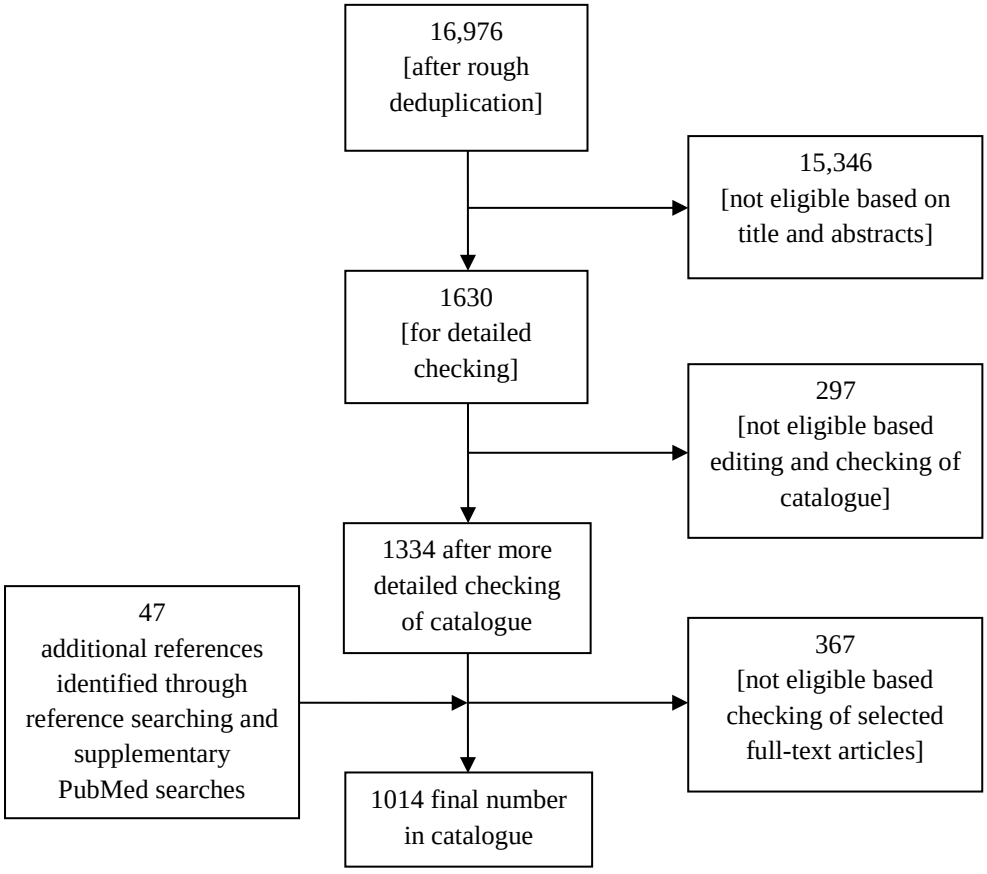
Chapter 3 – Clinical effectiveness results

Search results

Two independent reviewers, using *a priori* defined inclusion/exclusion criteria, screened abstracts and titles for a 20% sample (n=3388) of all retrieved bibliographic records. Overall, the proportion of agreement between the two reviewers for inclusions and exclusions was 93.9%. The calculated kappa statistic of 0.74 (95% CI: 0.70, 0.77) indicated 'substantial' agreement.

A flow chart of the search results is shown in Figure 1. The initial database searches yielded 25,539 records (16,976 after rough deduplication). The final version of the evidence catalogue contained 1014 bibliographic records. Reasons for exclusion included: absence of comparison group, irrelevant outcomes, study in healthy volunteers, ineligible intervention, ineligible condition, relevant intervention similar in all comparison groups, conference abstracts or commentaries, non-systematic review.

Figure 1. Flow chart of search results



Catalogue summary

The following section provides a brief summary of the data found in the Excel catalogue. Using the filtering function of the database, the user will be able to investigate additional parameters as needed. Studies can be filtered by given parameters or using free text. Also, the user can add new studies to the catalogue as they are published.

As not each of the 1014 records currently listed in the catalogue could be checked in detail, and as the records checked also include multiple articles referring to single studies, the summary data provided in this section only serve to give a general impression of the body of evidence, and not to give absolute values. Also, as some studies will fall in more than category and some studies have been classified as uncertain (but could not be checked), the numbers will not always add up to 1014.

As shown in Figure 2, the vast majority of relevant studies identified were RCTs and systematic reviews, with only a relatively small number of non-randomised comparative studies identified.

Figure 2. Break-down by study types

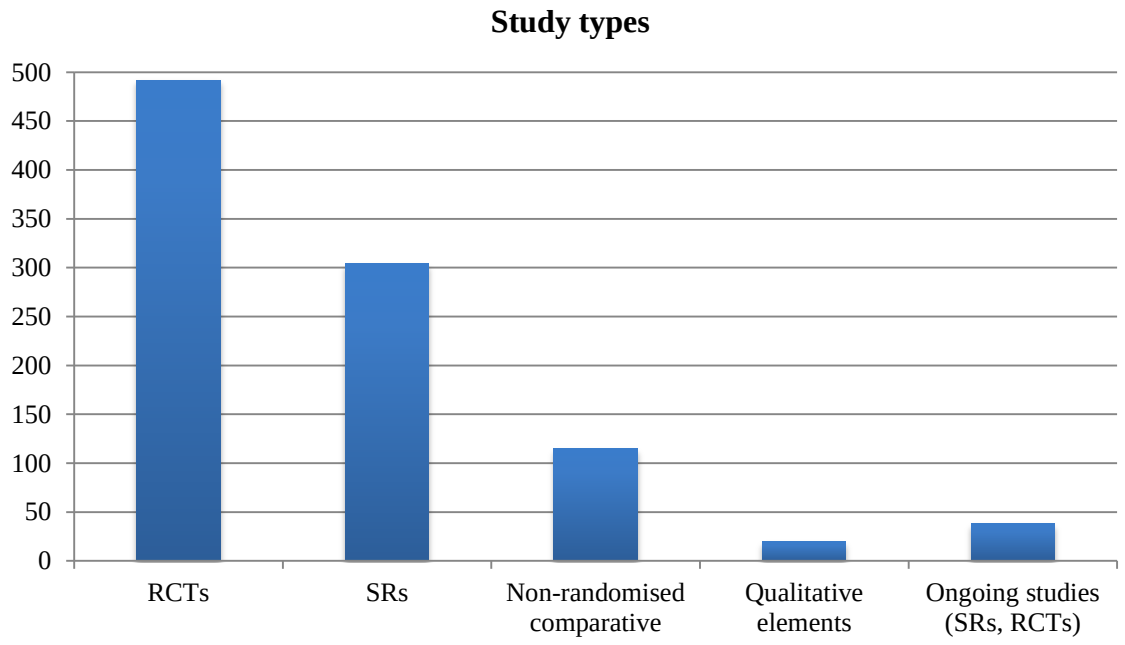
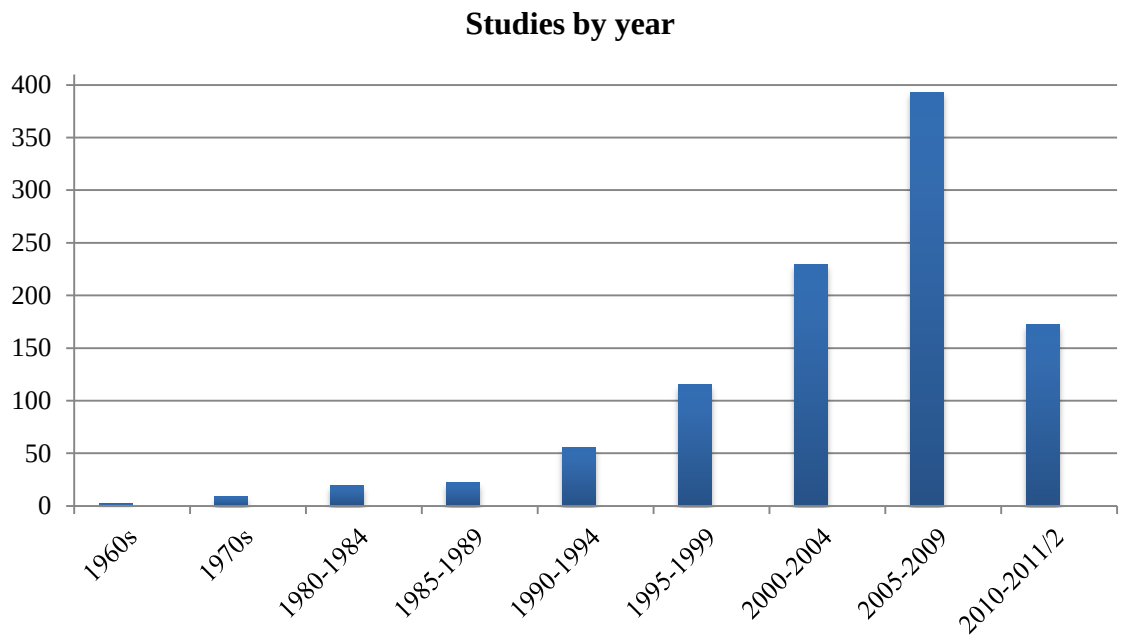


Figure 3 indicates that publication of relevant articles increased substantially in recent years and about 17% of the studies in the catalogue were studies published after the last search of the Bronfort report.

Figure 3. Break-down by year of publication



As shown in Figure 4, the vast majority of studies (about 75%) related to treatment of musculoskeletal conditions. This was true overall, as well as for published systematic reviews, comparative non-RCT evidence, and studies published after 2009.

Figure 4. Break-down by overall conditions (with indications on study type and newly published studies)

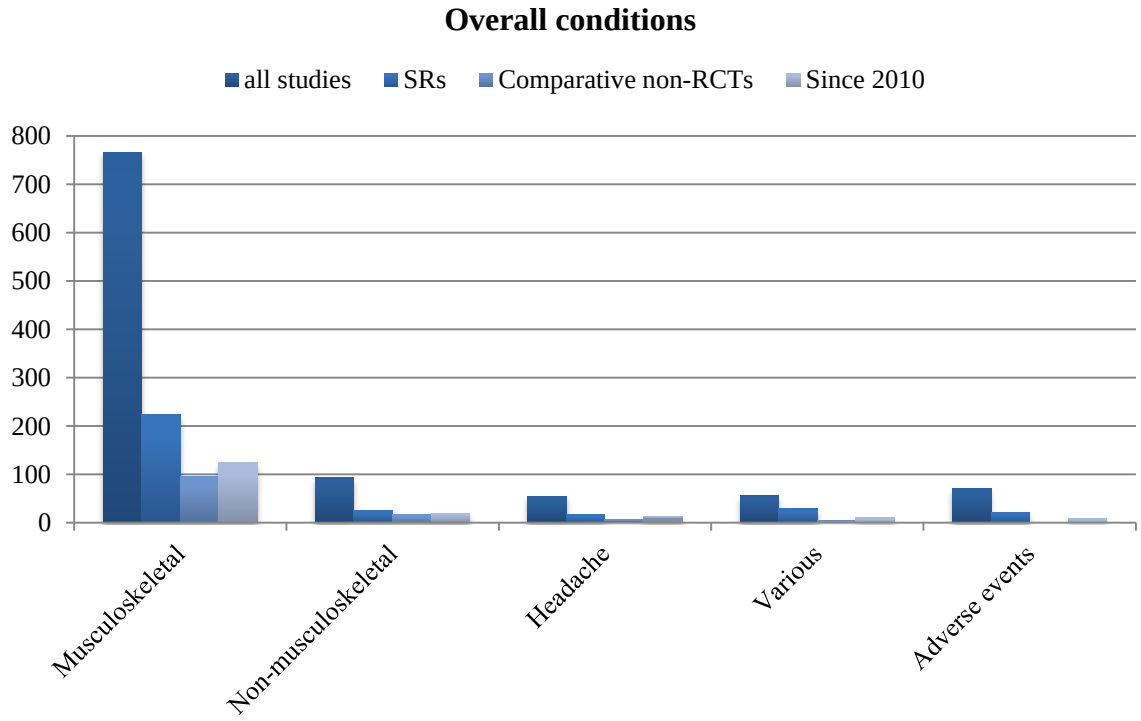
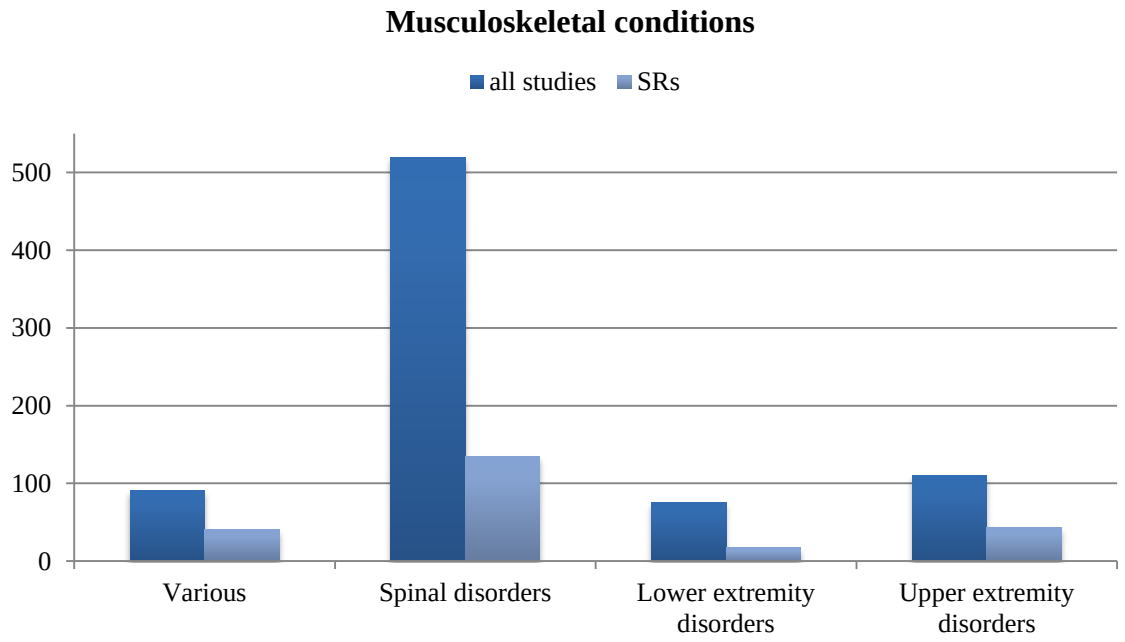


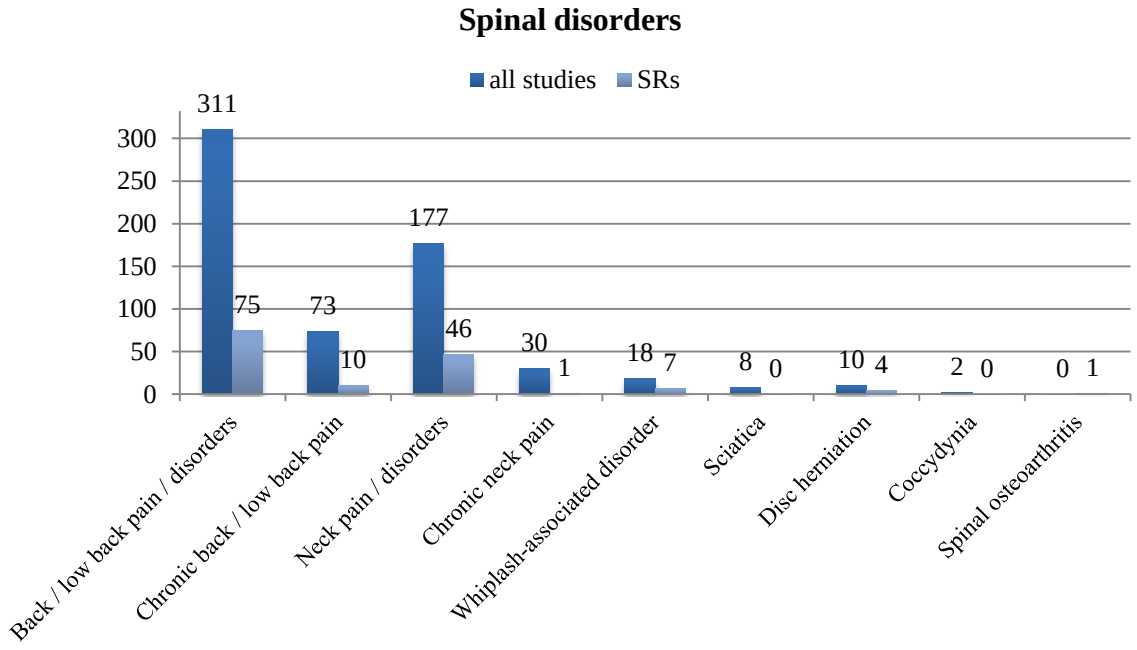
Figure 5 shows that the majority of studies dealing with musculoskeletal conditions (about 67%) was concerned with spinal disorders.

Figure 5. Break-down of studies on musculoskeletal conditions



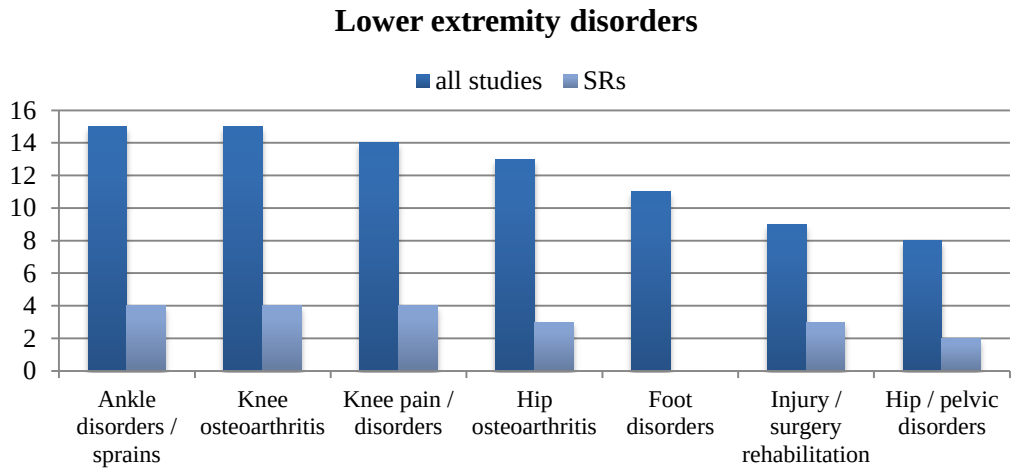
Among studies on spinal disorders (Figure 6), studies on back pain or disorders were most common, followed by studies on neck pain or disorders.

Figure 6. Break-down of studies on spinal disorders



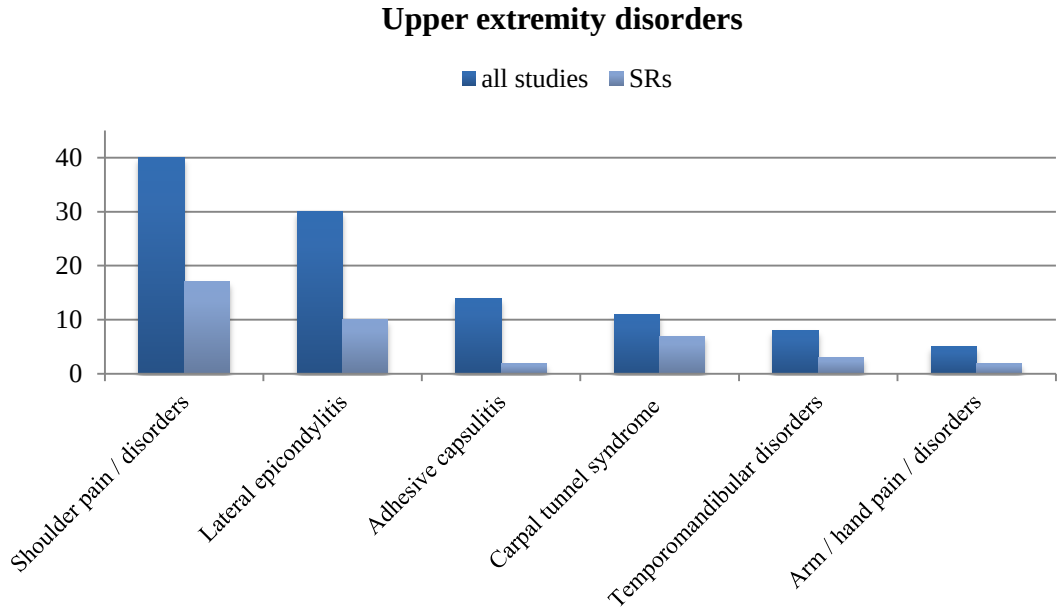
Among lower extremity disorders (Figure 7), there was a more equal distribution between studies concerning foot, ankle, knee, or hip disorders or surgery / injury rehabilitation.

Figure 7. Break-down of studies on lower extremity disorders



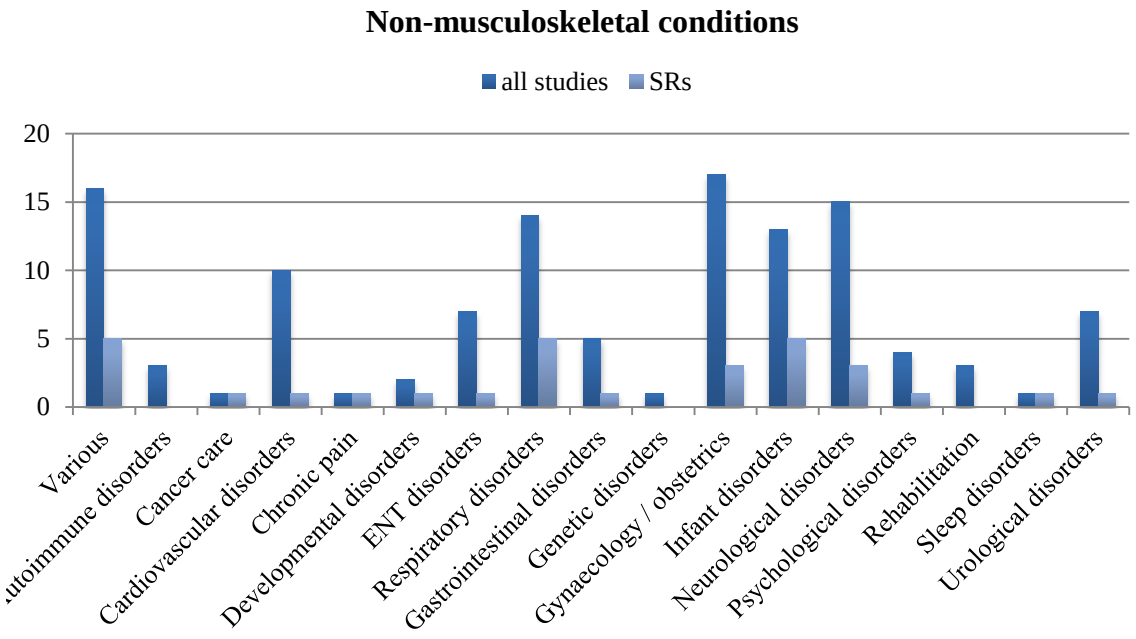
Among studies on upper extremity disorders (Figure 8), studies on shoulder disorders were most common, followed by studies of lateral epicondylitis (tennis elbow).

Figure 8. Break-down of studies on upper extremity disorders



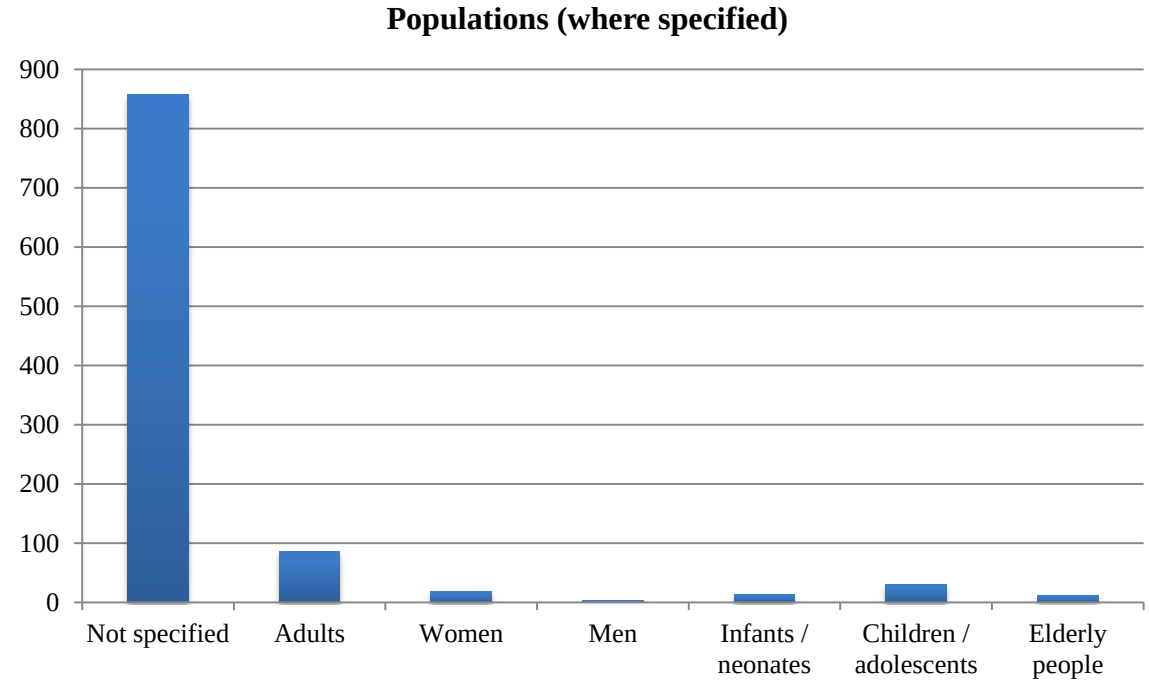
As shown in Figure 9, a whole range of non-musculoskeletal conditions was considered, but for many specific conditions, only a small number of relevant studies was available.

Figure 9. Break-down of studies on non-musculoskeletal conditions



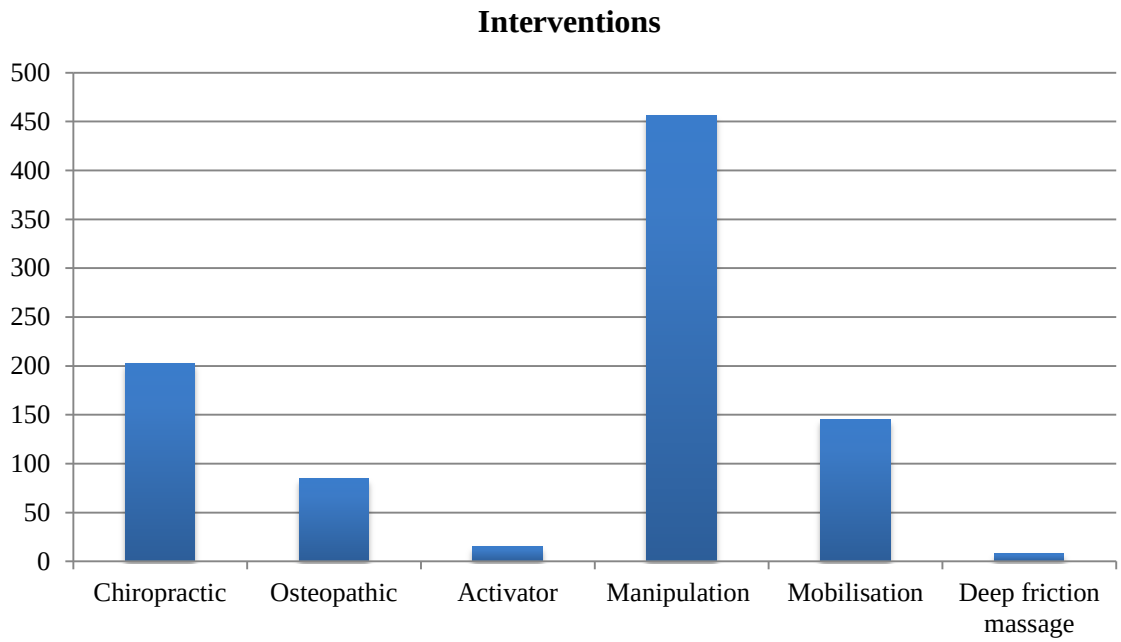
In most abstracts, specifics of the population included (other than defined by the condition) were not included, while some mentioned that the study was carried out in adults. Only a relatively small number of studies (shown in Figure 10) studied more specific populations, such as elderly people, children, women etc.

Figure 10. Break-down of studies carried out in specific populations



A selection of specific interventions examined by the studies is presented in Figure 11.

Figure 11. Break-down of studies by intervention type



Summary of new and additional studies

The current section summarises relevant studies not included in the Bronfort report and relevant studies published after the last search of the Bronfort report and compares new findings to the findings of the Bronfort report. An overview of additional studies by condition in comparison to studies included in the Bronfort report can be found in numerical form in Table 2. The same table with named studies can be found in Appendix II. Studies are summarised in more detail in the tables under each condition heading with associated detailed quality assessment tables in Appendix III. Table 3 provides an overview of the evidence summaries following the style of figures 3 to 6 in the Bronfort report. Ongoing studies are summarised in Appendix IV. This section contains a summary of considerably fewer studies than may be expected from evidence catalogue. This is because only studies definitely relevant to answer questions of effectiveness have been assessed in this section, whereas the catalogue also contains studies of possible interest but no direct relevance to questions of treatment effectiveness.

At the end of this section, a summary table of evidence findings is shown (Table 3). This lists the evidence ratings of the Bronfort report and compares them to the evidence ratings determined by the present report for the individual conditions and interventions. The orange colouring corresponds to inconclusive evidence, the green colouring to positive evidence, and the yellow colouring to negative evidence. The last column of the table indicates whether the evidence is based on any additional data not considered by the Bronfort report or whether no new information has become available since the Bronfort report.

Table 2. Numerical comparison of studies included in the Bronfort report and new / additional studies in the current review

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	***RCTs***	***Systematic reviews***	***RCTs***	***Other primary study types***
Conditions / Interventions with high / moderate quality positive evidence in the Bronfort report					
Musculoskeletal					
Non-specific Low Back Pain (LBP)	7	*Details of RCTs in reviews not listed, additional:* 13	15 completed 1 ongoing	24 completed 4 ongoing	1 qualitative 1 cohort
Mechanical neck pain	6	*Details of RCTs in reviews not listed, additional:* 7	8 *Adverse events:*1	39	
Whiplash-associated disorders	2	1	5	4 completed 1 ongoing	
Adhesive capsulitis		5	2	6	2 cohort
Hip pain	1	2	3	4 completed 4 ongoing	2 cohort
Knee pain / disorders	1	10	6	6	1
Patello-femoral pain syndrome		3	2	2	
Headache disorders					
Migraine Headache	2	4	3	2	1 cohort
Conditions / Interventions with inconclusive or negative evidence in the Bronfort report and additional conditions not covered by Bronfort					
Musculoskeletal					
Sciatica / radiating leg pain	3	*Details of RCTs in reviews not listed*		2 completed 1 ongoing	
Non-specific mid back pain	0	7 *[not all thoracic back pain]*	1	1 ongoing	
Coccydynia	0	1	0	0	
Shoulder pain	2	6	14	11	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	***RCTs***	***Systematic reviews***	***RCTs***	***Other primary study types***
Lateral epicondylitis	3	11	7	6 completed 1 ongoing	2 CCT 1 cohort
Carpal tunnel syndrome	4	2	4	3	
Ankle and foot conditions	2	16	2	5 completed 1 ongoing	
Temporo-mandibular disorders	2	5	1 ongoing	3	
Fibromyalgia	3	8	2	2	
Myofascial pain syndrome	1	15	2	3	
Headache disorders					
Tension-Type Headache	5	12		4	
Cervicogenic Headache	4	7	1	4	
Miscellaneous Headache	1	1	3	2	
Non-musculoskeletal					
ADHD / Learning disorders	*not reported*	*not reported*	2	4 completed 1 ongoing	1 qualitative
Asthma	4	5	1	2	1 qualitative
Birth / Pregnancy / Post-natal	*not reported*	*not reported*	2	1	4
Cancer care	*not reported*	*not reported*	1		
Cardiovascular disorders	*not reported*	*not reported*			1
Cerebral palsy	*not reported*	*not reported*		3	
Chronic fatigue	*not reported*	*not reported*	1		
Chronic pelvic pain	*not reported*	*not reported*		3	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	***RCTs***	***Systematic reviews***	***RCTs***	***Other primary study types***
Cystic fibrosis	*not reported*	*not reported*		1	
Diabetes complications	*not reported*	*not reported*		1	
Gastrointestinal	*not reported*	*not reported*	1	3	
Pneumonia / respiratory infections	1	1	1	2 completed 1 ongoing	
Vertigo	2	2	1	1	
Balance	*not reported*	*not reported*		2	
Infantile Colic	6	8	2		1
Menopausal symptoms	*not reported*	*not reported*		1	
Neurological disorders / Insomnia			2		
Nocturnal Enuresis	2	2	1		
Parkinson's	*not reported*	*not reported*		1	
Paediatric dysfunctional voiding	*not reported*	*not reported*		1	
Otitis media	3	2	0	1 ongoing	
Hypertension	1	3	1	2	1 CCT
Dysmenorrhoea	2	5	0	0	
Premenstrual Syndrome	3	3	0	0	
Surgery rehabilitation and related	*not reported*	*not reported*		3	2 CCT 1 cohort
Systemic sclerosis	*not reported*	*not reported*		2	
Adverse events	5	*Primary studies:* 6	11	*Primary studies:* 33	

Conditions / interventions that were 'inconclusive', 'negative' or not covered in the Bronfort report

Musculoskeletal conditions

Sciatica and back-related leg-pain

Three publications of randomised trials (McMorland 2010, Paatelma 2008, Schulz 2011)[77-79] were identified for this sub-section. One publication reported a study protocol (Schulz 2011).[79]

In their study (medium quality), McMorland and colleagues (McMorland 2010)[77] aimed to compare the effectiveness of spinal manipulation and surgical treatment on quality of life, disability, and pain intensity in patients with sciatica. Namely, the authors randomised 40 patients with sciatica to receive chiropractic spinal manipulation (high velocity, low-amplitude, short lever technique) or surgical microdiskectomy. The outcome of interest were quality of life (measured by Short Form-36), pain intensity scales (measured by McGill Pain Questionnaire, Aberdeen Back Pain Scale), and disability (measured by the Roland-Morris Disability Index) measured at 3, 6, 12, and 56 weeks after baseline. At 12 weeks of follow-up (primary intention-to-treat analysis), there was a significant post-baseline improvement in both study groups in regards to quality of life (total score), pain intensity (McGill Pain Questionnaire, Aberdeen Back Pain Scale), and disability (Roland-Morris Disability Index). However, the differences in pain (McGill scale p=0.754; Aberdeen scale p=0.836), quality of life (total SF-36 score p=0.683), and disability (p=0.760) observed between the two groups were not significantly different.

In a high quality randomised trial by Paatelma and colleagues (Paatelma 2008),[78] the authors attempted to evaluate the effectiveness of orthopaedic manual therapy and the McKenzie method relative to advice only with respect to pain intensity and disability in patients with non-specific low back pain (with/without sciatica in one or both legs). The authors randomised 134 patients to receive orthopaedic manual therapy (n=45; mobilisation, high velocity low-force manipulation, translatoric thrust manipulation), the McKenzie method (n=52; education, the book, instructions in exercises), or advice only (n=37; counselling from a physiotherapist). The study outcomes, pain intensity (VAS) and disability (Roland-Morris Disability Index) were measured post-baseline at 3, 6, and 12 months. Although at 6 and 12 months of follow-up, all three groups improved significantly in pain and disability compared to baseline, the mean improvements for the manipulation group in pain and disability were not significantly different from those observed for the McKenzie method (p-value not reported) and the advice only groups (12 months follow-up: leg pain p=0.273, low back pain p=0.714, disability p=0.068).

In a study protocol of one randomised trial (Schulz 2011),[79] the authors aimed to evaluate the effectiveness of adding chiropractic spinal manipulative therapy (SMT) to home exercise program (HEP) in patients with subacute or chronic back-related leg pain. The planned sample of 192 patients will be randomised to either chiropractic SMT (high velocity, low-amplitude manipulation, low velocity mobilisation, light soft-tissue techniques, and hot/cold

packs) plus HEP (teaching methods developing spinal posture awareness for activities of daily living; exercise to enhance mobility and increase trunk endurance) or HEP alone for 12 weeks. The outcomes of interest (e.g., leg pain, low back pain, bothersomeness of symptoms, disability, general health status, patient satisfaction, medication use, quality of life, etc.) will be measured at 3, 12, 26, and 52 weeks post-baseline.

Evidence summary. According to the Bronfort report,[40] evidence regarding the effectiveness of manipulation/mobilisation for sciatica has been inconclusive. The above-reviewed evidence from two medium to high quality trials, additional to the Bronfort report, suggests that in general, chiropractic or orthopaedic manipulation may be effective in reducing symptoms of sciatica in adults, however, it is not clear due to the small sample size of the trials, if these manual treatment techniques are more beneficial compared to surgery, McKenzie method, or advice only.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>McMorland 2010[77]
Canada

Focus: RCT to compare the effectiveness of spinal manipulation and surgical treatment on quality of life, disability, and pain intensity in patients with sciatica

Duration: 12 weeks (spinal manipulation)
Follow-up: 52 weeks
Quality: medium

PARTICIPANTS:
N: 40 (40% female)
Age: 36.4-42.85 years (range of means)

Inclusion: patients aged 18 years or older with leg-dominant symptoms with objective signs of nerve root tethering with or without neurologic deficit correlated with evidence of appropriate root compression on magnetic resonance imaging; must have failed to respond to at least 3 months of non-operative management (analgesics, lifestyle modification, physiotherapy, massage, and/or acupuncture; patients receiving concurrent or previous spinal manipulation

Exclusions: substance abuse, neurological deficits (cauda equine, foot drop), radicular symptoms < 3 months, systemic or visceral disease, haemorrhagic disorders, osteopenia, osteoporosis, pregnancy, dementia, unable to speak/read English</td>
<td>**Intervention type:** chiropractic
Intervention (n=20): chiropractic spinal manipulation (high velocity, low-amplitude, short lever technique)
Comparison (n=20): surgical microdiskectomy
Dose:
Chiropractic manipulation
2-3 visits per week (weeks 1-4), 1-2 visits per week (weeks 4-8), number of visits was based on patients' symptoms (weeks 8-12)
Surgical microdiskectomy
Single procedure
Providers: a doctor of chiropractic</td>
<td>**Results**

Follow-up of 12 weeks post-baseline

<table>
<tr><th>Change in outcome</th><th>Spinal manipulation</th><th>Surgery</th><th>p-value</th></tr>
<tr><td>Improvement rate (n/N)</td><td>12/20 (60%)</td><td>17/20 (85%)</td><td>NS (p=NR)</td></tr>
<tr><td>Pain intensity (McGill Pain Questionnaire)
Mean (SD)</td><td>19.4 (14.3)</td><td>13.0 (16.3)</td><td>NS (p=0.754)</td></tr>
<tr><td>Pain intensity (Aberdeen Back Pain Scale)
Mean (SD)</td><td>35.6 (18.9)</td><td>25.8 (23.7)</td><td>NS (p=0.836)</td></tr>
<tr><td>Disability (Roland-Morris Disability Index)
Mean (SD)</td><td>9.0 (6.2)</td><td>7.2 (6.9)</td><td>NS (p=0.760)</td></tr>
<tr><td>Quality of life (total SF-36 score)
Mean (SD)</td><td>484.6 (148.9)</td><td>500.3 (179.7)</td><td>NS (p=0.683)</td></tr>
</table>

Specific adverse effects: most common minor adverse events in both groups were post-procedural episodes of self-limiting increased soreness</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Paatelma 2008[78]
Finland

Focus: RCT to evaluate the effectiveness of orthopaedic manual therapy and McKenzie method compared to advice only with respect to pain intensity and disability in patients with non-specific low back pain (with/without sciatica in one or both legs)
Duration: 3 months
Follow-up: 3, 6, and 12 months
Quality: high

PARTICIPANTS:
N: 134 (35% female)
Age: 44 years
Inclusion: employed adults 18-65 years with acute or chronic non-specific low back pain (with/without sciatica in one or both legs)

Exclusion: pregnancy, low back surgery less than 2 months previously, serious spinal pathology</td>
<td>Intervention type: physiotherapy
Intervention (n=45): orthopaedic manual therapy (mobilisation, high velocity low-force manipulation, translatoric thrust manipulation of the thoracic-lumbar junction)
Intervention (n=52): McKenzie method (education, the book Treat Your Own Back, instructions in exercises repeated several times a day)
Comparison (n=37): advice only (counselling from a physiotherapist regarding the good prognosis for low back pain, pain tolerance, medication, early return to work; advice to avoid bed rest and be as active as possible through exercise activities)
Dose: orthopaedic manual therapy (3-7 visits each 30-45 minutes for 3 months); McKenzie method (3-7 visits each 30-45 minutes for 3 months); advice only (1 visit of 45-60 minutes for 3 months)
Providers: physical therapists with certification in the method used in the study; orthopaedic manual therapy was provided by a specialist with 20 years of experience in the field; McKenzie method was provided by a physiotherapist with 10 years of experience in the method; advice only programme was provided by a physiotherapist with 5 years of clinical experience in treating low back pain</td>
<td><u>Results</u>

The mean improvements for the manipulation group in pain and disability were not significantly different from those observed for the McKenzie method (data not reported) and the advice only groups. No numerical data was given for the comparison of orthopaedic manual therapy versus McKenzie method

<table>
<tr><th>Change in outcome
(12 months post-baseline)</th><th>Orthopaedic manual therapy</th><th>p-value (orthopaedic manual therapy versus advice only group)</th></tr>
<tr><td>Leg pain (VAS)
Mean difference
(95% CI)</td><td>-10 (-25, 5)</td><td>NS
(p=0.273)</td></tr>
<tr><td>Low back pain (VAS)
Mean difference
(95% CI)</td><td>-4 (-17, 9)</td><td>NS
(p=0.714)</td></tr>
<tr><td>Roland-Morris Disability Index
Mean difference
(95% CI)</td><td>-3 (-6, 0)</td><td>NS (p=0.068)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Neck pain (cervical manipulation / mobilisation alone)

Six new RCTs examined the effect of cervical spinal manipulation or mobilisation alone for neck pain of any duration (Aquino 2009, Gemmell 2010, Leaver 2010, Martel 2011, Schomacher 2009, Puentedura 2011).[80-85]

In their randomised trial of medium quality (Aquino 2009),[82] Aquino and colleagues compared the effects of joint mobilisation applied to either symptomatic or asymptomatic cervical levels in patients with chronic non-specific neck pain. The authors randomised 48 participants to one of the two groups, experimental (mobilisation applied to a randomly chosen cervical vertebral level) or control (mobilisation applied to the most symptomatic vertebral level). The outcomes of interest were immediate post-treatment mean pain scores at resting position, during most painful moment, and during vertebral palpation. Immediately after the end of treatment, significant within-group mean improvements from baseline ($p<0.001$) were observed for pain scores during most painful moment (experimental group: 2.67 and control group: 2.62) and during vertebral palpation (experimental group: 2.42 and control group: 2.37), but not for pain at resting position (experimental group: 0 and control group: 0.54). None of the differences between the two groups for any of the outcome measures was significant.

Gemmell and colleagues (Gemmell 2010)[83] attempted to determine the relative effectiveness and harms of cervical manipulation, mobilisation, and the activator instrument in patients with subacute non-specific neck pain (medium quality trial). The patients were randomised to receive a three-week treatment with cervical manipulation (cervical/upper thoracic segmental high velocity, low amplitude movements), mobilisation (cervical/upper thoracic segmental low velocity, low amplitude movements), or the activator instrument. The primary (Patient Global Impression of Change [PGIC]) and secondary (Short-Form Health Survey [SF-36], the neck Bournemouth Questionnaire for disability, and numerical rating scale [NRS] for pain intensity) outcomes were measured immediately, 3, 6, and 12 months after the end of treatment. Due to poor recruitment (47 randomised patients), the trial was stopped prematurely. At 12 months post-treatment, the proportion of patients who improved on PGIC was not significantly different across the three study groups (73% versus 77% versus 50%, respectively). However, there were significant within-group improvements from baseline in disability and pain intensity for the manipulation and activator instrument groups. The mobilisation group experienced a significant within-group improvement in two subscales of SF-36 (mental and physical components). At the 12 month of follow-up, none of the between-group differences for disability (the neck Bournemouth Questionnaire), pain intensity (NRS), or quality of life (SF-36) was statistically significant. Fifteen patients in the manipulation and four patients in each group of the mobilisation and activator experienced minor adverse events (e.g., mild headache, mild dizziness, mild arm weakness).

In a randomised trial (high quality) by Leaver and colleagues (Leaver 2010),[84] the authors compared the effectiveness of cervical manipulation (high-velocity, low-amplitude thrust technique) versus mobilisation (low-velocity, oscillating passive movements) administered to 182 patients with non-specific neck pain (less than 3 months of duration) for two weeks. The study outcomes were the median number of days to recovery (the first of seven consecutive days for which the patient rated the degree of interference as "not at all"), pain intensity (Numerical Rating Scale [NRS]), disability (Neck Disability Index [NDI]), function (Patient Specific Functional Scale [PSFS]), quality of life (physical and mental health components of 12-item Short-Form [SF-12]), and global perceived effect (from 'much worse' to 'completely recovered'). At 3 months of follow-up (post-baseline), the median

number of days to recovery was not significantly different between the manipulation and mobilisation groups (47 days versus 43 days, respectively; hazard ratio: 0.98, 95% CI: 0.66, 1.46). There was no significant difference between the two groups in the mean post-treatment pain intensity (mean difference: 0.2, 95% CI: -0.4, 0.7), disability (mean difference: -0.2, 95% CI: -2.1, 1.7), function (mean difference: 0.0, 95% CI: -0.6, 0.5), and global perceived effect (mean difference: -0.1, 95% CI: -0.6, 0.4). Two participants in the mobilisation group experienced serious adverse events that were unrelated to the treatment (cardiac surgery and severe arm pain/weakness). Most frequent adverse events were minor and included increased neck pain (22%) and headache (22%). Other less frequent events were dizziness (7%), nausea (6%), and paraesthesia (7%). The frequency of adverse events was not significantly different between the study groups.

In one randomised trial of medium quality (Martel 2011),[85] the authors investigated the efficacy of spinal manipulative therapy (SMT) compared to no treatment in patients with non-specific chronic neck pain. Specifically, 98 patients with neck pain were randomly assigned to one of the three treatment groups: SMT (standardised passive palpation on the cervical and thoracic spine), SMT plus home exercise (range of motion exercise, stretching/mobilisation, strengthening exercise of the cervical/upper thoracic spine, flexion/extension, rotation), or no treatment (attention group; clinical visits, distribution of diaries) for 10 months. The study outcomes were pain intensity (VAS score), quality of life (HRQOL), range of motion (ROM), rotation, lateral flexion, disability (Neck Disability Index), and physical/mental components of the SF-12 questionnaire. After the treatment phase, all study groups experienced significant improvements in disability and lateral flexion. However, the between-group differences for all outcome measures were statistically non-significant.

One randomised trial of medium quality (Puentedura 2011)[81] compared the effectiveness of 2-week thoracic thrust joint manipulation (TJM) plus cervical range of motion (ROM) exercise to that of cervical TJM plus cervical ROM exercise in 24 adults with acute neck pain. The study outcomes were 1 week-, 4 week-, and 6 month- post-treatment mean scores of the Neck Disability Index (NDI), Numeric Pain Rating Scale (NPRS), and Fear-Avoidance Beliefs Questionnaire (FABQ). At 6 months of follow-up, the cervical TJM group compared to the thoracic TJM group experienced significantly improved scores for NDI (3.7 versus 9.9, p=0.004), NPRS (0.1 versus 2.3, p<0.001), and FABQ (2.1 versus 5.2, p=0.04). Similarly, the overall success rate (based on pre-specified score improvements on NDI, NPRS, and global rating of change scales) was significantly higher in the cervical TJM group versus thoracic TJM group (71.4% versus 10%, p=NR). The mean change for both scores of NDI and NPRS met or exceeded the pre-specified minimal clinically important difference (MCID; 7 and 1.3 points, respectively). Minor transient adverse events (increased neck pain, fatigue, headache, upper back pain) were reported by 70%-80% of the participants in the thoracic TJM group versus 7% in the cervical TJM.

In one study of low quality (Schomacher 2009),[80] the author randomised 126 adult participants with chronic neck pain to receive a single 4-minute mobilisation technique (intermittent translatoric traction at the zygopophyseal joint between C2 and C7 with Kaltenborn's grade II force) applied to either symptomatic levels (concordant segment) versus asymptomatic levels (three levels below/above concordant segment) of the cervical spine. The study outcome was immediate post-treatment neck pain intensity and sensation of movement measured by an 11-point numeric Rating Scale (NRS). Although before and after the treatment, both treatment groups improved significantly (p<0.01) in terms of pain and sensation, the immediate post-treatment between-group differences for the mean change in pain (1.3 versus 1.7, p=0.12) and sensation of movement (1.9 versus 2.2, p=0.15) were not statistically significant.

Evidence summary. According to the Bronfort report, there is inconclusive to moderate grade evidence showing benefits in favor of mobilisation and/or thoracic/cervical manipulation for neck pain of acute/subacute, chronic, or any duration. In agreement with the Bronfort report, conclusions of one low, four medium and one high quality trials reviewed above also indicated after-treatment (versus baseline) benefits of thoracic/cervical mobilisation and/or manipulation for the treatment of neck pain. The reviewed evidence shows no difference in the effectiveness between different types of manipulation and/or mobilisation techniques.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Aquino 2009[82]
Brazil

Focus: RCT compared the effects of joint mobilisation applied to either symptomatic or asymptomatic cervical levels in patients with chronic non-specific neck pain
Duration: not reported
Follow-up: not reported
Quality: medium

PARTICIPANTS:
N: 48 (73% female)
Age: 33 years
Inclusion: adults 18-65 years with chronic neck pain (3 months or longer)
Exclusions: vertebral artery insufficiency, osteoporosis, tumour, infection, fracture, trauma, cervical spine surgery in the last 12 months, pregnancy, neurological deficit, treatment with physiotherapy</td>
<td>Intervention type: physiotherapy
Intervention 1 (n=24): mobilisation according to Maitland technique (postero-anterior central vertebral pressure, postero-anterior unilateral vertebral pressure, and transversal vertebral pressure) applied to a randomly chosen cervical vertebral level
Intervention 2 (n=24): mobilisation according to Maitland technique (postero-anterior central vertebral pressure, postero-anterior unilateral vertebral pressure, and transversal vertebral pressure) applied to the most symptomatic vertebral level
Dose: 1 session
Providers: well-trained physiotherapist</td>
<td><u>Results</u>

Immediately after the end of treatment, significant within-group mean improvements from baseline (p<0.001) for pain scores during most painful moment and during vertebral palpation, but not for pain at resting position (experimental group: 0.54 and control group: 0); none of the differences between the two groups for any of the outcome measures was significant

<table>
<tr><th>Change in outcome
(Immediately post-treatment after baseline)</th><th>Cervical mobilisation applied to randomly chosen cervical vertebral level</th><th>Cervical mobilisation applied to the most symptomatic vertebral level</th><th>Mean difference
95% CI
p-value</th></tr>
<tr><td>Pain at rest (11-point scale)
Mean (SD)</td><td>0.54 (2.48)</td><td>0 (2.57)</td><td>-0.52
(-1.87, 0.83)
NS</td></tr>
<tr><td>Pain during most painful moment (11-point scale)
Mean (SD)</td><td>2.67 (3.14)</td><td>2.62 (2.34)</td><td>-0.13
(-1.63, 1.38)
NS</td></tr>
<tr><td>Pain during vertebral palpation (11-point scale)
Mean (SD)</td><td>2.42 (2.20)</td><td>2.37 (1.84)</td><td>-0.16
(-1.31, 0.99)
NS</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Gemmell 2010[83]
UK

Focus: RCT attempted to determine the relative effectiveness and harms of cervical manipulation, mobilisation, and the activator instrument in patients with subacute non-specific neck pain
Duration: 3 weeks
Follow-up: 12 months post-treatment
Quality: medium

PARTICIPANTS:
N: 47 (69%-87% female)
Age: 45 years
Inclusion: adults18-64 years with subacute non-specific neck pain present for 4 weeks or longer but no longer than 12 weeks; baseline pain intensity at least 4 points on 11-point Numerical Rating Scale
Exclusions: treatment with any of the study therapy, tumour, infection, fracture, trauma, radiculopathy, inflammatory arthropathy, blood coagulation disorders, long-term use of corticosteroids, cervical spine surgery, stroke or transient ischaemic attack</td>
<td>Intervention type: chiropractic
Intervention 1 (n=16): cervical manipulation (cervical/upper thoracic segmental high velocity, low amplitude movements)
Intervention 2 (n=15): cervical mobilisation (cervical/upper thoracic segmental low velocity, low amplitude movements)
Intervention 3 (n=16): activator instrument (high velocity, low amplitude force in the physiological range of the joint applied to cervical/upper thoracic segments)
Dose: 2 treatments per week for 3 weeks treated until symptom free or received maximum of 6 treatments; single session 10-15 minutes of duration
Providers: 2 chiropractic clinicians with 15-30 years of experience</td>
<td><u>Results</u>

<u>12 months post-treatment</u>
• The proportion of patients who improved on PGIC was not significantly different across the manipulation, mobilisation, and activator instrument groups (73% versus 77% versus 50%)
• None of the between-group differences for disability (the neck Bournemouth Questionnaire), pain intensity (NRS), or quality of life (SF-36) were statistically significant

<table>
<tr><th>Change in outcome</th><th>Activator versus manipulation</th><th>Activator versus mobilisation</th><th>Manipulation versus mobilisation</th></tr>
<tr><td>Patient Global Impression of Change
OR 95% CI</td><td>3.8
0.39, 37.18</td><td>3.3
0.27, 40.61</td><td>1.2
0.09, 15.96</td></tr>
<tr><td>The neck Bournemouth Questionnaire
Mean (95% CI)</td><td>6.54
-9.03, 22.10</td><td>5.68
-12.33, 23.69</td><td>-0.86
-17.28, 15.59</td></tr>
<tr><td>Pain intensity (11-point NRS)
Mean (95% CI)</td><td>1.72
-1.17, 4.62</td><td>1.30
-2.05, 4.65</td><td>-0.42
-3.47, 2.63</td></tr>
<tr><td>SF-36 (mental component subscale)
Mean (95% CI)</td><td>0.42
-7.74, 8.59</td><td>-1.75
-11.19, 7.69</td><td>-21.17
-10.78, 6.44</td></tr>
<tr><td>SF-36 (physical component subscale)
Mean (95% CI)</td><td>-4.41
-12.48, 3.66</td><td>-4.53
-13.87, 4.80</td><td>-0.12
-8.64, 8.39</td></tr>
</table>

Specific adverse effects: Minor transient adverse events (e.g., mild headache, mild dizziness, mild arm weakness, etc.) reported by 15 participants in the manipulation group versus 4 participants in each mobilisation and activator group</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Leaver 2010[84]
Australia

Focus: RCT compared the effectiveness of cervical manipulation versus mobilisation in patients with acute non-specific neck pain
Duration: 2 weeks
Follow-up: 3 months
Quality: high

PARTICIPANTS:
N: 182 (65% female)
Age: 39 years
Inclusion: adults 18-70 years with non-specific neck pain less than 3 months
Exclusions: neck pain related to trauma, serious pathology (neoplasm), whiplash injury, infection, radiculopathy, myeolopathy, cervical spine surgery, neck pain less than 2 out of 10 on NRS</td>
<td>Intervention type: physiotherapy / chiropractic / osteopathy
Intervention (n=91): cervical manipulation (high-velocity, low-amplitude thrust technique)
Comparison (n=91): cervical mobilisation (low-velocity, oscillating passive movements)
Dose: 4 treatments over 2 weeks
Providers: practitioners with postgraduate qualifications in specific training of neck manipulation and mobilisation (from physiotherapy, chiropractic, osteopathy); all practitioners had at least 2 years of clinical experience in routinely using manipulation and mobilisation techniques</td>
<td><u>Results</u>

<u>3 months of follow-up</u>
The median number of days to recovery (the first of seven consecutive days for which the patient rated the degree of interference as “not at all”) was not significantly different between the manipulation and mobilisation groups (47 days versus 43 days, respectively; hazard ratio: 0.98, 95% CI: 0.66, 1.46)

<table>
<tr><th>Change in outcome
(6 months post-baseline)</th><th>Cervical manipulation
Mean (SD)</th><th>Cervical mobilisation
Mean (SD)</th><th>Mean difference
95% CI</th></tr>
<tr><td>Pain Numeric Rating Scale</td><td>1.6 (2.0)</td><td>1.4 (1.7)</td><td>0.2,
-0.4, 0.7 [NS]</td></tr>
<tr><td>Neck Disability Index (NDI)</td><td>5.3 (6.2)</td><td>5.5 (6.6)</td><td>-0.2,
-2.1, 1.7 [NS]</td></tr>
<tr><td>Patient Specific Functional Scale</td><td>8.6 (2.0)</td><td>8.6 (1.8)</td><td>0.0,
-0.6, 0.5 [NS]</td></tr>
<tr><td>Physical health (SF-12)</td><td>50.2 (6.2)</td><td>50.6 (7.8)</td><td>-0.4,
-2.5, 1.7 [NS]</td></tr>
<tr><td>Mental health (SF-12)</td><td>52.2 (8.9)</td><td>52.7 (8.7)</td><td>-0.5,
-3.1, 2.2 [NS]</td></tr>
<tr><td>Global perceived effect*</td><td>3.3 (1.7)</td><td>3.4 (1.9)</td><td>-0.1,
-0.6, 0.4 [NS]</td></tr>
</table>
* from ‘much worse’ (-5) to ‘completely recovered’ (+5)

Specific adverse effects: Two participants in the mobilisation group had serious adverse events unrelated to the treatment (cardiac surgery and severe arm pain/weakness). Most frequent adverse events were minor: increased neck pain (28%) and headache (22%). Other less frequent events were dizziness (7%), nausea (6%), and paraesthesia (7%). The frequency of adverse events was not significantly different between the study groups.</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Martel 2011[85]
Canada

Focus: RCT investigated the efficacy of spinal manipulative therapy (SMT) compared to no treatment in patients with non-specific chronic neck pain
Duration: 10 months
Follow-up: 10 months
Quality: medium

PARTICIPANTS:
N: 98 (40%-80% female)
Age: 40 years
Inclusion: adults 18-60 years with neck pain 12 weeks or more, no current chiropractic therapy
Exclusions: neck pain related to trauma, serious pathology (neoplasm), whiplash injury, infection, osteoarthritis, cardiovascular disease, cervical spine surgery, pregnancy</td>
<td>Intervention type: chiropractic
Intervention (n=33): spinal manipulative therapy (standardised passive palpation on the cervical and thoracic spine) plus home exercise (range of motion exercise, stretching/mobilisation, strengthening exercise of the cervical/upper thoracic spine, flexion/extension, rotation)
Intervention (n=36): spinal manipulative therapy (standardised passive palpation on the cervical and thoracic spine)
Comparison (n=29): no treatment (attention group; clinical visits, distribution of diaries)
Dose: spinal manipulative therapy (maximum of 4 treatments per session given once a month which lasted 10-15 minutes); home exercise (3 sessions of 20-30 minutes per week)
Providers: chiropractors with at least 3 years of experience</td>
<td><u>Results</u>

<u>10 months of follow-up</u>
After the treatment phase, all study groups experienced significant improvements in disability and lateral flexion; however, the between-group differences for all outcome measures were statistically non-significant

<table>
<tr><th>Outcome</th><th>SMT + home exercise
Mean (SD)</th><th>SMT
Mean (SD)</th><th>No treatment
Mean (SD)</th></tr>
<tr><td>Pain (VAS score)</td><td>1.6 (2.3)</td><td>2.1 (2.3)</td><td>2.9 (2.9)</td></tr>
<tr><td>Neck Disability Index (NDI)</td><td>11.3 (11.8)</td><td>13.7 (12.1)</td><td>21.5 (14.0)</td></tr>
<tr><td>Flexion-extension (degrees)</td><td>115.6 (22.5)</td><td>114.1 (21.0)</td><td>106.1 (23.3)</td></tr>
<tr><td>Rotation (degrees)</td><td>126.7 (25.7)</td><td>126.9 (29.5)</td><td>119.5 (15.4)</td></tr>
<tr><td>Lateral flexion (degrees)</td><td>70.8 (23.7)</td><td>67.1 (13.6)</td><td>70.5 (11.1)</td></tr>
<tr><td>Physical health (SF-12)</td><td>54.1 (7.2)</td><td>53.1 (6.9)</td><td>52.1 (8.2)</td></tr>
<tr><td>Mental health (SF-12)</td><td>49.8 (8.7)</td><td>52.3 (8.4)</td><td>49.9 (10.1)</td></tr>
</table>

Specific adverse effects: no serious adverse events</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Puentedura 2011[81]
USA

Focus: RCT compared the effectiveness of thoracic TJM plus cervical ROM exercise versus cervical TJM in adults with acute neck pain
Duration: 2 weeks
Follow-up: 6 months
Quality: medium

PARTICIPANTS:
N: 24 (67% female)
Age: 33 years
Inclusion: adults18-60 years with acute neck pain with NDI score of 10/50 or greater; participant had to meet at least 4 of the 6 criteria (symptom duration < 30 days, no symptom distal to the shoulder, no aggravation of symptoms by looking up, FABQ physical activity subscale < 12, decreased thoracic spine kyphosis T3-T5, cervical ROM<30°)
Exclusions: serious pathology (neoplasm), cervical stenosis, nerve root compression, whiplash injury within 6 weeks prior to study, cervical spine surgery, rheumatoid arthritis, osteoporosis, osteopenia, or ankylosing spondylitis</td>
<td>Intervention type: physiotherapy
Intervention 1 (n=10): thoracic thrust joint manipulation (high velocity, midrange/end range, distraction or anterior-posterior force applied to the mid/upper thoracic spine on the lower/mid thoracic spine in a sitting position) plus cervical ROM exercise (3-finger cervical rotation) followed by standardised exercise programme (3-finger cervical rotation, bilateral shoulder shrugs / adductions / abductions, scapular retractions, upper/lower cervical flexion and extension, Thera-Band rows, and lateral pull downs)
Intervention 2 (n=14): cervical TJM plus cervical ROM exercise followed by standardised exercise programme
Dose: 5 sessions over 2 weeks; thoracic TJM plus cervical ROM (2 sessions), cervical TJM plus cervical ROM exercise (2 sessions), standardised exercise programme (3 sessions)
Providers: physical therapists</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome
(6 months post-baseline)</th><th>Cervical thrust joint manipulation</th><th>Thoracic thrust joint manipulation</th><th>p-value</th></tr>
<tr><td>Neck Disability Index (NDI) score</td><td>3.7 (SD 5.7)</td><td>9.9 (SD 3.9)</td><td>p=0.004</td></tr>
<tr><td>Numeric Pain Ratins Scale (NPRS)</td><td>0.1 (SD 0.1)</td><td>2.3 (SD 1.1)</td><td>p<0.001</td></tr>
<tr><td>Fear-Avoidance Beliefs Questionnaire (FABQ)</td><td>2.1 (SD 3.5)</td><td>5.2 (SD 3)</td><td>p=0.04</td></tr>
<tr><td>Success rate (met or exceeded pre-specified minimal clinically important difference for NDI, NPRS, and global rating of change scales)*</td><td>10/14 (71.4%)</td><td>10% (1/10)</td><td>p=NR</td></tr>
</table>
* Minimal clinically important difference: NDI (7 points), NPRS (1.3 points), and global rating of change (at least +5)

Specific adverse effects: Minor transient adverse events (increased neck pain, fatigue, headache, upper back pain) reported by 70%-80% of the participants in the thoracic TJM group versus 7% in the cervical TJM</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Schomacher 2009[80]
Germany

Focus: RCT to compare the effects of analgesic mobilisation applied either to symptomatic or asymptomatic segments of the cervical spine in adults with chronic neck pain
Duration: 4 minutes
Follow-up: immediate post-treatment
Quality: low

PARTICIPANTS:
N: 126 (NR female)
Age: 49 years
Inclusion: adults >17 years with chronic neck pain (no diagnosis necessary), able to sit and lie down, demonstrate active/passive movements
Exclusion: conditions in which active and passive movements could harm the patient, nerve root compression, and acute inflammation</td>
<td>Intervention type: physiotherapy
Intervention (n=59): mobilisation technique (intermittent translatoric traction at the zygopophyseal joint between C2 and C7 with Kaltenborn’s grade II force) applied to symptomatic levels of the cervical spine (concordant segment)
Comparison (n=67): mobilisation technique applied to asymptomatic levels of the cervical spine (3 levels below/above concordant segment)
Dose: a single 4-minute mobilisation technique
Providers: a physiotherapist-researcher with training in musculoskeletal treatment and orthopaedic manual therapy; 20 years of experience</td>
<td><u>Results</u>

Both treatment groups improved significantly (p<0.01) in terms of pain and sensation after treatment versus before treatment. The between–group post-treatment differences were not statistically significant

<table>
<tr><th>Change in outcome</th><th>Manual therapy (localised segment)</th><th>Manual therapy (3 levels below/above localised segment)</th><th>p-value</th></tr>
<tr><td>(Immediate after treatment)</td><td></td><td></td><td></td></tr>
<tr><td>Neck pain intensity (NRS) endpoint mean scores</td><td>1.8 (SD 1.4)</td><td>2.0 (SD 1.6)</td><td>NS (p=NR)</td></tr>
<tr><td>Sensation of movement (NRS) endpoint mean scores</td><td>2.0 (SD 1.3)</td><td>2.1 (SD 1.7)</td><td>NS (p=NR)</td></tr>
<tr><td>Neck pain intensity (NRS) mean change score</td><td>1.3 (SD 1.2)</td><td>1.7 (SD 1.5)</td><td>NS (p=0.12)</td></tr>
<tr><td>Sensation of movement (NRS) mean change score</td><td>1.9 (SD 1.4)</td><td>2.2 (SD 1.6)</td><td>NS (p=0.15)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Non-specific mid-back pain

One systematic review (Vanti 2008)[86] and one ongoing study (Crothers 2008)[87] were identified on non-specific mid-back pain.

The systematic review included only one trial eligible for the current review, and this trial had already been included in the Bronfort report (Schiller 2001)[88]. The systematic review was of low quality and concluded that it cannot be established whether manual therapy is more effective than non-treatment, placebo, or other treatments. The ongoing RCT (Crothers 2008)[87] compares chiropractic spinal manipulative therapy with the Graston technique (soft tissue massage therapy using hand-held stainless steel instruments) and placebo (de-tuned ultrasound) in 60 adults with non-specific thoracic spinal pain. The treatment lasts three to four weeks, with the participants obtaining 10 sessions of spinal manipulation or placebo or two treatments a weeks with the Graston therapy. Follow-up is at one year.

Evidence summary. No change from the Bronfort report (inconclusive evidence in a favourable direction for the effectiveness of spinal manipulation in patients with thoracic back pain).

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Vanti 2008[86] **Focus:** validity and reliability of manual assessment and effectiveness of manual treatment for non-specific adult thoracic pain **Quality:** low	**INCLUSION CRITERIA** **Study design:** controlled studies **Participants:** studies concerning thoracic spine or rib cage **Interventions:** manual procedures **Outcomes:** pain relief, range of motion / mobility **METHODOLOGY** 5 relevant databases searched, no date limit, 6 languages included; no details on study selection and data extraction; low quality studies excluded but no further details on quality assessment; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 9 controlled trials (8 RCTs) **Study quality:** not reported **Study characteristics:** most studies included did not measure outcomes relevant to the present review; the only relevant RCT (Schiller 2001)[88] is already included in the Bronfort report **Excluded studies eligible for current review:** not reported	**RESULTS** Schiller 2001: significantly greater reduction in pain in the spinal manipulation group than in the control group **CONCLUSIONS** studies gave discordant results, did not distinguish between acute and chronic patients and most had short follow-up; it cannot be established whether manual therapy is more effective than non-treatment, placebo, or other treatments

Coccydynia

No additional / new studies found.

Evidence summary. No change from the Bronfort report (inconclusive evidence in a favourable direction for the use of spinal manipulation in the treatment of coccydynia).

Ankle and foot conditions

Two additional systematic reviews (Lin 2008, Bleakley 2008),[89;90] five additional RCTs (Joseph 2010, Kuhar 2007, du Plessis 2011, Renan-Ordine 2011, Wilson 1991),[91-95] and one ongoing RCT (Davenport 2010)[96] were identified on the treatment of ankle and foot conditions using manual therapy. However, the medium quality systematic review by Bleakley 2008[88] did not include any eligible trials over and above those included in the Bronfort report and will therefore not be described in detail. The authors examined the effectiveness of conservative strategies when added to controlled mobilisation with external support after acute ankle sprain and (based on two RCTs) concluded that there is moderate evidence that manual therapy (manipulation or mobilisation) added to a standard regime is effective in increasing ankle range of movement. The trial by Wilson 1991 was included in the systematic review by Lin 2008 and will be considered in the context of that trial. The ongoing RCT (Davenport 2010) is examining the effectiveness of ankle manual therapy versus placebo for post-acute ankle sprains in 189 adults aged 16 to 60 years. The trial compares two four week treatment regimes, one of talocrural traction manipulation and one of talocrural traction mobilisation, both with range of motion exercises, with a sham protocol and examines the effect on a range of function and psychosocial measures for a follow-up period of up to two years.

The high quality Cochrane review by Lin 2008[90] examined the effect of rehabilitation interventions for ankle fractures. With respect to manual therapy, only one trial with a high risk of bias was identified (Wilson 1991). The trial included only 12 participants in total, who had an ankle fracture treated with or without surgery. The intervention group received physiotherapy including Kaltenborn-based manual therapy to the talocrural and talocalcaneal joints, both groups also received an exercise intervention. After five weeks of treatment, there was no statistically significant improvement in activity limitation or ankle plantarflexion range of motion, but the ankle dorsiflexion range of motion was statistically significant in favour of manual therapy. The review authors concluded that there is limited evidence that manual therapy after a period of immobilisation may improve ankle range of motion in patients after ankle fracture.

Another low quality RCT (Joseph 2010)[92] examined the effects of a muscle energy technique versus manipulation in the treatment of 40 patients with chronic recurrent ankle sprain. After six chiropractic treatments over three weeks, there was significant improvement over time in the One Leg Standing Test (eyes open and closed), the McGill Pain Questionnaire, the Functional Evaluation Scale, and in dorsiflexion and plantarflexion; however, there was no significant difference between the two groups. Adverse events were reported but no serious adverse events were seen.

Du Plessis 2011[91] conducted a medium quality trial of chiropractic treatment in patients with hallux abducto valgus. Thirty patients were included and the intervention group was treated four times over two weeks with graded joint mobilisation of the first metatarsophalyngeal joint plus joint

manipulation, while the control group received a night splint. At the end of the intervention, there was no significant difference between the groups in terms of pain and foot function scores (with both groups showing improved values). However, these improvements were not maintained in the control group, while they were maintained in the intervention group (significant difference between groups in favour of the manual therapy group at the one month follow-up, $p<0.01$). Hallux dorsiflexion was significantly greater in the manual therapy group both at the end of the intervention and at the end of the one month follow-up. Adverse events were reported but no serious adverse events were seen.

Another medium quality RCT (Renan-Ordine 2011)[94] examined the effects of manual therapy in the treatment of plantar heel pain. The trial included 60 patients treated four times weekly for four weeks. Both groups received a self-stretching intervention (directed at the calf muscles and plantar fascia) and the intervention group also received myofascial trigger point manual therapy. After the intervention, results for pressure pain thresholds were significantly better for the manual therapy than for the stretching only group ($p<0.03$) and results for the physical function and bodily pain subscales on the SF-36 quality of life questionnaire were also improved in favour of manual therapy. No significant differences were seen in any other subscales of the SF-36. Similarly, a low quality RCT by Kuhar 2007[93] examined the effects of myofascial therapy in 30 patients with plantar fasciitis and found significantly pain and foot function values in the intervention group compared to control.

One additional systematic review published after the date of our main search was identified. Brantingham 2012[97] conducted a systematic review (review update) of manipulative therapy for lower extremity conditions. They identified one high, ten moderate and two low quality trials concerning manual therapy after ankle inversion sprain, one high and one moderate quality trial concerning plantar fasciitis, one moderate and one low quality trial concerning metatarsalgia, four moderate quality trials concerning decreased proprioception / balance / function secondary to foot and ankle injury / decreased range of motion / joint dysfunction, one moderate quality trial concerning hallux limitus and two moderate quality trials concerning hallus abducto valgus. They concluded that there was moderate evidence for manual therapy (mobilisation / manipulation) of the knee and/or full kinetic chain and of the ankle and/or foot, combined with multimodal or exercise therapy for ankle inversion sprain and limited evidence regarding long term effects. There was also moderate evidence for manual therapy (mobilisation / manipulation / stretching) of the ankle and/or foot combined with multimodal or exercise therapy for short-term treatment of plantar fasciitis. There was limited evidence for manual therapy (manipulation / mobilisation) of the ankle and/or foot combined with multimodal or exercise therapy for short-term treatment of metatarsalgia and hallux limitus/rigidus and for loss of foot and/or ankle proprioception and balance. There was insufficient evidence for manual therapy (mobilisation / manipulation) of the ankle and/or foot for hallux abducto valgus. The authors suggested that further high quality research is needed.

Evidence summary. There is inconclusive evidence in a favourable direction that manipulation, mobilisation, and a muscle energy technique are of benefit in the treatment of ankle sprains. For rehabilitation following ankle fracture, there is moderate quality evidence that mobilisation is of no additional benefit to exercise and inconclusive evidence in a favourable direction for the effectiveness of Kaltenborn-based manual therapy. For hallux abducto valgus, there is inconclusive evidence in a favourable direction that mobilisation / manipulation is more effective in leading to improvements in the intermediate term than night splints. For plantar fasciitis, there is inconclusive evidence in a favourable direction for the effectiveness of trigger point therapy and moderate positive evidence for the effectiveness of manipulation / mobilisation with exercise. For metatarsalgia, hallux limitus/rigidus, and loss of foot and/or ankle proprioception and balance there is limited evidence for

manual therapy (manipulation / mobilisation) of the ankle and/or foot combined with multimodal or exercise therapy.

Systematic review

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Lin 2008[90] **Focus:** rehabilitation for ankle fractures in adults **Quality:** high	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** patients presenting for rehabilitation following ankle fracture **Interventions:** any intervention employed by any health professional to assist with rehabilitation following ankle fracture **Outcomes:** activity limitation, quality of life, patient satisfaction, ankle dorsiflexion and plantarflexion, strength, swelling, adverse events **METHODOLOGY** 7 relevant databases searched, no date, language or publication restriction; duplicate study selection, data extraction and quality assessment; details on quality assessment and individual studies; excluded studies listed **Data analysis:** text, tables, meta-analysis **Subgroups / sensitivity analyses:** rehabilitation after surgical versus after conservative management; true versus quasi-randomisation, concealed versus unconcealed allocation, blind versus non-blind outcome assessment, minimal versus significant drop-outs	**N included trials:** 1 RCT of manual therapy (Wilson 1991) **Study quality:** Wilson 1991: 3/10 (high risk of bias) **Study characteristics:** Wilson 1991: n=12, ankle fracture treated with or without surgery, physiotherapy after cast removal, Kaltenborn-based manual therapy, 5 weeks **Excluded studies eligible for current review:** no	**RESULTS** • Wilson 1991: after 5 weeks' treatment, no statistically significant improvement in activity limitation or ankle plantarflexion range of motion, ankle dorsiflexion range of motion statistically significant in favour of manual therapy **CONCLUSIONS** • limited evidence that manual therapy after a period of immobilisation may improve ankle range of motion; more well designed an adequately powered studies are needed

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Kuhar 2007[93]
India

Focus: RCT of the effects of myofascial release in the treatment of plantar fasciitis
Duration: 10 days
Follow-up: no post-intervention follow-up
Quality: low

PARTICIPANTS:
N: 30 (55% female)
Age: 43 SD10 years
Inclusion: clinically diagnosed with plantar fasciitis ≥6 weeks, heel pain felt maximally over plantar aspect of heel, pain in the heel on the first step in the morning, no history of heel pain at rest</td>
<td>Intervention type: physiotherapy
Intervention (n=15): conventional therapy (ultrasound, contrast bath, towel curl, active ankle exercises, Archilles tendon stretching, plantar fascia stretching with tennis ball) plus myofascial release using thumb, finger cupping and fingers technique for 15 mins
Comparison (n=15): conventional treatment only
Dose: daily treatments for 10 days
Providers: not reported</td>
<td><u>Results</u>

<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>Pain (VAS)</td><td>1.6 SD0.73</td><td>3.67 SD1.49</td><td>0.000</td></tr>
<tr><td>Foot function index</td><td>16.20 SD3.89</td><td>19.80 SD4.36</td><td>0.024</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Joseph 2010[92]
South Africa

Focus: RCT of the effect of muscle energy technique versus manipulation in the treatment of chronic recurrent ankle sprain
Duration: 3 weeks
Follow-up: no post-intervention follow-up
Quality: low

PARTICIPANTS:
N: 40 (53% female)
Age: 28.4 to 30.5 years
Inclusion: age 18 to 50 years, mild to moderate chronic recurrent ankle inversion sprain; most recent sprain at least 7 weeks before presentation; at least two of the following: 1. Ankle pain with a rating of 3 to 6 on the numerical rating scale, 2. Additional episodes of giving way, 3. Ankle stiffness</td>
<td>Intervention type: chiropractic
Intervention 1 (n=20): high velocity low amplitude ankle axial elongation manipulation
Intervention 2 (n=20): muscle energy technique (MET) to the ankle joint: 5 repetitions of ankle dorsiflexion to patient resistance with simultaneous anterior to posterior pressure against the talus; post-isometric contraction was followed with gentle increase into dorsiflexion and additional anterior to posterior pressure against the talus
Dose: 6 treatments over 3 weeks
Providers: not reported</td>
<td><u>Results</u>
• One Leg Standing Test (OLST) eyes open and closed, McGill Pain Questionnaire, Functional Evaluation Scale, dorsiflexion and plantarflexion: significant improvement over time in both groups, but no significant difference between groups

<table>
<tr><th></th><th>Manipulation (95% CI)</th><th>MET (95% CI)</th><th>p</th></tr>
<tr><td>Pain (NRS)</td><td>37.13 (32.7, 41.6)</td><td>39.6 (33.0, 46.3)</td><td>NS</td></tr>
<tr><td>OLST eyes closed (s)</td><td>10.45 (13.2, 7.7)</td><td>10.05 (13.2, 6.9)</td><td>NS</td></tr>
<tr><td>Dorsiflexion (°)</td><td>9.75 (13.1, 6.4)</td><td>7.65 (9.6, 5.7)</td><td>NS</td></tr>
</table>

Specific adverse effects: no significant or sever soreness or stiffness in the ankles reported as result of treatment, no one left the trial because of any minor or severe adverse reactions</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>du Plessis 2011[91]
South Africa

Focus: RCT of the effects of manual and manipulative therapy compared to night splints for hallux abducto valgus
Duration: 2 weeks
Follow-up: 1 month
Quality: medium

PARTICIPANTS:
N: 30 (% female equal but not reported)
Age: 42 years (25 to 65)
Inclusion: symptomatic hallux abducto valgus, pain and reduced function of the first metatarsophalangeal joint (MTP), inability to wear shoes comfortably, age 26 to 64 years</td>
<td>Intervention type: chiropractic
Intervention 1 (n=15): graded joint mobilisation of the first MTP, joint manipulation, mobilisation/manipulation of other foot and ankle joints as indicated, post-treatment cold therapy
Intervention 2 (n=15): night splint
Dose: manual therapy: 4 treatments over 2 weeks
Providers: chiropractors</td>
<td><u>Results</u>
• No significant difference between intervention and control for pain and function at the end of the intervention, but improvement maintained in the manual therapy group and not in the night splint group

At 1 month follow-up
<table>
<tr><th></th><th>Manual therapy (95% CI)</th><th>Night splint (95% CI)</th><th>p</th></tr>
<tr><td>Pain (VAS, %)</td><td>1.2
(0, 3)</td><td>17.7
(10, 24)</td><td><0.01</td></tr>
<tr><td>Foot function scores (%)</td><td>2.3
(0, 6)</td><td>32.4
(19, 45)</td><td><0.01</td></tr>
<tr><td>Hallux dorsiflexion (°)</td><td>50.8
(47, 55)</td><td>37.7
(33, 46)</td><td>0.02</td></tr>
</table>

Specific adverse effects: 2 manual therapy patients experienced transient discomfort and/or stiffness that quickly resolved</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Renan-Ordine 2011[94]
Brazil

Focus: RCT of the effects of myofascial trigger point manual therapy combined with a stretching programme for the management of plantar heel pain
Duration: 1 month
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 60 (85% female)
Age: 44 SD10 years
Inclusion: age 18 to 60 years, unilateral plantar heel pain: 1. Insidious onset of sharp pain under the plantar heel surface upon weight bearing after a period of non-weight bearing, 2. Plantar heel pain that increases in the morning with the first steps after waking up, 3. Symptoms decreasing with slight level of activity, such as walking; no red flags</td>
<td>Intervention type: physiotherapy
Intervention (n=30): self-stretching (including calf muscles and plantar fascia specific exercises) plus soft tissue trigger point manual therapy (examined for active trigger points in the gastrocnemius muscle, trigger point pressure release plus neuromuscular technique (longitudinal stroke) over both gastrocnemius muscles)
Comparison (n=30): self-stretching
Dose: 4 treatments per week for 4 weeks
Providers: clinician with 5 years of postgraduate orthopaedic manual therapy training</td>
<td><u>Results</u>
• SF-36 at end of intervention (0 to 100 on each subscale)

<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>SF-36</td><td></td><td></td><td></td></tr>
<tr><td>Physical function</td><td>65.2 SD12.2</td><td>52.8 SD19.4</td><td>0.001</td></tr>
<tr><td>Physical role</td><td>63.5 SD27.6</td><td>50.9 SD32.9</td><td>NS</td></tr>
<tr><td>Bodily pain</td><td>56.1 SD13.8</td><td>44.7 SD17.5</td><td>0.005</td></tr>
<tr><td>General health</td><td>60.8 SD12.2</td><td>54.9 SD16.2</td><td>NS</td></tr>
<tr><td>Vitality</td><td>52.1 SD15.7</td><td>44.1 SD19.0</td><td>NS</td></tr>
<tr><td>Social function</td><td>68.3 SD18.8</td><td>57.0 SD17.8</td><td>NS</td></tr>
<tr><td>Emotional role</td><td>78.6 SD27.5</td><td>51.9 SD32.5</td><td>NS</td></tr>
<tr><td>Mental health</td><td>62.0 SD19.8</td><td>60.1 SD22.2</td><td>NS</td></tr>
<tr><td>Pressure pain thresholds</td><td></td><td></td><td></td></tr>
<tr><td>Gastrocnemius muscle</td><td>2.7 SD0.6</td><td>2.3 SD0.5</td><td><0.03</td></tr>
<tr><td>Soleus muscle</td><td>3.0 SD0.9</td><td>2.4 SD0.5</td><td><0.03</td></tr>
<tr><td>Calcaneus</td><td>3.2 SD1.3</td><td>2.6 SD0.9</td><td><0.03</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Carpal tunnel syndrome

Four additional systematic reviews (Ellis 2008, Hunt 2009, Huisstede 2010, Muller 2004)[98-101] and three additional RCTs (Bialosky 2009, Burke 2007, Hains 2010)[102-104] on the effectiveness of manual therapy in carpal tunnel syndrome were identified. However, the medium quality reviews by Ellis 2008[98] and Hunt 2009 and the high quality review by Muller 2004[101] did not include any eligible trials not already considered by the Bronfort report and therefore will not be considered in detail here. Ellis 2008[98] examined the effects of neural mobilisation in various conditions (including carpal tunnel syndrome) and concluded that there is only limited evidence to support the use of neural mobilisation. Hunt 2009 examined the evidence for chiropractic treatment for carpal tunnel syndrome and concluded that there is insufficient evidence to conclude that chiropractic is effective in this condition. Muller 2004[101] examined the effects of hand therapy interventions in the primary management of carpal tunnel syndrome and concluded that carpal bone mobilisation combined with flexor retinaculum stretch may be effective in reducing pain from carpal tunnel syndrome. The trials by Bialosky 2009[102] and Burke 2007[103] are both included in the additional review by Huisstede 2010[99] summarised here, so will not be described in detail. The trial by Hains 2010[104] was not included in any of the new reviews.

The systematic review by Huisstede 2010[99] was medium quality and summarised evidence on the effectiveness of non-surgical treatments for carpal tunnel syndrome. Four RCTs (two high and two low quality) on manual therapy were included (Bialosky 2009, Burke 2007, Davis 1998, Tal-Akabi 2000). The trials used a variety of manual techniques and only one of them found a significant difference between intervention groups. The review authors concluded that there is limited evidence that carpal bone mobilisation is more effective with respect to symptom improvement than no treatment in the short term in the treatment of carpal tunnel syndrome. There was no evidence found for the effectiveness of neurodynamic treatment versus carpal bone mobilisation in the short term, for the effectiveness of a neurodynamic technique plus splinting compared with a sham therapy plus splinting group in the short term, or for the effectiveness of Graston instrument-assisted soft tissue mobilisation plus home exercises compared with soft tissue mobilisation plus home exercises in the midterm. There was no evidence for the effectiveness of chiropractic therapy compared with medical treatment for in the midterm.

The RCT by Hains 2010[104] was medium quality and compared 15 sessions of trigger point therapy over five weeks with sham treatment in 55 patients with carpal tunnel syndrome. After the end of the intervention, there was significant improvement in the severity of symptoms, functional status and perceived improvement in the intervention group compared to control ($p<0.05$).

Evidence summary. There is inconclusive evidence in a favourable direction for carpal bone mobilisation and for trigger point therapy in the treatment of carpal tunnel syndrome. There is inconclusive evidence in an unclear direction for neurodynamic treatment, soft-tissue mobilisation (with or without Graston instrument), and diversified chiropractic care in the management of carpal tunnel syndrome.

Systematic review

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Huisstede 2010[99] **Focus:** effectiveness of non-surgical treatments for carpal tunnel syndrome **Quality:** medium	**INCLUSION CRITERIA** **Study design:** systematic reviews or RCTs **Participants:** patients with carpal tunnel syndrome (not caused by acute trauma or systemic disease) **Interventions:** any non-surgical **Outcomes:** pain, function, recovery **METHODOLOGY** 5 relevant databases searched, no date or language limit; duplicate study selection, data extraction and quality assessment; details on quality assessment and individual studies; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 4 RCTs of manual therapy (Bialosky 2009, Burke 2007, Davis 1998, Tal-Akabi 2000) **Study quality:** Bialosky 2009, Burke 2007: high quality; Davis 1998, Tal-Akabi 2000: low quality **Study characteristics:** Tal Akabi 2000: n=21, carpal bone mobilisation versus neurodynamic treatment (median nerve mobilisation) versus control, 3 weeks; Bialosky 2009: n=40, neurodynamic technique plus splinting versus splinting, 3 weeks; Burke 2007; n=22, Graston-instrument assisted soft tissue mobilisation plus exercise versus manual soft tissue mobilisation plus exercise, 6 months; Davis 1998: n=91, chiropractic treatment (manual thrusts, myofascial massage and loading, ultrasound, wrist splint versus medical treatment (ibuprofen) and wrist splint, 13 weeks **Excluded studies eligible for current review:** not reported	**RESULTS** • Tal Akabi 2000: carpal bone mobilisation led to significantly greater improvement in symptoms than control; no significant difference between carpal bone mobilisation and neural mobilisation (pain, function, improvement) • Bialosky 2009: no significant differences between groups with respect to pain, disability (Dash questionnaire) or grip strength • Burke 2007: no significant difference between groups with respect to pain, range of motion, grip strength, the Boston Carpal Tunnel questionnaire • Davis 1998: no significant difference for hand function **CONCLUSIONS** • limited evidence that carpal bone mobilisation is more effective than no treatment in the short term • no evidence found for the effectiveness of neurodynamic versus carpal bone mobilisation in the short term, for the effectiveness of a neurodynamic technique plus splinting compared with a sham therapy plus splinting group in the short term, or for the effectiveness of Graston instrument-assisted soft tissue mobilisation plus home exercises compared with soft tissue mobilisation plus home exercises to treat carpal tunnel syndrome in the midterm • no evidence for the effectiveness of chiropractic therapy compared with medical treatment for carpal tunnel syndrome in the midterm

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Hains 2010[104]
Canada

Focus: RCT of the effects of ischaemic compression therapy for chronic carpal tunnel syndrome
Duration: 5 weeks
Follow-up: 6 months
Quality: medium

PARTICIPANTS:
N: 55 (62% female)
Age: 46 SD6.7 to 47 SD7.2 years
Inclusion: age 20 to 60 years, suffer from numbness in the hand affecting the thumb, the index finder, the middle finger and half the ring finger on a daily basis for at least 3 months, at least 2 of the following: Tinnel positive sign, Phallen positive sign, sleep problems caused by hand discomfort</td>
<td>Intervention type: chiropractic
Intervention (n=37): participants examined for trigger points along the biceps, the bicipital aponeurosis, the pronatorv teres muscle, the axilla of the shoulder; during treatment, pressure was applied for 5 to 15 seconds to each of the identified trigger points; thumb tip pressure (one thumb over the other) was then applied for 5 seconds every 2 cms, along the biceps; for trigger points located in the hollow of the elbow (pronator teres, biceps aponeurosis) and in the axilla (subscapularis), the pressure was maintained for 15 seconds; trigger points were treated using a light pressure, which was gradually increased until it reached the participant’s maximum pain tolerance level
Comparison (n=18): control treatment: ischaemic compressions of latent or active trigger points located in the posterior region of the clavicle (supraspinatus area), on the deltoid (anterior and lateral region), and on the center of the shoulder blade (infraspinatus area); were offered the opportunity to receive further treatment after the end of the control treatment, 13 agreed and received the experimenatal treatment
Dose: 15 treatments, 3 treatments per week
Providers: chiropractor</td>
<td><u>Results</u>
• Standardised symptom and functional status questionnaire; perceived improvement numerical scale

<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>Improvement in severity of symptoms and functional status</td><td>15 treatments:
42% SD21
6 months:
36% SD23</td><td>15 treatments:
26% SD18

after 15 experimental treatments:
48% SD15</td><td><0.05 (after 15 treatments)</td></tr>
<tr><td>Perceived improvement numerical scale</td><td>15 treatments:
67% SD26
6 months:
56% SD35</td><td>15 treatments:
50% SD25

after 15 experimental treatments:
75% SD21</td><td><0.021 (after 15 treatments)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Lateral epicondylitis (tennis elbow)

Eight additional systematic reviews (Aguilera 2009, Barr 2009, Ellis 2008, Herd 2008, Kohia 2008, Nimgade 2005, Pagorek 2009, Trudel 2004)[98;105-111], six additional RCTs (Blanchette 2011, Kochar 2002, Nagrale 2009, Stasinopoulos 2006, Stratford 1989, Vasseljen 1992),[112-117] one ongoing RCT (Coombes 2009),[118] and three non-randomised comparative studies (Amro 2010, Cleland 2004, Rompe 2001)[119-121] were identified that considered the effects of manual therapy in lateral epicondylitis.

However, the systematic reviews by Aguilera 2009, Barr 2009, Ellis 2008, and Pagorek 2009 did not include any studies over and above those included in the Bronfort report. Aguilera 2009[105] concluded that there was good evidence to support the use of lateral glide techniques and wrist manipulation in carpal tunnel syndrome. Barr 2009[106] concluded that when comparing physiotherapy to corticosteroid injection for treating lateral epicondylitis, corticosteroid injection was effective in the short term, but physiotherapy interventions are effective at the intermediate and longer term follow-up (this included two higher quality studies involving friction massage in one and elbow manipulation in the other). Ellis 2008[98] concluded that there is limited evidence for neural mobilisation (including passive manual techniques in lateral epicondylitis). Pagorek 2009[110] reported that there was good evidence to support the use of manual mobilisation with movement for decreasing pain an increasing strength in adults with lateral epicondylitis. Of the additional RCTs, four were already included in the new additional reviews and will therefore not be described separately here (Kochar 2002, Stasinopoulos 2006, Stratford 1989, Vasseljen 1992).[113;115-117]

Thus, this section includes a more detailed review of the four remaining systematic reviews (Herd 2008, Kohia 2008, Nimgade 2005, Trudel 2004),[107-109;111] three RCTs (Blanchette 2011, Nagrale 2009, Coombes 2009)[112;114;118] and three non-randomised studies (Amro 2010, Cleland 2004, Rompe 2001).[119-121] One of the randomised trials was an ongoing study and was reported as a protocol (Coombes 2009).

One systematic review of medium quality (Herd 2008)[107] evaluated the effectiveness of manipulative therapy (MT) in treating adults with lateral epicondylitis. This review searched five relevant databases (up to 2007) and included comparative controlled studies of manual therapy (joint manipulation / mobilisation) published in English. Unpublished or non-English literature was not considered in the review. The study quality was assessed using PEDro scale. The review identified and included 13 randomised and non-randomised trials. The mean (range) quality score of the included studies was 5.15 (1-8), indicating fair quality. The review results indicated beneficial effects of Mulligan's mobilisation with movement (versus no treatment, placebo, or corticosteroid injection) and manual therapy applied to the cervical spinal region (versus placebo). Cyriax physiotherapy was found more effective than conventional therapy (stretching, exercise, and modalities), but less effective than corticosteroid injection or supervised exercise.

Kohia and colleagues (Kohia 2008)[108] systematically reviewed the effectiveness of various physical therapy treatments for lateral epicondylitis in adults (medium quality). The authors searched four relevant databases from 1994 to 2006 and included only RCT reports published in English. In total, 16 RCTs of physical therapy (e.g., Cyriax physiotherapy, standard physical therapy, ultrasound, bracing, shockwave therapy) were included in the review. The findings indicated in the short-term (6 months or less), corticosteroid injections were more beneficial than physical therapy (elbow manipulation and exercise) or Cyriax physiotherapy. However, in a longer-term (six months or longer), there was no difference between physical therapy (elbow manipulation and exercise) versus corticosteroid

injections or no treatment. Moreover, radial head mobilisation was more effective compared to standard treatment (ultrasound, massage, stretching, exercise for wrist) in a short-term follow-up (15 weeks). The physical therapy protocol (pulsed ultrasound, friction massage, and stretching, exercise for wrist) was more effective than a brace with or without pulsed ultrasound. Cyriax physiotherapy was more beneficial than light therapy but less beneficial than supervised exercise of wrist extensors. And finally, the use of wrist manipulation led to greater improvements in lateral epicondylitis than a combination of ulstrasound, friction massage, and muscle strengthening. According to the review authors, no single treatment technique was shown to be the most effective in treatment of lateral epicondylitis.

In one systematic review of medium quality (Nimgade 2005),[109] the authors explored the effectiveness of physiotherapy, steroid injections, and relative rest for the treatment of adult lateral epicondylitis. The searches were performed in three databases (for the period of 1966-2004) and bibliographic citations of relevant studies were also scanned. The included studies were randomised and non-randomised controlled clinical trials published in English and evaluating the effects of physiotherapy relative to other treatments. The studies were appraised using the Cochrane Collaboration guidelines for grading controlled trials (11 items for internal validity, 6 items for external validity, and two items for statistical criteria). The review identified and included 30 studies whose quality score ranged from 2 to 9 (out of 11). In a short-term follow-up (at 6 weeks), steroid injections and multimodal physiotherapy (arm stretching, strengthening, ultrasound, and massage) were more effective than relative rest. However, after 3 months, the multimodal physiotherapy was better than steroid injections but as effective as relative rest. The authors conclude that early active interventions such as steroid injections and multimodal physiotherapy may improve symptoms of lateral epicondylitis in adults.

In a systematic review (medium quality), Trudel and colleagues (Trudel 2004),[111] summarised evidence on the effectiveness of conservative treatments (e.g., ultrasound, acupuncture, rebox, exercise, wait and see, mobilisation/manipulation, laser) for lateral epicondylitis in adults. The authors searched four relevant databases from 1983 to 2003 and included controlled clinical trial reports published in English. Included individual studies were appraised using a set of 23 criteria by MacDermid and then evidence was rated using Sackett's levels of evidence. In total, 31 trials of conservative treatment were included, of which four trials had reported on effectiveness of mobilisation/manipulation relative to placebo, standard physiotherapy, corticosteroid injections, or manipulation in combination with treatments. The results indicated that mobilisation/manipulation led to greater improvements in symptoms of lateral epicondylitis compared to placebo or standard physiotherapy. However, at one year of follow-up, there was no difference between corticosteroid injections and manipulation/mobilisation (Cyriax group). The authors concluded that level 2b (Sackett's evidence rating) evidence had indicated benefits of mobilisation/manipulation in treating lateral epicondylitis.

In one pilot study of low quality (Blanchette 2011),[112] which compared the effectiveness of chiropractic mobilisation (augmented soft tissue technique) and 'no treatment' (information on natural history of lateral epicondylitis and advice about ergonomic, stretching exercises of the flexors, and the wrist extensor muscles) for treating lateral epicondylitis, the authors randomised 30 adults with lateral epicondylitis to receive either the chiropractic mobilisation or no treatment for five weeks. The participants were assessed with respect to pain and pain-free grip strength immediately after the treatment (at week six post-baseline) and at three month post-baseline. The outcome measures were post-treatment mean scores of Patient-Rated Tennis Elbow Evaluation (PRTEE), pain (VAS), and pain-free grip strength scales. At both follow-ups, the groups demonstrated significant improvements

in all three measures when compared to baseline. However, no between-group difference for these measures was statistically significant.

In one trial of medium quality (Nagrale 2009),[114] sixty adult participants with lateral epicondylitis were randomised to 4-week Cyriax physiotherapy versus phonophoresis with diclofenac gel and supervised exercise. The outcomes were pain (VAS scale), pain-free grip strength (dynamometer), and functional status (Tennis Elbow Function Scale; TEFS) measured at 2, 4 and 8 weeks post-baseline. At 4 and 8 weeks, both groups demonstrated significant improvements in all three measures when compared to baseline. At both follow-ups, the Cyriax physiotherapy compared to the phonophoresis experienced significantly greater mean improvements in pain (5.03 versus 2.50), pain-free grip strength (25.46 versus 10.93), and functional status (20.93 versus 11.90).

In a non-randomised controlled experimental trial of low quality (Amro 2010),[119] Amro and colleagues compared the effect of Mulligan technique (mobilisation, movement and taping) plus traditional treatment (thermal treatment, massage, ultrasound, exercise) to that of traditional treatment alone given for 4 weeks to 34 participants with lateral epicondylitis. The outcomes of function (PRTEE score), pain (VAS score), and maximum pain-free grip strength (in kg; dynamometer) were measured at week 4 after baseline. At 4 weeks after baseline (immediately after treatment), both groups demonstrated significant improvements in all three measures when compared to baseline ($p<0.001$). The mean score improvements from baseline in pain (5.3 versus 3.2, $p<0.01$) and PRTEE (40.7 versus 27.7, $p<0.05$) were significantly greater in the Mulligan technique group compared to the traditional treatment alone. The mean change from baseline in maximum pain-free grip strength was not significantly different between the two study groups (4.8 versus 1.0, $p>0.05$).

In one observational cohort study of low quality (Cleland 2004),[120] Cleland and colleagues retrospectively compared the effectiveness of adding cervical spine manual therapy (passive mobilisation, mobilisation with movement, muscle energy techniques) to local management directed at the elbow (pulsed ultrasound, iontophoresis, deep tissue massage, stretching, strengthening exercise for muscles of the upper extremity, cold packs, elbow joint mobilisation) administered to patients with lateral epicondylitis. The authors reviewed and divided charts of 112 participants into two groups of the cervical spine manual therapy plus local management (n=51) versus local management alone (n=61). The self-reported outcome of success (i.e., return to all functional activities without recurrence of elbow symptoms after discharge from physical therapy) was ascertained via telephone follow-up interviews (72-74 weeks after discharge) with a response rate of 85% (95 responders). Compared to the local management group, the cervical spine manual therapy group experienced numerically higher rate of success (80% versus 75%, p-value not reported) in fewer visits (5.6 versus 9.7).

In a non-randomised controlled experimental trial of low quality (Rompe 2001),[121] Rompe and colleagues compared the effect of manual therapy (soft mobilisation of the cervical spine/cervicothoracic junction and flexion mobilisation in the cervical joints) plus extracorporeal low-energy shockwave therapy (ESWT) to that of ESWT alone given to 60 participants with chronic lateral epicondylitis. The outcomes of pain (VAS score; the Roles and Maudsley score) were measured at 3 and 12 months after treatment. At 12 months of follow-up, both treatment groups experienced significant improvements compared to baseline. However, the differences between the two groups in VAS and Roles and Maudsley scores (excellent outcome: 56% versus 60%, $p>0.05$) were not statistically significant.

In a study protocol of one randomised trial (Coombes 2009),[118] the authors aimed to evaluate the clinical effectiveness, harms, and cost-effectiveness of adding physiotherapy (elbow manipulation and exercise) to corticosteroid injections for treatment of adult patients with lateral epicondylitis over an 8-week period. The planned sample of 132 patients will be randomised to one of four treatment groups: a) corticosteroid injection with physiotherapy, b) corticosteroid injection, c) saline injection, or d) saline injection with physiotherapy. The outcomes of interest (e.g., global perceived improvement, success, recurrence, pain severity, PRTEE, pain-free grip force, pressure pain threshold, anxiety/depression, quality of life, adverse events, costs, etc.) will be measured at 4, 8, 12, 26, and 52 weeks post-baseline.

Evidence summary. According to the Bronfort report,[40] there is moderate grade evidence indicating that mobilisation plus exercise for lateral epicondylitis is less effective than corticosteroid injections in a short-term follow-up. However, longer-term data suggests superiority of mobilisation plus exercise over corticosteroid injections. The reviewed evidence additional to the Bronfort report is in agreement regarding the short-term superiority of corticosteroid injections over manipulation/mobilisation, but also suggests there is no difference in outcomes between these two treatments in a longer term (one year and beyond). In general, the reviewed evidence (low to moderate grade) indicates some benefits of manual physiotherapy in reducing symptoms in patients with lateral epicondylitis, when in combination with other treatments (exercise, traditional physiotherapy, local management, standard therapy), when compared to no treatment, or baseline values (within-group change). However, when compared to other treatments (e.g., placebo, phonophoresis, low-energy shockwave therapy, relative rest), the results are either inconsistent or inconclusive, as seen in the Bronfort report. The combination of different manual techniques across studies (e.g., Mulligan, Cyriax, Maitland, and others), different comparators, paucity of evidence, small sample size, and low methodological quality (lack of blinding, no randomisation, dropouts, effects of confounders) of individual studies makes it difficult to draw definitive conclusions on benefits of manual therapy techniques compared to other treatments in reducing symptoms related to lateral epicondylitis.

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Herd 2008[107] **Focus:** effectiveness of manipulative therapy in treating lateral epicondylalgia (LE) **Quality:** medium	**INCLUSION CRITERIA** **Study design:** RCTs and non-RCTs **Participants:** adults with LE **Interventions:** joint manipulation/mobilisation **Outcomes:** pain, grip strength, pressure pain threshold, range of motion **METHODOLOGY** **Data analysis:** narrative, tables, methodological quality assessment PEDro score **Subgroups / sensitivity analyses:** not reported	**N included trials:** 13 **Study quality:** mean PEDro score 5.15 (1-8) **Study characteristics:** studies included adult men/women with LE, 5 studies had short-term follow-up (< 3months), 4 studies had long-term follow-up (6 months or longer), and 2 studies had a year-long follow-up **Excluded studies eligible for current review:** none	**RESULTS** Mulligan's mobilisation with movement and MT to the cervical spine were effective **CONCLUSIONS** The review identified paucity and low quality of evidence

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Kohia 2008[108] **Focus:** effectiveness of various physical therapy (PT) treatments for LE in adults **Quality:** medium	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** adults with LE **Interventions:** Cyriax physiotherapy, wrist manipulation, standard physical therapy, ultrasound, bracing, shockwave therapy **Outcomes:** global improvement, pain, grip strength, pressure pain threshold, range of motion, pain-free grip, quality of life , self-reported progression of the condition **METHODOLOGY** **Data analysis:** four relevant databases searched from 1994 to 2006; narrative synthesis, tables; methodological quality assessment using Megens and Harris criteria and Sackett's hierarchical levels (I-V) and three grades of recommendation (A, B, and C) **Subgroups / sensitivity analyses:** not reported	**N included trials:** 16 **Study quality:** level I – grade A (7 trials), level II – grade B (9 trials) **Study characteristics:** randomised studies in LE adults reporting effectiveness of physical therapy interventions such as Cyriax physiotherapy, wrist manipulation, standard physical therapy, ultrasound, bracing, shockwave therapy **Excluded studies eligible for current review:** none	**RESULTS** Corticosteroid injections more beneficial versus PT (elbow manipulation and exercise) or Cyriax physiotherapy (6 months or less) (**Grade-A recommendation**); no difference between PT (elbow manipulation and exercise) versus corticosteroid injections or no treatment (6 months or longer) (**Grade-A recommendation**); radial head mobilisation better than standard treatment (ultrasound, massage, stretching, exercise for wrist) in a short-term follow-up (15 weeks); PT protocol (pulsed ultrasound, friction massage, and stretching, exercise for wrist) better than a brace with/without pulsed ultrasound (**Grade-A recommendation**); Cyriax PT better than light therapy, but worse than supervised exercise of wrist extensors; wrist manipulation better than a combination of ultrasound, friction massage, and muscle strengthening (**Grade-B recommendation**) **CONCLUSIONS** no single treatment technique shown to be the most effective in treatment of LE

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Nimgade 2005[109] **Focus:** the effectiveness of physiotherapy, steroid injections, and relative rest for the treatment of adult LE **Quality:** medium	**INCLUSION CRITERIA** **Study design:** RCTs and non-RCTs **Participants:** adults with LE **Interventions:** physiotherapy, steroid injections, and relative rest **Outcomes:** pain, strength, and function **METHODOLOGY** Searched 3 databases (for the period of 1966-2004) and bibliographic citations of relevant studies **Data analysis:** narrative synthesis, tables; methodological quality assessment using the Cochrane Collaboration guidelines for grading controlled trials (internal validity: 11 items, external validity: 6 items, and statistical criteria: 2 items) **Subgroups / sensitivity analyses:** not reported	**N included trials:** 30 **Study quality:** study quality score ranged from 2 to 9 (out of 11) **Study characteristics:** randomised and non-randomised studies in LE adults (males and females) reporting effectiveness of physiotherapy, steroid injections, and relative rest **Excluded studies eligible for current review:** none	**RESULTS** At 6 weeks, steroid injections and multimodal physiotherapy (arm stretching, strengthening, ultrasound, and massage) were more effective than relative rest. After 3 months, the multimodal physiotherapy was better than steroid injections, but as effective as relative rest **CONCLUSIONS** The active interventions such as steroid injections and multimodal physiotherapy may improve symptoms of LE in adults but this needs to be confirmed in future large and high quality studies

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Trudel 2004[111] **Focus:** the effectiveness of conservative treatments for LE in adults **Quality:** medium	**INCLUSION CRITERIA** **Study design:** randomised/non-randomised controlled clinical trials **Participants:** adults with LE **Interventions:** conservative treatments (e.g., ultrasound, acupuncture, rebox, exercise, wait and see, mobilisation, and/or manipulation, laser) **Outcomes:** pain, grip strength, pressure pain threshold, range of motion, pain-free grip, muscle function, endurance for activity **METHODOLOGY** Searched 4 databases (for the period of 1983 to 2003) and bibliographic citations of relevant studies **Data analysis:** narrative synthesis, tables; methodological quality assessment using 23 criteria by MacDermid; the evidence was rated using Sackett's levels of evidence **Subgroups / sensitivity analyses:** not reported	**N included trials:** 31 **Study quality:** level 2b studies **Study characteristics:** randomised and non-randomised studies in LE adults (males and females) reporting effectiveness of conservative treatment (physiotherapy, manipulation/mobilisation) **Excluded studies eligible for current review:** none	**RESULTS** Mobilisation/manipulation was more effective in improving symptoms of LE compared to placebo or standard physiotherapy. At one year of follow-up, there was no difference between corticosteroid injections and manipulation/mobilisation (Cyriax group) **CONCLUSIONS** The authors concluded that level 2b (Sackett's evidence rating) evidence indicates benefits of mobilisation/manipulation in treating LE

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Blanchette 2011[112]
Canada

Focus: RCT compared the effectiveness of chiropractic mobilisation and no treatment in adults with LE
Duration: 5 weeks
Follow-up: 3 months
Quality: low

PARTICIPANTS:
N: 30
Age: 46 years
Inclusion: adults 18 years or older with diagnosis of LE (Cozen, Mill tests)</td>
<td>Intervention type: chiropractic
Intervention (n=15): chiropractic mobilisation (augmented soft tissue technique)
Comparison (n=15): no treatment“ (information on natural history of LE and advice about ergonomic, stretching exercises of the flexors, the wrist extensor muscles, analgesics)
Dose: chiropractic mobilisation (2 treatments for 5 weeks); no treatment/advice (1 face-to-face session)
Providers: chiropractor with Master’s degree in kinesiology</td>
<td><u>Results</u>

At both follow-ups, the groups demonstrated significant improvements in PRTEE, VAS, and pain-free grip, when compared to baseline. However, no between-group difference for these measures was statistically significant

<table>
<tr><th>Change in outcome
At 3 months</th><th>Chiropractic mobilisation</th><th>No treatment/advice</th><th>p-value</th></tr>
<tr><td>Patient-Rated Tennis Elbow Evaluation Mean (SD)</td><td>16 (10)</td><td>17 (13)</td><td>NS (>0.05)</td></tr>
<tr><td>Pain intensity (VAS) Mean (SD)</td><td>17 (17)</td><td>21 (17)</td><td>NS (>0.05)</td></tr>
<tr><td>Pain-free grip Mean (SD)</td><td>27 (13)</td><td>28 (14)</td><td>NS (>0.05)</td></tr>
</table>

Specific adverse effects: 14 patients in the mobilisation group reported aches and bruises</td>
</tr>
<tr>
<td>Nagrale 2009[114]
India

Focus: RCT compared the effectiveness of Cyriax physiotherapy and phonophoresis with supervised exercise in adults with LE
Duration: 4 weeks
Follow-up: 8 weeks
Quality: medium

PARTICIPANTS:
N: 60
Age: 38.6 years
Inclusion: adults 30-60 years with diagnosis of LE> 1 month</td>
<td>Intervention type: physiotherapy
Intervention (n=30): Cyriax physiotherapy (10 minutes of deep transverse friction massage followed by single application of Mill’s manipulation)
Comparison (n=30): phonophoresis with supervised exercise and non-steroidal anti-inflammatory gel for 5 minutes
Dose: 12 sessions (3 times in 4 weeks)
Providers: not reported</td>
<td><u>Results</u>

At 4 and 8 weeks, both groups demonstrated significant improvements in all three measures when compared to baseline. The Cyriax physiotherapy versus phonophoresis experienced significantly greater mean improvements:

<u>Pain (VAS score) at 8 weeks</u>
5.03 (95% CI 4.62, 5.44) versus 2.50 (95% CI 2.122, 2.87)
<u>Pain-free grip strength (in kg) at 8 weeks</u>
25.46 (95% CI 23.13, 27.80) versus 10.93 (95% CI 9.38, 12.48)
<u>Functional status (TEFS score) at 8 weeks</u>
20.93 (95% CI 19.30, 22.56) versus 11.90 (95% CI 10.64, 13.15)

Specific adverse effects: not reported</td>
</tr>
</table>

Non-randomised comparative studies

Study and Participants	Interventions	Outcomes
Amro 2010[119] Palestine **Focus:** compared the effect of Mulligan technique plus traditional treatment versus traditional treatment alone in participants with LE **Duration:** 4 weeks **Follow-up:** 4 weeks **Quality:** low **PARTICIPANTS:** **N:** 34 **Age:** 37 years **Inclusion:** adults with diagnosis of subacute LE, positive results on two or more tennis elbow tests	**Intervention type:** physiotherapy **Intervention (n=17):** Mulligan technique (mobilisation, movement and taping) plus traditional treatment (thermal treatment, massage, ultrasound, exercise) **Comparison (n=17):** traditional treatment (thermal treatment, massage, ultrasound, exercise) **Dose:** 3 sessions per week for 4 weeks; each session lasted 30-45 minutes **Providers:** physiotherapists trained by the researchers	**Results** At 4 weeks after baseline (immediately after treatment), both groups demonstrated significant improvements in all three measures when compared to baseline ($p<0.001$). The Mulligan technique group versus traditional treatment demonstrated significantly greater mean improvements in pain and PRTEE but not in pain-free grip strength scores: Pain (VAS score) at 4 weeks: 5.3 (SD 0.9) versus 3.2 (SD 2.1), $p<0.01$ Patient-Rated Tennis Elbow Evaluation (PRTEE): 40.7 (SD 15.1) versus 27.7 (SD 21.7), $p<0.05$ Pain-free grip strength (in kg) at 4 weeks: 4.8 (SD 1.8) versus 1.0 (SD 1.8), $p>0.05$ (NS) ***Specific adverse effects:*** not reported
Cleland 2004[120] USA **Focus:** observational cohort study retrospectively compared the effectiveness of adding cervical spine manual therapy to local management directed at the elbow administered to adult patients with LE **Duration:** not reported **Follow-up:** 72-74 weeks **Quality:** low **PARTICIPANTS:** **N:** 112 **Age:** 42 years **Inclusion:** adults with diagnosis of LE, pain during palpation of LE, pain with resisted wrist/middle finger extension	**Intervention type:** physiotherapy **Intervention (n=51):** cervical spine manual therapy (passive intervertebral mobilisation, mobilisation with movement, muscle energy techniques) plus local management directed at the elbow (pulsed ultrasound, iontophoresis, deep tissue massage, stretching, strengthening exercise for muscles of the upper extremity, cold packs, elbow joint mobilisation) **Comparison (n=61):** local management directed at the elbow (pulsed ultrasound, iontophoresis, deep tissue massage, stretching, strengthening exercise for muscles of the upper extremity, cold packs, elbow joint mobilisation) **Dose:** average number of visits ranging from 4 to 11.5 **Providers:** physical therapists	**Results** The response rate: 85% (95 responders) Self-reported outcome of success rate (i.e., return to all functional activities without recurrence of elbow symptoms after discharge from physical therapy) was numerically greater in the cervical spine manual therapy versus local management (80% versus 75%, p-value not reported) ***Specific adverse effects:*** not reported

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Rompe 2001[121]
Germany

Focus: compared manual therapy plus extracorporeal low-energy shockwave therapy (ESWT) versus ESWT alone in participants with LE
Duration: NR
Follow-up: 3 and 12 months
Quality: low

PARTICIPANTS:
N: 60
Age: 47 years
Inclusion: adults with diagnosis of chronic LE (>6 months), pain during palpation of LE, pain with resisted wrist/middle finger extension, chair test, signs of cervical dysfunction with pain at C4-5 and/or C5-6 level with the head in a protracted position</td>
<td>Intervention type: physiotherapy
Intervention (n=30): manual physiotherapy (soft mobilisation of the cervical spine/cervicothoracic junction and flexion mobilisation in the cervical joints to relieve pain in C4-5 and/or C5-6 levels and correct protraction) plus extracorporeal low-energy shockwave therapy (ESWT)
Comparison (n=30): ESWT
Dose: 10 sessions of manual therapy
Providers: physiotherapists certified for manual therapy</td>
<td><u>Results</u>

<u>Roles and Maudsley scores after12 months</u>
Both treatment groups experienced significant improvements compared to baseline. The difference between the two groups in Roles and Maudsley scores was not statistically significant (excellent outcome: 56% versus 60%, p>0.05)

<u>Pain</u>
Both treatment groups experienced significant improvements compared to baseline. The differences between the two groups in pain scores were not statistically significant
<table>
<tr><th>Change in outcome
At 12 months</th><th>Manual physiotherapy</th><th>Low-energy shockwave therapy</th><th>p-value</th></tr>
<tr><td>Pressure pain
Mean (SD)</td><td>2.27 (2.59)</td><td>1.97 (2.05)</td><td>0.82</td></tr>
<tr><td>Thomsen Test
Mean (SD)</td><td>1.93 (1.97)</td><td>2.09 (2.01)</td><td>0.71</td></tr>
<tr><td>Resisted finger extension
Mean (SD)</td><td>1.45 (1.84)</td><td>1.66 (1.79)</td><td>0.57</td></tr>
<tr><td>Chair test
Mean (SD)</td><td>1.91 (2.51)</td><td>1.97 (2.27)</td><td>0.76</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Shoulder conditions

Fourteen new or additional systematic reviews (Brantingham 2011, Braun 2010, Carmarinos 2009, Ellis 2008, Faber 2006, Ho 2009, Kromer 2009, Kuhn 2009, Michener 2004, Pribicevic 2010, Trampas 2006, Verhagen 2007a, Verhagen 2007b, von der Heyde 2011)[98;122-134] were identified that included assessments of manual therapy for shoulder pain and disorders with inconclusive results in the Bronfort report, as well as eleven new or additional RCTs (Bennell 2010, Bergman 2010, Bialoszewski 2011, Bron 2011, Chen 2009, Hains 2010, McClatchie 2009, Munday 2007, Senbursa 2007, Surenkok 2009, Teys 2008).[135-145]

However, ten of the reviews were either included in other more comprehensive reviews or did not include any studies in addition to those in the Bronfort report (Ellis 2008, Faber 2006, Ho 2009, Kromer 2009, Kuhn 2009, Michener 2004, Trampas 2006, Verhagen 2007a, Verhagen 2007b, von der Heyde 2011),[98;125-129;131-134] and nine of the RCTs were included in relevant new reviews and will therefore not be described separately here (Bennell 2010, Bergman 2010, Chen 2009, Hains 2010, McClatchie 2009, Munday 2007, Senbursa 2007, Surenkok 2009, Teys 2008).[135;136;139-145] Ellis 2008[98] concluded that there is limited evidence for neural mobilisation (including passive manual techniques in people with shoulder pain). Faber 2006[125] concluded that in the treatment of shoulder impingement syndrome there is moderate evidence that exercise combined with manual therapy is more effective than exercise alone.

Ho 2009[126] found in their review that for patients with adhesive capsulitis, manual therapy was no more effective than other rehabilitative interventions in the short term for decreasing pain and improving range of motion and function. However, there was moderate evidence that high grade manual therapy was more effective than low grade manual therapy for improving range of motion and function in the long term. There was conflicting evidence for patients with shoulder impingement syndrome with respect to short term improvement in pain and function, with moderate evidence that manual therapy was no more effective than other interventions in improving range of motion. However, there was some evidence that at combination of soft tissue and joint mobilisation techniques in addition to exercise may be more effective than exercise alone. For the management of non-specific shoulder pain there was conflicting evidence regarding the use of manual therapy for improving pain and function in the short term compared to other interventions. There was moderate evidence that manual therapy was no more effective in improving function and decreasing pain in the longer term. However, massage and mobilisation with movement techniques were shown to be beneficial in managing patients with musculoskeletal disorders of the shoulder for short term outcomes compared to no treatment.

Kromer 2009,[127] Kuhn 2009,[128] and Mitchener 2004[129] considered the use of manual therapy in the context of physiotherapy or exercise programmes for shoulder impingement syndrome and found that there was evidence to show that manual therapy augmented the effects of exercise with respect to pain relief. The same conclusions were reached in the reviews by Verhagen 2007a and 2007b.[132;133] Trampas 2006[131] also considered treatments for shoulder impingement syndrome and, based on newer studies than the other reviews, suggested that there was limited evidence suggest that manual therapy plus exercise was more effective than exercise alone for pain relief and improving function.

Von der Heyde 2011[134] found limited level I evidence that Cyriax joint manipulation coupled with friction massage and high grade mobilisation is effective in the treatment of adhesive capsulitis (frozen

shoulder). They also found limited evidence for the use of joint mobilisations and exercise in shoulder impingement syndrome.

Of the new systematic reviews, Brantingham 2011[122] conducted a medium quality review examining the effects of manipulative therapy with or without multimodal therapy for shoulder disorders. They identified 23 RCTs, five non-randomised trials, and seven non-controlled primary studies. The included studies used a variety of intervention techniques including mobilisation, manipulation with and without exercise, combination with soft tissue treatment in some studies, mobilisation with movement, myofascial treatments, and cervical lateral glide mobilisation. Each condition category examined (other than shoulder osteoarthritis) included at least one high quality study. The authors concluded that for rotator cuff disorders and for shoulder complaints, dysfunctions, disorders or pain, there was fair evidence for manual and manipulative therapy of the shoulder, shoulder girdle and/or full kinetic chain combined with multimodal or exercise therapy; similarly for frozen shoulder (adhesive capsulitis), there was fair evidence for manual and manipulative therapy of the shoulder, shoulder girdle and/or full kinetic chain combined with multimodal or exercise therapy (manual therapy included high velocity low amplitude manipulation, mid- or end-range mobilisation, mobilisation with movement). For shoulder soft tissue disorders there was fair evidence for using soft tissue or myofascial treatments (ischaemic compression, deep friction massage, therapeutic stretch). For minor neurogenic shoulder pain there was limed evidence for cervical lateral glide mobilisation and / or high velocity low amplitude manipulation with soft tissue release and exercise. There was insufficient evidence for the manual treatment of shoulder osteoarthritis (no trials in this patient group).

The medium quality systematic review by Braun 2009[123] examined the effectiveness of manual therapy for impingement-related shoulder pain. They considered systematic reviews, RCTs and quasi-RCTs of manual or exercise therapy in patients with pain arising locally in a shoulder with grossly abnormal mobility. The review included eight systematic reviews and six RCTs, of which three included exercise interventions only and three included both exercise and manual therapy (mobilisation). Of the included reviews, five reported evidence to favour manual therapy plus exercise over exercise alone. The evidence from the three additional RCTs was inconclusive, but with a tendency towards improved outcomes with interventions including both manual therapy and exercise. No evidence was found for the effectiveness of mobilisation alone. None of the systematic reviews and only one of the RCTs included a specific statement on adverse events; in the one RCT no adverse events were reported. The authors concluded that there is limited evidence to support the effectiveness of manual therapy and exercise interventions for impingement-related shoulder pain. This primarily related to subacute and chronic complaints and short and medium term effectiveness, with the conclusions being based on research of varying methodological quality, with varying risk of bias, and affected by weaknesses in the reporting quality. Cautious interpretation was also warranted due to heterogeneity of populations, interventions and outcomes.

The medium quality systematic review by Camarinos 2009[124] examined the effectiveness of manual physical therapy for painful shoulder conditions. Treatment had to be by physical therapists and manual therapy interventions including low and high velocity mobilisations had to be directed at the glenohumeral joint only, without mobilisation of adjacent structures. Seven RCTs with a mean PEDro quality score of 7.86 of 10 (range 6 to 9) were included, and interventions included mobilisation with movement, the Cyriax approach, and static mobilisation performed at end-range or mid-ranges of motion. Of the included trials, three examined mobilisation with movement and two of these found a significant improvement in range of motion in the intervention group compared to control, while the

highest percentage change in range of motion was found in the intervention group in the third study. Significant improvement in pain compared to control was seen in one of two studies, and significant functional improvement in one study and highest percentage change in function in a second study. One study on Cyriax manual therapy found significant improvement in range of motion compared to control, while three studies examining mobilisation at the end-range of motion all found a significant improvement in range of motion and end-range mobilisation compared to control, while two studies reported no significant change in pain measures and two of three studies reported significantly improved function compared to control. Mid-range mobilisation appeared to be less effective with no effect on range of motion or function and only one of four studies reporting a significant improvement in pain. The review authors concluded that the included studies demonstrated a benefit of manual therapy for improvements in mobility and a trend towards improving pain measures, while increases in function and quality of life were questionable.

Similarly, Pribicevic 2010[130] examined in their medium quality review the effectiveness of manipulative therapy for the treatment of shoulder pain (excluding adhesive capsulitis). Treatment had to include a manipulative thrust technique (chiropractic or physiotherapy). The authors included 22 case reports, four case series, and four RCTs. The RCTs had quality scores of 5 to 8 out of 10. One included chiropractic manipulations and three included physiotherapeutic manipulations. All trials provided some limited evidence that the groups receiving the manipulation intervention had better outcomes (in terms of pain, recovery, improvement) than the control groups. The authors concluded that the evidence was limited, as only two RCTs of reasonably sound methodology could be identified and that there is need for well-designed trials investigating multi-modal chiropractic treatment.

The study by Bialoszewski 2011[137] was a low quality RCT examining the effects of manual therapy (mobilisation of the glenohumeral joint and soft tissues using Kaltenborn's roll-glide techniques, Cyriax deep transverse massage, Mulligan's mobilisation with movement and typical techniques of glenohumeral joint mobilisation in the anteroposterior direction) in 30 patients with chronic rotator cuff injury. The duration of the treatment was unclear (at least 15 treatments) and the intervention was combined with standard rehabilitation (TENS, ultrasound, exercise). A range of mobility parameters as well as pain were significantly more improved in the manual therapy group than in the control group after the intervention. The authors did not report on adverse effects.

The second RCT (Bron 2011)[138] was high quality and examined the effects of myofascial trigger point treatment in 72 patients with chronic unilateral non-traumatic shoulder pain (excluding adhesive capsulitis). The treatment involved inactivation of active myofascial trigger points by manual compression, which was combined with other manual techniques, namely deep stroking or strumming and intermittent cold application. Patients were also instructed to perform simple gentle static stretching and relaxation exercises at home several times a day and to apply heat and received ergonomic advice. There was a 'wait and see' control group that received physiotherapy after the trial period. Treatment was given once weekly for up to 12 weeks. After 12 weeks, the patients in the intervention group had significantly improved values for disability (DASH questionnaire), current pain, pain in the past seven days and most severe pain in the past seven days compared to control. The Global Perceived Effect was also significantly better in the intervention than in the control group (55% versus 14% with improvement), as was the number of muscles with active trigger points. The authors did not report on adverse effects.

Evidence summary. There is moderate positive evidence for the use of manual therapy (mobilisation) combined with exercise in the treatment of shoulder impingement syndrome and for rotator cuff

disorders. There is moderate positive evidence that high grade mobilisation is effective in adhesive capsulitis. There is moderate positive evidence for the use of mobilisation with movement techniques in the treatment of shoulder pain / disorders. There is inconclusive evidence in a favourable direction for using cervical lateral glide mobilisation and / or high velocity low amplitude manipulation with soft tissue release and exercise in minor neurogenic shoulder pain. There is moderate positive evidence for using myofascial treatments (ischaemic compression, deep friction massage, therapeutic stretch) for soft tissue disorders of the shoulder.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Brantingham 2011[122] **Focus:** effectiveness of manipulative therapy for shoulder pain and disorders **Quality:** medium	**INCLUSION CRITERIA** **Study design:** systematic reviews or primary studies **Participants:** patients with a shoulder peripheral diagnosis **Interventions:** manipulative therapy with or without multimodal or adjunctive therapy **Outcomes:** as reported **METHODOLOGY** 5 relevant databases searched from 1983, English language; no details on study selection, independent data extraction by three authors; quality assessment using PEDro and whole systems research scores; details on individual studies; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** different shoulder disorders	**N included trials:** 23 RCTs, 5 CCTs, 7 before and after studies, case reports and case series **Study quality:** rotator cuff disorders: 7 high or very high quality studies, 3 medium, 1 low; shoulder complaints / disorders: 6 high or very high, 1 medium; frozen shoulder: 3 high or very high, 3 medium; shoulder soft tissue disorders: 2 high, 1 medium; neurogenic shoulder pain: 2 high; shoulder osteoarthritis: no specific RCTs **Study characteristics:** n=1 to 172; interventions: mobilisation, manipulation with and without exercise, combined in some studies with soft tissue treatment, mobilisation with movement, myofascial treatments, cervical lateral glide mobilisation **Excluded studies eligible for current review:** not reported	**RESULTS / CONCLUSIONS** • *Rotator cuff disorders:* fair evidence for manual and manipulative therapy of the shoulder, shoulder girdle and/or full kinetic chain combined with multimodal or exercise therapy • *Shoulder complaints, dysfunctions, disorders or pain:* fair evidence for manual and manipulative therapy of the shoulder/shoulder girdle and full kinetic chain combined with exercise or a multimodal treatment approach • *Frozen shoulder (adhesive capsulitis):* fair evidence for manual and manipulative therapy of the shoulder, shoulder girdle and/or full kinetic chain combined with multimodal or exercise therapy (manual therapy included high velocity low amplitude manipulation, mid- or end-range mobilisation, mobilisation with movement) • *Shoulder soft tissue disorders:* fair evidence for using soft tissue or myofascial treatments (ischaemic compression, deep friction massage, therapeutic stretch) • *Neurogenic shoulder pain:* limed evidence for cervical lateral glide mobilisation and / or high velocity low amplitude manipulation with soft tissue release and exercise in the treatment of minor neurogenic shoulder pain • *Osteoarthritis of the shoulder:* insufficient evidence (no trials in this patient group)

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Braun 2009[123] **Focus:** effectiveness of manual therapy for impingement-related shoulder pain **Quality:** medium	**INCLUSION CRITERIA** **Study design:** systematic reviews, RCTs, quasi-RCTs **Participants:** patients with pain arising locally in a shoulder with grossly abnormal mobility; diagnosed 'shoulder impingement' disorders; shoulder bursitis; tendinitis, tendinopathy and degenerative changes of any rotator cuff muscle; positive findings for 'painful arc'; impingement signs or tests; pain in the shoulder with emphasis on provocation through elevation or lowering of the arm; impaired rotator cuff function or integrity **Interventions:** manual or exercise therapy compared to any conservative or surgical or no treatment **Outcomes:** pain, function, disability, symptoms, quality of life, range of motion, strength, work absenteeism, costs, adverse events **METHODOLOGY** 6 relevant databases searched, primary studies post cut-off dates of reviews (Jan 2005) to Oct 2008, English or German; duplicate selection or data extraction not mentioned; quality assessment using AMSTAR and PEDro scale; details on quality assessment and individual studies; excluded studies listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 8 systematic reviews (Desmeules 2003, Ejnisman 2004, Faber 2006, Green 2003, Green 2002, Johansson 2002, Michener 2004, Trampas 2006), 6 RCTs (Cloke 2008, Dickens 2005, Giombini 2006, Haahr 2006, Lombardini 2008, Senbursa 2007) **Study quality:** both systematic reviews and RCTs had a range of quality deficits **Study characteristics:** n=30 to 112, 3 RCTs included exercise only, 3 included exercise and manual therapy (mobilisation) **Excluded studies eligible for current review:** no	**RESULTS** • 5 reviews: evidence to favour manual therapy plus exercise over exercise alone • Evidence of three relevant additional trials inconclusive (with a tendency towards improved outcomes with manual therapy and exercise) • No evidence found for the effectiveness of mobilisation alone • None of the systematic reviews and only one of the RCTs included a specific statement on adverse events; in the one RCT no adverse events were reported **CONCLUSIONS** There is limited evidence to support the effectiveness of manual therapy and exercise interventions for impingement-related shoulder pain; this primarily relates to subacute and chronic complaints and short and medium term effectiveness; the conclusions are based on research of varying methodological quality, with varying risk of bias, and are affected by weaknesses in the reporting quality; cautious interpretation is warranted due to heterogeneity of populations, interventions and outcomes

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Camarinos 2009[124] **Focus:** effectiveness of manual physical therapy for painful shoulder conditions **Quality:** medium	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** adults 18 to 80 years with shoulder **Interventions:** physical therapy for conservative management of shoulder pain, treatment by physical therapists; the interventions of interest were manual therapy interventions including low and high velocity mobilisations directed to the glenohumeral joint *without* additional mobilisation of adjacent structures **Outcomes:** active or passive range of motion, a functional outcome measure specific to the shoulder, quality of life measure, pain measure **METHODOLOGY** 4 relevant databases searched, English language, published between 1996 and 2009; reference lists, hand searching of a couple of relevant journals; study selection, data extraction and quality assessment by more than one author; details on quality assessment (PEDro scores) and individual studies; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 7 RCTs (Conroy 1998, Guler-Uysal 2004, Johnson 2007, Kachingwe 2008, Teys 2008, Vermeulen 2006, Yang 2007)[145-151] **Study quality:** average PEDro score 7.86, range 6 to 9 **Study characteristics:** participants: n=14 to 100, interventions: mobilisation with movement, Cyriax approach, static mobilisation performed at end-range or mid-ranges of motion **Excluded studies eligible for current review:** none	**RESULTS** • *Mobilisation with movement (n=3):* significant improvement in range of motion in two of three studies, highest percentage change in range of motion in third study; significant improvement in pain in one of two studies; significant functional improvement in one study and highest percentage change in function in second study • *Cyriax manual therapy (n=1):* significant improvement in range of motion compared to control • *Mobilisations at end-range of motion (n=3):* improvement in range of motion and end-range mobilisation reported in all studies; two studies reported no significant difference in pain measures, two of three studies reported significantly improved function compared to control • *Mid-range mobilisation (n=4):* no effect on range of motion, only one reported a significant improvement in pain and none reported a significant difference in function **CONCLUSIONS** The included studies demonstrated a benefit of manual therapy for improvements in mobility and a trend in improving pain measures, while increases in function and quality of life were questionable

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Pribicevic 2010[130] **Focus:** effectiveness of manipulative therapy for the treatment of shoulder pain **Quality:** medium	**INCLUSION CRITERIA** **Study design:** case reports, case series, RCTs **Participants:** patients with shoulder pain or related specific clinical diagnosis; adhesive capsulitis excluded **Interventions:** treatment by registered practitioner of chiropractic, physiotherapy or medicine; treatment typical of the profession and included manipulative thrust technique **Outcomes:** any outcomes **METHODOLOGY** 5 relevant databases searched, from 1985, English language; bibliographies searched; methods of study selection and data extraction unclear; quality assessment using PEDro scale; details on quality assessment and individual studies; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 22 case reports, 4 case series, 4 RCTs (Winters 1997, Bergman 2004, Savolainen 2004, Munday 2007) **Study quality:** RCTs scored 5 to 8 out of 10 **Study characteristics:** case reports and case series all of chiropractic treatment; RCTs: n=15 to 172, interventions: 1 RCT with chiropractic manipulations, 3 with physiotherapeutic manipulations **Excluded studies eligible for current review:** not reported	**RESULTS** • Munday 2007: manipulation superior to placebo in the short term treatment of shoulder impingement syndrome • Winters 1997: manipulation significantly better than classic physiotherapy in reducing pain and recurrence (general shoulder complaints) • Bergman 2004: after 12 weeks significantly more patients in the manipulation than usual care group reported full recovery or very large improvement; no difference at 12 months (shoulder dysfunctions) • Savolainen 2004: at 12 months, VAS pain was reduced in favour of the thoracic manipulation group (neck and shoulder pain in occupational health) **CONCLUSIONS** Evidence is limited, only two RCTs of reasonably sound methodology; need for well-designed trials investigating multi-modal chiropractic treatment

RCTs

Study and Participants	Interventions	Outcomes
Bialoszewski 2011[137] Poland **Focus:** RCT of the effects of manual therapy on range of motion and pain in patients with chronic glenohumeral rotator cuff injuries **Duration:** unclear **Follow-up:** unclear **Quality:** low **PARTICIPANTS:** **N:** 30 (40% female) **Age:** 51.3 years (38 to 61) **Inclusion:** confirmed diagnosis of chronic rotator cuff injury without indications for surgical treatment	**Intervention type:** physiotherapy **Intervention (n=15):** standard rehabilitation (TENS to the glenohumeral joint (20 min session), ultrasound to the supraspinatus insertion region (4 to 9 min session), kinesiotherapy to strengthen the glenohumeral rotator cuff (active, passive and self-assisted exercises)) plus manual therapy (mobilisation of the glenohumeral joint and soft tissues using Kaltenborn's roll-glide techniques, Cyriax deep transverse massage, Mulligan's mobilisation with movement and typical techniques of glenohumeral joint mobilisation in the anteroposterior direction) **Comparison (n=15):** standard rehabilitation only **Dose:** at least 15 treatments **Providers:** not reported	**Results** • The study reports 4 examinations but it is unclear at what points in the progress of the study patients were examined • Shoulder girdle elevation through flexion, shoulder girdle elevation through abduction, external rotation, internal rotation and pain significantly more improved in the group receiving manual therapy compared to standard rehabilitation only ***Specific adverse effects:*** not reported

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Bron 2011[138]
The Netherlands

Focus: RCT of the effects of myofascial trigger point treatment in patients with chronic shoulder pain
Duration: 12 weeks
Follow-up: no post-intervention follow-up
Quality: high

PARTICIPANTS:
N: 72 (61% female)
Age: 42.8 to 45.0 years (38.7 to 49.9)
Inclusion: unilateral non-traumatic shoulder pain for at least 6 months, aged between 18 and 65 years; adhesive capsulitis excluded</td>
<td>Intervention type: physiotherapy
Intervention (n=34): inactivation of active myofascial trigger points by manual compression, combined with other manual techniques (deep stroking or strumming), intermittent cold application; instruction to perform simple gentle static stretching and relaxation exercises at home several times a day; instructed to apply heat; ergonomic advice
Comparison (n=31): wait and see, started physiotherapy after the end of the trial period
Dose: once weekly for up to 12 weeks
Providers: 5 physiotherapists</td>
<td><u>Results</u>

• Disabilities of Arm, Hand and Shoulder Questionnaire (DASH) (0 to 100, higher score = greater disability), minimal clinically important difference is 10 points
• Pain (VAS), minimal clinically important difference is 14 mm, VAS-P1: pain at current moment, VAS-P2: average pain during last 7 days, VAS-P3: most severe pain during last 7 days
• Global Perceived Effect (GPE, 1 (much worse) to 8 (completely recovered))
• PROM (passive range of motion) – no significant change

<u>Results after 12 weeks</u>
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>DASH</td><td>18.4 SD12.3</td><td>26.1 SD13.8</td><td><0.05</td></tr>
<tr><td>VAS-P1</td><td>17.2 SD19.5</td><td>31.0 SD21.0</td><td><0.05</td></tr>
<tr><td>VAS-P2</td><td>22.5 SD16.4</td><td>33.2 SD23.3</td><td><0.05</td></tr>
<tr><td>VAS-P3</td><td>34.0 SD21.9</td><td>47.8 SD27.3</td><td><0.05</td></tr>
<tr><td>GPE improved</td><td>55%</td><td>14%</td><td><0.05</td></tr>
<tr><td>No. of muscles with active trigger points</td><td>4.8 SD3.0</td><td>7.5 SD3.2</td><td><0.05</td></tr>
<tr><td>No. of muscles with latent trigger points</td><td>4.7 SD2.3</td><td>4.4 SD2.3</td><td>NS</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Temporomandibular disorders

One systematic review protocol (Freitas de Souza 2008)[152] and three randomised trials (Cuccia 2010, Kalamir 2010, Yoshida 2005)[153-155] were identified for this sub-section.

The authors of one systematic review protocol (Freitas de Souza 2008)[152] set out to investigate the effectiveness/safety of different therapy options for treatment of temporomandibular joint osteoarthritis. The eligibility criteria were the following: study type (randomised trials), types of participants (adults with clinical/radiological diagnosis of temporomandibular joint osteoarthritis), types of interventions (any form of non-invasive or surgical treatment, placebo, or no treatment), and types of outcomes (pain, extent of mandibular movement, temporomandibular joint sounds, quality of life, number of visits, morphological changes, number of days absent from work, adverse events, and costs). The authors planned to search five relevant databases (MEDLINE, Embase, CENTRAL, PEDro, Cochrane Oral Health Group Trials Register) supplemented by hand searches without language restriction. The authors will use the Cochrane risk of bias (ROB) tool to assess ROB in individual studies included in the review. The synthesis of evidence is planned to be performed using meta-analytic methods (fixed and random-effects models as appropriate) along with heterogeneity assessments through subgroup and sensitivity analyses.

One randomised trial of low quality (Yoshida 2005)[155] compared the effectiveness of a single manipulation procedure plus non-steroidal anti-inflammatory drugs (NSAIDs) to that of NSAIDs alone in 305 adults with temporomandibular joint disc displacement (closed lock). The success rate of treatment was defined as: a) the mouth opened ≥36 mm and b) the mandibular lateral movement increased to ≥6 mm and measured immediately or up to one year post-treatment. Other outcome measures were pain (VAS score), maximum mouth opening, and the presence of clicking or crepitus. The total success rate for the manual therapy group during the entire follow-up time was 172/204 (84.3%) while the success rates in the control group were 0%. No formal comparisons between intervention and control groups were presented.

In a study of high quality by Kalamir and colleagues (Kalamir 2010),[154] 30 participants with myogenous temporomandibular disorders were randomly assigned to receive one of the three treatments for 5 weeks: intra-oral myofascial therapy (IMT), IMT plus self-care (mandibular home exercises) and education (lecture on basic temporomandibular joint anatomy, biomechanics, disc displacement, dysfunction), or no treatment. At 6 months of post-treatment follow-up, both IMT groups compared to no treatment group experienced significant improvements in pain scores at rest, opening, and clenching ($p<0.01$). Moreover, the IMT alone group had a significant improvement in pain at rest ($p=0.04$), pain on opening ($p<0.01$), and opening range ($p<0.01$) compared to IMT combination with education and self-care.

In one randomised trial (Cuccia 2010)[153] of low quality, 50 adults with temporomandibular disorders were randomised to receive osteopathic manual therapy or conventional conservative therapy (oral appliance, physical therapy, hot/cold packs, transcutaneous electrical nerve stimulation) for 6 months. The outcomes such as jaw pain intensity (VAS score; 0-10), maximal mouth opening (MOV; in mm), and lateral movement of the head around its axis (ROM; in degrees) were measured at 6 months (end of treatment) and 8 months (2 months post-treatment) post-baseline. At 8 months of follow-up, the OMT group compared to the conventional conservative therapy group experienced significant improvement in maximal mouth opening (42.9 versus 40.4, $p=0.001$) and lateral movement of the

head around its axis (80.5 versus 72.4, p=0.000). At 8 months of follow-up, the mean jaw pain score between the two groups was not significantly different (3.8 versus 4.4, p>0.05).

Evidence summary. According to the Bronfort report, the evidence on the benefits/safety of manual therapy (mobilisation, massage) for temporomandibular disorders is inconclusive in a favourable direction for mobilisation or massage. No evidence on the benefits/safety of myofascial or osteopathic manipulation for temporomandibular disorders was found in the Bronfort report. Due to the paucity and mostly low quality of the reviewed evidence (myofascial or osteopathic manipulation) in addition to the Bronfort report (mobilisation, massage), results regarding comparative effectiveness/safety of manual therapy for temporomandibular disorders remain inconclusive in a favourable direction for mobilisation, massage, myofascial or osteopathic manipulation.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Yoshida 2005[155]
Japan

Focus: RCT investigated the effectiveness of simple manipulation with or without non-steroidal anti-inflammatory drugs (NSAIDs) in adults with temporomandibular joint disc displacement (closed lock)
Duration: single treatment
Follow-up: one year
Quality: low

PARTICIPANTS:
N: 305 (75% female)
Age: 18-74 years
Inclusion: adults >18 years with temporomandibular joint disc displacement (closed lock); exclusions: inability to understand the proposed therapy, current orthodontic treatment, bilateral closed lock, history of drug abuse, psychoses, periodontal disease in the incisor areas</td>
<td>Intervention type: physiotherapy
Intervention (n=204): jaw manipulation (thumb pressure applied against the labial side of upper anterior tooth while the lingual side of the lower incisor was pulled with the forefinger) plus NSAIDs
Comparison (n=101): NSAIDs
Dose: single jaw manipulation, NSAIDs (single administration)
Providers: not reported</td>
<td><u>Results</u>

The success rate of treatment:
a) The mouth opened ≥36 mm and
b) The mandibular lateral movement increased to ≥6 mm

<table>
<tr><th>Change in outcome</th><th>Manual therapy plus NSAIDS</th><th>NSAIDS</th><th>p-value</th></tr>
<tr><td>N (%) treatment success rate at one year</td><td>172/204 (84.3%)</td><td>0%</td><td>NR</td></tr>
<tr><td>Pain (VAS)</td><td>1.8 after 1 wk with effective therapy, 4.0 with ineffective therapy</td><td>NR</td><td>NR</td></tr>
<tr><td>Maximum mouth opening</td><td>39.4 mm with effective therapy, 27.1 mm with ineffective therapy</td><td>not significantly changed from initial value of 28.4 mm</td><td>NR</td></tr>
<tr><td>Presence of clicking or crepitus</td><td>present in patients with improvement</td><td>not present</td><td>NR</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Kalamir 2010[154]
Australia

Focus: RCT investigated the effectiveness of IMT (with or without education and self-care) compared to no treatment in adults with myogenous temporomandibular disorders (TMD)
Duration: 5 weeks
Follow-up: 6 months post-treatment
Quality: high

PARTICIPANTS:
N: 30 (60% female)
Age: 32 years
Inclusion: adults 18-50 years with myogenous TMD for at least 3 months; exclusions: malignancy in the last 5 years, toothless, arthritides, fractures, dislocations, instability of jaws or neck, metabolic disease, rheumatologic disorders, haematological disorders</td>
<td>Intervention type: chiropractic
Intervention 1 (n=10): IMT (intra-oral temporalis release; intra-oral medial and lateral pterygoid technique; intra-oral sphenopalatine ganglion technique)
Intervention 2 (n=10): IMT + education (lecture on basic temporomandibular joint anatomy, biomechanics, disc displacement, dysfunction) + self-care (mandibular home exercises)
Comparison (n=10): no treatment
Dose: mandibular home exercises twice a day; IMT two 15-min sessions per week; education (2-min lectures in 4 visits)
Providers: chiropractic practitioner</td>
<td><u>Results</u>

6 months post treatment

<table>
<tr><th>Change in outcome</th><th>Manual therapy</th><th>Manual therapy + education + self-care</th><th>No treatment</th><th>p-value</th></tr>
<tr><td>Pain at rest (graded chronic pain scale) Mean</td><td>0.60 [0.0, 1.20]</td><td>1.80 [0.74, 2.86]</td><td>3.40 [2.13, 4.67]</td><td><0.01</td></tr>
<tr><td>Pain on opening (graded chronic pain scale) Mean [95% CI]</td><td>1.10 [0.01, 2.19]</td><td>2.70 [1.69, 3.71]</td><td>4.40 [2.71, 6.09]</td><td><0.01</td></tr>
<tr><td>Pain on clenching (graded chronic pain scale) Mean [95% CI]</td><td>1.50 [0.47, 2.53]</td><td>1.70 [0.87, 2.53]</td><td>5.30 [3.68, 6.92]</td><td><0.01</td></tr>
<tr><td>Opening range (mm) Mean [95% CI]</td><td>41.50 [38.76, 44.24]</td><td>48.30 [44.59, 52.01]</td><td>36.60 [30.11, 42.90]</td><td>0.01</td></tr>
</table>

Specific adverse effects: none in any participant</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Cuccia 2010[153]
Italy

Focus: RCT investigated the effectiveness of osteopathic manual therapy compared to conventional conservative treatment in adults with temporomandibular disorders
Duration: 6 months
Follow-up: 2 months post-treatment
Quality: low

PARTICIPANTS:
N: 50 (56% female)
Age: 38.4 SD15.33 to 40.6 SD11.03 years
Inclusion: adults 18-50 years with temporomandibular disorders (temporomandibular index ≥ 0.08), pain intensity of VAS ≥ 40mm; exclusions: adverse event with osteopathic manual therapy, previous treatment for temporomandibular disorders, use of analgesics, anti-inflammatory drugs, dental prosthesis, any other oro-facial pain condition, neurological or psychiatric disorder</td>
<td>Intervention type: osteopathy
Intervention (n=25): osteopathic manual therapy directed to cervical and temporomandibular joint regions (myofascial release, balanced membraneous tension, muscle energy, joint articulation, high velocity low amplitude thrust, and cranial-sacral therapy)
Comparison (n=25): conventional conservative treatment (oral appliance, gentle muscle stretching, relaxing exercise, hot/cold packs, transcutaneous electrical nerve stimulation)
Dose: osteopathic manual therapy 15-25 min sessions each, conventional not reported
Providers: osteopathic manual therapy: doctor of osteopathy, conventional: gnathology specialist</td>
<td><u>Results</u>

2 months post treatment (8 months post-baseline)

<table>
<tr><th>Change in outcome</th><th>Osteopathic manual therapy</th><th>Conventional conservative treatment</th><th>p-value</th></tr>
<tr><td>Pain (VAS scale) Mean ± SD</td><td>3.8 ± 1.26</td><td>4.4 ± 1.75</td><td>>0.05 (NS)</td></tr>
<tr><td>Maximal mouth opening (mm) Mean ± SD</td><td>42.9 ± 2.69</td><td>40.4 ± 2.41</td><td>0.001</td></tr>
<tr><td>Lateral movement of the head around its axis (degrees) Mean ± SD</td><td>80.5 ± 5.44</td><td>72.4 ± 2.95</td><td>0.000</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Headache and other conditions

Cervicogenic headache

This sub-section included one systematic review (Posadzki 2011)[156] and one RCT (von Piekartz 2011)[157].

One systematic review of high quality (Posadzki 2011)[156] evaluated the effects of spinal manipulative therapy (SMT) on cervicogenic headache. This review searched seven relevant databases and included RCTs. Unpublished studies were not sought for this review. The review identified and included nine randomised trials. The study quality was assessed using the Cochrane tool. The results from six trials suggested that the SMT was more beneficial in treating the headaches compared to physical therapy, light massage, drug therapy, or no intervention. The remaining three trials showed no significant difference in headache intensity, duration, or frequency between SMT and placebo, physical therapy, massage, or wait list controls. Given the clinical heterogeneity, inconsistency in results, and low methodological quality of the reviewed studies, the evidence regarding the effectiveness of SMT for cervicogenic headache remains inconclusive.

One high quality RCT (von Piekartz 2011)[157] compared effects of temporomandibular plus cervical manual therapy to cervical manual therapy alone in 43 adults with cervicogenic headache. The outcomes were headache intensity (Coloured Analogical Scale), neck disability (Neck Disability Index), and temporomandibular outcomes such as mouth opening range (in mm), pain intensity during mouth opening (visual analogue scale), and the presence of mandibular deviation/sounds (%). At 6 months of follow-up, the experimental group experienced significantly reduced headache intensity and temporomandibular measures (pain intensity during mouth opening, presence of deviation, and sounds).

An additional systematic review identified in an update of our searches (Chaibi 2012)[158] did not include any new evidence in addition to the studies already identified and concluded that while the relevant RCTs suggest that physiotherapy and spinal manipulative therapy might be and effective treatment in the management of cervicogenic headache but that studies are difficult to evaluate as only one included a non-treatment control group and most included participants with infrequent cervicogenic headache.

Evidence summary. Limited (in amount and consistency) additional evidence indicates that spinal manipulative therapy may be more beneficial for treating cervicogenic headaches compared to physical therapy, light massage, drug therapy, or no intervention (no change from Bronfort report). One additional high quality RCT suggests that some mobilisation techniques may be beneficial (change of evidence compared to the Bronfort report in the direction of moderate positive evidence). Due to lack of sufficient data, the evidence on the effects of manual therapy on adverse events in this population is inconclusive.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Posadzki 2011[156] **Focus:** effectiveness/safety of spinal manipulation therapy (SMT) in cervicogenic headache (CGH) **Quality of systematic review:** High	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** adults with CGH **Interventions**: manipulative procedures (chiropractic, osteopathy) **Outcomes:** headache intensity, duration, frequency **METHODOLOGY** 7 relevant databases searched; no language limit; some details on study selection; quality assessment of studies presented; studies not presenting original data, abstracts, conference proceedings, outcomes of interest not reported were excluded; excluded studies not listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 9 randomised trials (Ammer 1990, Bitterli 1977, Borusiak 2010, Haas 2004, Haas 2010, Howe 1983, Jull 2002, Li 2007, Nilsson 1995) **Study quality:** Cochrane Risk of Bias tool and Jadad score; most trials had major methodological flaws; two trials (Borusiak 2010 and Jull 2002) had low risk of bias with Jadad score of 4 and three trials (Bitterli 1977, Howe 1983, Li 2007) had high risk of bias with Jadad score of 0-1 **Study characteristics:** populations across studies were relatively homogenous, but control interventions were different ranging from sham manipulation, light massage, drugs, physical therapy to no intervention **Excluded studies eligible for current review:** not reported	**RESULTS** 6 trials, which were conducted by chiropractors, suggested the benefit of SMT in treating the headaches over physical therapy, light massage, drug therapy, or no intervention. The remaining 3 trials, which were conducted by non-chiropractors, showed no significant difference in headache intensity, duration, or frequency between SMT and placebo, physical therapy, massage, or wait list controls **CONCLUSIONS** Given the clinical heterogeneity, inconsistency in results, and low methodological quality of the reviewed studies, the evidence regarding the effectiveness of SMT for CGH is rendered inconclusive

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>von Piekartz 2011[157]
The Netherlands

Focus: RCT investigating effects of temporomandibular (TMD) and cervical manual therapy compared to cervical manual therapy alone in adults with cervicogenic headache (CGH) on headache intensity, neck disability, and TMD outcomes
Duration: maximum of 42 days
Follow-up: 6 months
Quality: high

PARTICIPANTS:
N: 43 (64% female)
Age: 36 years
Inclusion: patients with CGH > 3 months, no prior TMD treatment, neck disability index (NDI)>15 points, and at least 1 of the 4 TMD signs present (joint sounds, deviation during mouth opening, extraoral muscle pain, and pain during passive mouth opening); exclusions were orthodontic treatment or experience of neurologic pain in the head in the past 3 years</td>
<td>Intervention type: physiotherapy
Intervention (n=22): manual therapy (orofacial treatment) applied to the TMD region – consisting of accessory movements to TMD region, masticatory muscle techniques (tender-trigger point treatment and muscle stretching), active/passive movements facilitating optimal function of cranial nerve tissue, coordination exercises, and home exercises; plus usual care (cervical manual therapy applied to the cranio-cervical region)
Comparison (n=21): usual care (cervical manual therapy)
Dose: each session of 30 minutes daily, 6 sessions

Providers: first contact practitioners trained for manual therapy; experimental arm investigators were additionally trained for 200 hours focusing on the assessment of craniomandibular and craniofacial pain</td>
<td>RESULTS

<table>
<tr><th>Change in outcome</th><th>Orofacial therapy + usual manual therapy</th><th>Usual manual therapy</th><th>p-value</th></tr>
<tr><td>Pain intensity (coloured analog scale 0-10) at 6 month follow-up</td><td>2.1</td><td>7.0</td><td>≤ 0.05</td></tr>
<tr><td>Neck disability index at 6 month follow-up</td><td>6.3</td><td>16.0</td><td>NS</td></tr>
<tr><td>Mouth opening (mm) at 6 month follow-up</td><td>53.5 SD3.2</td><td>41.6 SD4.3</td><td>NS</td></tr>
<tr><td>Pain intensity during mouth opening (VAS mm) at 6 month follow-up</td><td>0.9 SD8.0</td><td>53.0 SD7.0</td><td>≤ 0.05</td></tr>
<tr><td>Deviation present (%) at 6 month follow-up</td><td>10.0</td><td>33.9</td><td>≤ 0.05</td></tr>
<tr><td>Sound (click) present (%) at 6 month follow-up</td><td>25.0</td><td>42.0</td><td>≤ 0.05</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Tension-type headache

Four new and additional RCTs (Anderson 2006, Castien 2011, Castien 2009, van Ettekoven 2006, Vernon 2009)[159-163] were identified assessing the effects of manual therapy in tension-type headache. One trial (Castien 2011, Castien 2009) was reported in two publications (one protocol report and one completed trial report).[160;161]

In their study (medium quality), Anderson and colleagues (Anderson 2006),[159] compared the effect of adding osteopathic manual treatment (OMT) to progressive muscular relaxation (PMR) exercise in patients with tension-type headache. The authors randomised 29 adult patients to receive either a combination of OMT and PMR or PMR only for three consecutive weeks and assessed four headache outcomes (headache rating, headache index, headache frequency, and headache intensity) within two weeks after the end of treatment. At the follow-up, patients who received the combination treatment (OMT plus PMR exercise) experienced a significantly reduced frequency of headache (number of headache free days per week) compared to patients assigned to the PMR exercise alone (1.79 days versus 0.26 days, p=0.016, respectively). The between-group differences for other headache parameters (headache rating, headache index, and headache intensity) were not statistically significant.

In a randomised trial (medium quality), Castien and colleagues (Castien 2011, Castien 2009)[160;161] compared the effectiveness of manual therapy (cervical/thoracic spine mobilisation, exercises, postural correction) and usual care by the general practitioner (provided information, re-assurance and advice, and discussed the benefits of life-style changes) in patients with chronic tension-type headache. The authors randomised 82 adult patients to receive either manual therapy or general practitioner care for 8 weeks and assessed several headache outcomes (e.g., headache frequency, use of pain medication, headache pain intensity, headache-related disability, cervical active range of movement, endurance of the neck flexor muscles, participants' perceived improvement, sick leave, etc.) at 8 weeks (immediately post-treatment) and 26 weeks post-baseline. Immediately after the end of treatment (at eight weeks post-baseline), patients in the manual therapy group compared to GP care group, experienced significantly greater improvements in headache frequency, headache pain intensity, headache-related disability, cervical range of movement, and endurance of the neck flexor muscles, but not in the use of pain medication, which was similar across the study groups. At 26 weeks of follow-up, the between-group differences were maintained significant only for headache frequency and headache pain intensity in favour of manual therapy. The use of pain medication was similar across the study groups (p=0.92).

One high quality randomised trial (van Ettekoven 2006),[162] investigated the effectiveness of exercise (craniocervical flexion) combined with physiotherapy (Western massage including friction massage, oscillation techniques (low-velocity, passive cervical joint mobilisation according to Maitland), and instruction on postural correction) in patients with tension-type headache. Specifically, 81 participants were randomly assigned to physiotherapy plus craniocervical flexion exercise versus physiotherapy alone for 6 weeks. The study outcomes (e.g., headache frequency, intensity, and duration; quality of life, pain medication intake) were assessed

post-baseline at 6 weeks (immediately post-treatment) and 6 months thereafter. Although at the end of treatment, both study groups showed significant improvements compared to baseline in headache frequency, intensity, and duration, none of the differences observed between the two groups was significant. At 6 months of follow-up, however, the craniocervical flexion group experienced significantly reduced headache frequency (mean change: 1.95, 95% CI: 1.14, 2.76), intensity (mean change: 1.78, 95% CI: 0.82, 2.74), and duration (mean change: 2.07, 95% CI: 0.12, 4.03) compared to physiotherapy alone group. Mean change scores for four of the 10 quality of life domains (emotional well-being, limitations due to mental health, vitality, and bodily pain) of the Short-Form General Health Survey (SF-36) were significantly improved in the combination versus physiotherapy alone group. Moreover, the combination group experienced a greater mean reduction in medication intake.

In their randomised trial of medium quality, Vernon and colleagues (Vernon 2009),[163] compared the effectiveness of cervical manipulation, medical treatment (10-25mg/d amitriptyline), and the combination of two treatments in adults with tension-type headache. The treatment duration was 14 weeks. The main study outcome, headache frequency (number of headache days in the last 28 days of the trial) was measured at the end of treatment period, i.e., 14 weeks post-baseline. After 30 months, the trial was prematurely terminated due to problems related to participant recruitment and a high dropout rate. Instead of the planned total sample of 344 participants (based on sample size calculations), only 40 (6%) had been recruited and 20 (3%) had been randomised. The adjusted analysis of the study results showed a statistically significant and a clinically important effect of the combination of cervical manipulation and medical treatment (-8.4, 95% CI: -15.8, -1.1), whereas neither main effect of cervical manipulation (2.0, 95% CI: -3.0, 7.0) nor medical treatment (3.1, 95% CI: -1.6, 7.8) was statistically significant or clinically important.

Evidence summary. According to the Bronfort review,[40] evidence regarding the effectiveness of manual therapy (manipulation/mobilisation used alone or in combination with other treatments) in most of tension-type headaches is inconclusive in an unclear direction. Additional evidence to the Bronfort report from one high[162] and three medium quality randomised trials[159;160;163] has shown some benefits of manual therapy (i.e., osteopathic manipulation, chiropractic manipulation, massage, or mobilisation) in combination with exercise or medical treatment with respect to reducing headache-related pain intensity, frequency and/or disability.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Anderson 2006[159]
Canada

Focus: RCT the effect of adding osteopathic manual treatment (OMT) to progressive muscular relaxation (PMR) exercise in patients with tension-type headache
Duration: 3 weeks
Follow-up: 5 weeks
Quality: medium

PARTICIPANTS:
N: 29 (NR% female)
Age: NR
Inclusion: adults>16 years with tension-type headache (frequent episodic, chronic, or probable)
Exclusions: pts taking pain medication or receiving manual therapy</td>
<td>Intervention type: osteopathy
Intervention (n=14): OMT (unwinding, inhibition, and stretching techniques with a focus on pelvis, cranium, cervical and upper thoracic spine, upper ribs; joint mobilisations including functional, muscle energy, strain/counterstrain, and osteoarticular techniques) + progressive muscular relaxation
Comparison (n=12): progressive muscular relaxation (pts were given audio tape and typed instructions on exercise on contracting major muscle groups, moving feet up, sensation experience, and then relaxation)
Dose: OMT (once a week for 3 weeks) (once a day 20 min session for 3 weeks)
Providers: not reported</td>
<td><u>Results</u>

3 weeks post-treatment

<table>
<tr><th>Change in outcome</th><th>Osteopathic manual treatment</th><th>Progressive muscular relaxation</th><th>p-value</th></tr>
<tr><td>Number of headache free days per week Mean (SD)</td><td>1.79 (1.42)</td><td>0.21 (1.68)</td><td>0.016</td></tr>
<tr><td>Headache degree of improvement on VAS Mean (SD)</td><td>1.88 (1.39)</td><td>0.65 (1.95)</td><td>0.075</td></tr>
<tr><td>Headache diary rating (% improvement) Mean (SD) on VAS</td><td>57.56 (27.32)</td><td>15.63 (73.46)</td><td>0.059</td></tr>
<tr><td>Improvement in worst headache intensity Mean (SD) on VAS</td><td>1.50 (1.09)</td><td>0.92 (1.50)</td><td>0.264</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Castien 2011[160]
Castien 2009[161]
The Netherlands

Focus: RCT compared the effectiveness of manual therapy (MT) and usual care by the general practitioner in patients with chronic tension-type headache
Duration: 8 weeks
Follow-up: 26 weeks
Quality: medium

PARTICIPANTS:
N: 82 (78% female)
Age: 40 years
Inclusion: adults 18-65 years who met chronic tension-type headache criteria according to the classification of headaches of the International Headache Society (occurring on at least 15 days per month for > 3 months, lasting for hours or continuous; at least one of the following characteristics present: bilateral location, pressing quality, mild/moderate intensity, photophobia, phonophobia, mild nausea)
Exclusion: rheumatoid arthritis, malignancy, pregnancy, intake of opioids/analgesics on regular basis for > 3 months, receiving MT 2 months before the study enrolment</td>
<td>Intervention type: physiotherapy
Intervention (n=41): MT consisted of cervical/thoracic spine mobilisation, craniocervical exercises, postural correction
Intervention (n=41): usual care by the general practitioner provided information, re-assurance and advice, and discussed the benefits of life-style changes; if necessary, pain medication and NSAIDs were prescribed
Dose: usual care by the general practitioner (2-3 visits); MT (up to 9 sessions each 30 minutes duration)
Providers: trained manual therapists, registered members of the national association of manual therapists with an average experience of 10 years who additionally completed a course on the mechanical diagnosis and management of disorders of the cervical spine provided by the McKenzie Institute</td>
<td><u>Results</u>
<table>
<tr><th>Change in outcome</th><th>Manual therapy</th><th>Usual care by the general practitioner</th><th>Difference p-value (95% CI)</th></tr>
<tr><td>8 weeks post-baseline</td><td></td><td></td><td></td></tr>
<tr><td>50% reduction in headache frequency (n/N)</td><td>35/40 (87.5%)</td><td>11/40 (27.5%)</td><td><0.05
3.2 (1.9, 5.3)</td></tr>
<tr><td>Headache days frequency</td><td>-9.1 SD3.8</td><td>-2.7 SD4.3</td><td>-6.4 (-8.32, -4.56)</td></tr>
<tr><td>Headache pain intensity (score 0-10)</td><td>-2.7 SD0.9</td><td>-0.9 SD2.4</td><td>-1.8 (-3.07, -0.67)</td></tr>
<tr><td>Headache Disability Inventory (score 0-100)</td><td>-17.4 SD16.1</td><td>-5.8 SD12.8</td><td>-11.6 (-18.1, -5.1)</td></tr>
<tr><td>Cervical range of movement (degrees)</td><td>18.8 SD32.5</td><td>2.0 SD31.4</td><td>16.8 (2.42, 31.32)</td></tr>
<tr><td>Endurance of the neck flexor (sec)</td><td>13.0 SD16.8</td><td>2.9 SD17.2</td><td>10.0 (2.35, 17.74)</td></tr>
<tr><td>Headache Impact Test-6</td><td>-8.9 SD7.1</td><td>-2.4 SD6.5</td><td>-6.5 (-9.62, -3.52)</td></tr>
<tr><td>26 weeks post-baseline</td><td></td><td></td><td></td></tr>
<tr><td>50% reduction in headache frequency (n/N)</td><td>31/38 (81.6%)</td><td>15/37 (40.5%)</td><td><0.05
2.0 (1.3, 3.0)</td></tr>
<tr><td>Headache days frequency</td><td>-9.1 SD4.2</td><td>-4.1 SD4.4</td><td>-4.9 (-6.95, -2.98)</td></tr>
<tr><td>Headache pain intensity</td><td>-3.1 SD2.8</td><td>-1.7 SD2.5</td><td>-1.4 (-2.69, -0.16)</td></tr>
<tr><td>Headache Disability Inventory (score 0-100)</td><td>-20.0 D22.6</td><td>-9.9 SD18.0</td><td>-10.1 (-19.5, -0.64)</td></tr>
<tr><td>Cervical range of movement (degrees)</td><td>15.6 SD37.8</td><td>5.3 SD45.0</td><td>10.2 (-9.16, 29.63)</td></tr>
<tr><td>Endurance of the neck flexor (sec)</td><td>13.3 SD20.7</td><td>13.0 SD25.0</td><td>0.3 (-10.38, 11.03)</td></tr>
<tr><td>Headache Impact Test-6</td><td>-10.6 SD8.4</td><td>-5.5 SD8.6</td><td>-5.0 (-9.02, -1.16)</td></tr>
<tr><td>Perceived recovery (n/N)</td><td>35/38 (87.5%)</td><td>10/37 (25.0%)</td><td>62.5 (48.4, 79.3)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>van Ettekoven 2006[162]
The Netherlands

Focus: RCT investigated the effectiveness of exercise (craniocervical flexion) combined with physiotherapy in patients with tension-type headache
Duration: 6 weeks
Follow-up: 7 months
Quality: high

PARTICIPANTS:
N: 81 (81% female)
Age: 45 years
Inclusion: adults 18-65 years who met chronic tension-type headache criteria according to the classification of headaches of the International Headache Society (occurring on at least 15 days per month for > 3 months, lasting for hours or continuous; at least one of the following characteristics present: bilateral location, pressing quality, mild/moderate intensity, photophobia, phonophobia, mild nausea)
Exclusion: other types of headache, cervical function problems, physiotherapy for the treatment of tension-type headache received within the last 6 months</td>
<td>Intervention type: physiotherapy
Intervention (n=39): craniocervical flexion exercise (low-load endurance exercise using a latex band) plus physiotherapy (Western massage, oscillation techniques, and instruction on postural correction)
Intervention (n=42): physiotherapy (Western massage incl. friction massage, oscillation techniques (low-velocity, passive cervical joint mobilisation), and instruction on postural correction)
Dose: craniocervical flexion exercise (max 15 minute session; exercise done at home twice a day for 10 minute session
Providers: explicitly trained experienced senior physiotherapists</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Physiotherapy plus craniocervical flexion</th><th>Physiotherapy</th><th>Difference p-value (95% CI)</th></tr>
<tr><td>6 weeks post-baseline</td><td></td><td></td><td></td></tr>
<tr><td>≥50% reduction in headache frequency (n/N)</td><td>32/39 (82%)</td><td>22/42 (52%)</td><td>NR</td></tr>
<tr><td>Headache days frequency Mean (SD)</td><td>NR</td><td>NR</td><td>0.94 (-0.71, 1.81)</td></tr>
<tr><td>Headache pain intensity (score 0-10) Mean (SD)</td><td>NR</td><td>NR</td><td>-0.04 (-1.09, 1.01)</td></tr>
<tr><td>Headache duration (h/day) Mean (SD)</td><td>NR</td><td>NR</td><td>-0.18 (-2.07, 1.70)</td></tr>
<tr><td>6 months post-baseline</td><td></td><td></td><td></td></tr>
<tr><td>≥50% reduction in headache frequency (n/N)</td><td>33/39 (85%)</td><td>14/42 (35%)</td><td>NR</td></tr>
<tr><td>Headache days frequency Mean (SD)</td><td>NR</td><td>NR</td><td>1.95 (1.14, 2.76)</td></tr>
<tr><td>Headache pain intensity (score 0-10) Mean (SD)</td><td>NR</td><td>NR</td><td>1.78 (0.82, 2.74)</td></tr>
<tr><td>Headache duration (h/day) Mean (SD)</td><td>NR</td><td>NR</td><td>2.07 (0.12, 4.03)</td></tr>
<tr><td>Quality of life (SF-36)</td><td></td><td></td><td></td></tr>
<tr><td>Emotional well-being</td><td>NR</td><td>NR</td><td>p=0.014</td></tr>
<tr><td>Limitations due to mental health</td><td>NR</td><td>NR</td><td>p=0.05</td></tr>
<tr><td>Vitality</td><td>NR</td><td>NR</td><td>p=0.039</td></tr>
<tr><td>Bodily pain</td><td>NR</td><td>NR</td><td>p=0.017</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Study and Participants	Interventions	Outcomes
Vernon 2009[163] Canada **Focus:** RCT compared the effectiveness of cervical manipulation, medical treatment, and the combination of two treatments in adults with tension-type headache **Duration:** 10-14 weeks **Follow-up:** 26 weeks **Quality:** medium **PARTICIPANTS:** **N:** 20 (80% female) **Age:** mean range (29-43 years) **Inclusion:** adults 18-50 years who met chronic tension-type headache criteria according to the classification of headaches of the International Headache Society (occurring 10-25 days per month, no more than two unilateral headaches per month, <50 on Zung Depression scale, no contraindications to manipulation/amitriptyline, no history of whiplash injury, not receiving manual treatment within the past year of the trial enrolment) **Exclusion**: not reported	**Intervention type:** chiropractic **Intervention 1 (n=5**): chiropractic cervical manipulation 10 weeks of duration (brief minimal preparatory soft tissue massage to the cervical paraspinal tissues followed by high velocity, low amplitude thrusting manipulation to any dysfunctional joints from occiput to third thoracic vertebrae) **Intervention 2 (n=7):** medical treatment (10-25mg/d amitriptyline for 14 weeks) **Intervention 3 (n=3):** chiropractic cervical manipulation plus medical treatment (amitriptyline) **Comparison (n=5):** sham chiropractic plus placebo **Dose:** manual therapy (3 times per week for 6 weeks followed by once per week for 4 weeks); medical treatment (amitriptyline given at 10 mg/d for the first 2 weeks and followed by 25 mg/d for the remaining 12 weeks) **Providers:** chiropractors with >5 years of experience	**Results** **The adjusted analysis** Number of headache days in the last 28 days of the trial (at 14 weeks follow-up) Effect of manipulation plus medical treatment: -8.4, 95% CI: -15.8, -1.1 (SS) Main effect of manipulation: 2.0, 95% CI: -3.0, 7.0 (NS) Main effect of medical treatment: 3.1, 95% CI: -1.6, 7.8 (NS) ***Specific adverse effects:*** Nine participants had adverse events, four with manipulation (chiropractic-related events such as minor aggravation of neck pain) and five with amitriptyline (nausea, tiredness, change in sleep, dry mouth, and constipation)

Miscellaneous headaches

One evidence-based clinical guideline (Bryans 2011),[164] one systematic review (Maltby 2008)[165] and two randomised trials (Hertogh 2009, Foster 2004)[166;167] were identified for this sub-section.

Based on systematic review methodology (high quality), Bryans and colleagues (Bryans 2011)[164] developed evidence-based clinical practice guidelines and recommendations for chiropractic treatment of headaches in adults. For this purpose, the authors investigated evidence on benefits and harms of manual therapy/chiropractic treatment in adults with miscellaneous headaches (migraine, tension-type headache, cervicogenic headache). The electronic searches were performed in 8 relevant databases and were restricted to English language publications. Unpublished or non-English literature was not sought. The reference lists of relevant systematic reviews were also scanned to identify additional publications. The inclusion criteria were limited to systematic reviews, RCTs, and CCTs. Observational studies, case-series, and case-reports were excluded. The quality of primary studies and systematic reviews was assessed using the methods recommended by the Cochrane Collaboration Back Review Group and Oxman and Guyatt. The development of recommendations was based on summarised trial results, quality appraisal, and strength of body of evidence. For determination of strength of evidence (strong, moderate, limited, conflicting, or no evidence), the authors considered the number, quality, and consistency of study results. Any given treatment modality was judged to be beneficial if it was supported by minimum of moderate level of strength of evidence. The review included 21 relevant publications including the following: 11 randomised trials, 5 controlled trials, and 5 systematic reviews. The reviewed evidence indicated benefits of spinal manipulation for adults with episodic/chronic migraine and cervicogenic headache, but not for those with episodic tension-type headache. Evidence regarding benefits of spinal manipulation for chronic tension-type headache was inconclusive. Craniocervical mobilisation and joint mobilisation were shown to be of benefit for episodic/chronic tension-type headaches and cervicogenic headache, respectively. Evidence regarding benefits of manual traction, connective tissue manipulation, Cyriax' mobilisation or exercise for tension-type headaches was inconclusive. Harms were adequately reported in only 6 trials and overall risks were low.

The guideline panel recommended the use of spinal manipulation for the management of adults with episodic/chronic migraine (moderate evidence level) and cervicogenic headache (moderate evidence level). The guideline panel does not recommend the use of spinal manipulation for the management of episodic tension-type headache (moderate evidence level). The guideline panel recommended the use of craniocervical mobilisation and joint mobilisation for episodic/chronic tension-type headaches and cervicogenic headache, respectively (moderate evidence level). No recommendation could be drawn on spinal manipulation, manual traction, connective tissue manipulation, Cyriax's mobilisation or exercise for chronic tension-type headache.

One systematic review (Maltby 2008)[165] investigated if 6-12 visits to chiropractor to receive spinal manipulative therapy or mobilisation would confer benefits for adults with headaches. The electronic searches were performed in 4 relevant databases. The review included 47 randomised

trials. The results did not support claims of restricting chiropractic care to 6-12 visits. The data indicated that a minimum of 24 visits would be needed to stabilise headaches.

One randomised trial of medium quality (Hertogh 2009)[166] compared the effectiveness of 6-week manual therapy (combination of spinal mobilisation and stabilising exercise) plus usual care (education, prophylactic and attack medication) to that of usual care alone in 37 adults with miscellaneous headaches (tension-type, cervicogenic, migraine). The primary (i.e., global perceived effect and headache impact test-6) and secondary (i.e., headache frequency, pain intensity, medication intake, and absenteeism) outcomes were measured at 7, 12, and 26 weeks post-baseline. Due to problems related to participant recruitment, the trial was prematurely terminated. Specifically, instead of the planned total sample of 186 participants (based on sample size calculations), only 37 were recruited. There were no significant between-group differences in all primary and secondary outcomes at all follow-up points. The results were rendered as inconclusive due to early termination of the trial.

In the pilot study of medium quality by Foster and colleagues (Foster 2004),[167] 33 participants taking pain medication for miscellaneous chronic headaches (i.e., tension-type, cluster, migraine) were randomly assigned to receive one of the three treatments for 6 weeks: manual therapy (Trager approach: gentle mobilisation of the joint areas of the head, neck, upper back, and shoulders), attention treatment (visit and discussion with physician about medication intake, previous week's headaches, and perception of well-being), or no treatment (i.e., only medication group). At 6 weeks of follow-up, both the manual therapy and attention groups experienced significantly greater mean reduction (from baseline) in headache duration (in hours) compared to the no treatment control group (-0.6 and –0.3 versus 1.8, respectively; $p<0.05$). Similarly, the post-treatment mean headache quality of life score improvement in the manual therapy and attention groups was significantly greater than in the no treatment group (0.4 and 0.8 versus –0.5, respectively; $p=0.001$). The post-treatment between-group differences in mean change of medication use (total number of pills taken biweekly during baseline and treatment periods), headache intensity (score range: 0-100), and the number of headache episodes (per week) were not statistically significant.

Evidence summary. The conclusions based on the evidence reviewed by Bryans and colleagues (Bryans 2011)[164] confirms those of the Bronfort report that there is moderate evidence showing the benefit of spinal manipulation for treating adults diagnosed with migraine and cervicogenic types of headaches. Although the Bronfort review reports that there is inconclusive evidence on effectiveness of spinal manipulation for tension-type headaches, the more recent review by Bryans showed that there is moderate quality evidence of no benefit, and therefore, they do not recommend using spinal manipulation for treating tension-type headaches.

The Bryans review concluded that there is moderate evidence that craniocervical and joint mobilisation are effective in treating tension-type and cervicogenic headaches, respectively. Similarly, the results from randomised trial by Foster and colleagues showed that craniocervical and joint mobilisation was beneficial for improving duration and quality of life in adults with

miscellaneous headaches (tension-type, cluster, migraine). These conclusions differ from that of the Bronfort report, in which, the similar evidence was rendered inconclusive.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Bryans 2011[164] **Focus:** effectiveness/safety of spinal manipulation therapy (SMT), mobilisation, or manual traction in adults with miscellaneous headaches (migraine, tension-type headache, cervicogenic headache) **Quality of systematic review:** high	**INCLUSION CRITERIA** **Study design:** systematic reviews, RCTs, CCTs **Participants:** adults with miscellaneous headaches (migraine, tension-type headache, cervicogenic headache) **Interventions**: spinal manipulation therapy (SMT), mobilisation, or manual traction **Outcomes:** headache intensity, duration, frequency, quality of life, disability, medicine use **METHODOLOGY** 8 relevant databases searched; English publications; hand search of reference lists; details on study selection; quality assessment of studies presented; excluded studies and reasons for exclusions are listed; assessed strength of evidence using pre-defined rules and recommendations for practice are developed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 11 randomised trials (Boline 1995, Bove 1998, Donkin 2002, Jull 2002, Lawler 2006, Nelson 1998, Nilsson 1997, Soderberg 2006, Lemstra 2002, van Ettekoven 2006, Tuchin 2000), 5 controlled trials (Dittrich 2008, Demirturk 2002, Marcus 1998, Narin 2003, Torelli 2004), and 5 systematic reviews (Bronfort 2004, Fernandez-de-Las-Penas 2006, Hurwitz 1996, Lenssinck 2004, Fernandez-de-Las-Penas 2005) **Study quality:** the Cochrane Collaboration Back Review Group (controlled studies; score range: 3-9) and Oxman and Guyatt (systematic reviews; score range: 6-9) **Study characteristics:** studies differed in inclusion criteria and included adults with miscellaneous headaches (migraine, tension-type headache, or cervicogenic headache). Most studies reported pain relief, pain duration, frequency, pain medication use, and quality of life **Excluded studies eligible for current review:** not reported	**RESULTS** • Spinal manipulation was shown beneficial for adults with episodic/chronic migraine and cervicogenic headache, but not for those with episodic tension-type headache • Craniocervical mobilisation and joint mobilisation were effective for episodic/chronic tension-type headaches and cervicogenic headache, respectively • It is not clear if spinal manipulation, manual traction, connective tissue manipulation, Cyriax' mobilisation or exercise are effective for tension-type headaches • Risks of harms reported in 6 trials were low **CONCLUSIONS** • The guideline panel recommend the use of spinal manipulation for the management of adults with episodic/chronic migraine (moderate evidence level) and cervicogenic headache (moderate evidence level) • The guideline panel cannot recommend the use of spinal manipulation for the management of episodic tension-type headache (moderate evidence level) • The guideline panel recommend the use of craniocervical mobilisation and joint mobilisation for episodic/chronic tension-type headaches and cervicogenic headache, respectively • No recommendation on spinal manipulation, manual traction, connective tissue manipulation, Cyriax' mobilisation or exercise for chronic tension-type headache

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>de Hertogh 2009[166]
The Netherlands

Focus: RCT compared manual therapy plus usual care to usual care alone in adults with miscellaneous headaches (migraine, tension-type headache, cervicogenic headache)
Duration: 6 weeks
Follow-up: 27 weeks
Quality: Medium

PARTICIPANTS:
N: 37 (76% female)
Age: 43 years
Inclusion: adults>18 years with miscellaneous headaches (migraine, tension-type headache, cervicogenic headache) accompanied by neck pain at least for 2 months, twice a month or more often, headache impact test (HIT-6) score > 56; exclusions: cluster headache, trigeminal neuralgia, peripheral neuropathies, chronic musculoskeletal disorders, rheumatoid arthritis, Down syndrome, history of surgery in cervical region, pregnancy, manipulation treatment in the past 12 months</td>
<td>Intervention type: physiotherapy
Intervention (n=18): manual therapy (cervical joint mobilisation and stabilising exercise – craniocervical flexion exercise)
Comparison (n=19): usual care (education, prophylactic and attack medication)
Dose: 12 sessions 30 min each (twice a week over 6 weeks)
Providers: not reported</td>
<td>RESULTS

<table>
<tr><th>Change in outcome</th><th>Manual therapy + usual care</th><th>Usual care</th><th>p-value</th></tr>
<tr><td>Global perceived effect (n/N of responders)</td><td>6/14</td><td>7/13</td><td>NS</td></tr>
<tr><td>Headache impact test–6 Mean (SD)</td><td>55.21 (9.75)</td><td>56.80 (6.46)</td><td>NS</td></tr>
<tr><td>Headache intensity at 26 weeks Mean (SD)</td><td>19.92 (29.09)</td><td>13.55 (24.23)</td><td>NS</td></tr>
<tr><td>50% reduction in headache frequency (n/N achieved)</td><td>12/14</td><td>12/13</td><td>NS</td></tr>
<tr><td>Absenteeism (n/N absent)</td><td>2/13</td><td>2/11</td><td>NS</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Foster 2004[167]
USA

Focus: RCT of manual therapy (Trager method) and medication effects in with miscellaneous headaches (migraine, tension-type, cluster)
Duration: 6 weeks
Follow-up: 6 weeks
Quality: medium

PARTICIPANTS:
N: 33 (86% female)
Age: 30 years
Inclusion: adults 18-65 years with miscellaneous chronic headaches (migraine, tension-type, cluster) for > 6 months (>1 headache per week), pain intensity range: 25-85 on a VAS of 0-100 scale
Exclusion: life threatening aetiology of headache, contraindications to manual therapy</td>
<td>Intervention type: Trager method
Intervention 1 (n=14): manual therapy/Trager (gentle mobilisation of the joint areas of the head, neck, upper back, and shoulders with slow movements to encourage relaxation and movement patterns) plus medication
Intervention 2 (n=7): attention therapy (visit and discussion with physician about medication intake, previous week’s headaches, and perception of well-being) plus medication
Comparison (n=12): no treatment (only medication)
Dose: manual therapy (one hour sessions) for 6 weeks; attention therapy (15-20 minute sessions) for 6 weeks
Providers: physician</td>
<td>RESULTS

<table>
<tr><th>Change in outcome
(6 weeks post-baseline)</th><th>Manual therapy-trager</th><th>Attention treatment</th><th>No treatment</th><th>p-value</th></tr>
<tr><td>Headache duration (hours)
Mean change (SD)</td><td>-0.6 (3.6)</td><td>–0.3 (1.6)</td><td>1.8 (2.7)</td><td><0.05 (Trager or attention versus no treatment)</td></tr>
<tr><td>Headache QOL score
Mean change (SD)</td><td>0.4 (0.8)</td><td>0.8 (0.8)</td><td>-0.5 (0.7)</td><td>0.001 (Trager or attention versus no treatment)</td></tr>
<tr><td>Medication use (total N of pills taken biweekly)
Mean change (SD)</td><td>-6.7 (9.2)</td><td>-3.8 (7.9)</td><td>6.2 (18.6)</td><td>NS</td></tr>
<tr><td>Headache intensity (VAS score range: 0-100)
Mean change (SD)</td><td>0.3 (20.1)</td><td>-4.2 (20.6)</td><td>6.6 (10.4)</td><td>NS</td></tr>
<tr><td>Headache episodes (N per week)
Mean change (SD)</td><td>-2.5 (4.6)</td><td>-0.3 (9.7)</td><td>1.3 (5.4)</td><td>NS</td></tr>
</table>

Specific adverse effects: not observed</td>
</tr>
</table>

Fibromyalgia

Two new systematic reviews were identified that included the assessment of manual therapy in patients with fibromyalgia (Baranowsky 2009 and Porter 2010).[168;169] However, none of these reviews included studies not already included in the Bronfort report and both concluded that there is insufficient evidence to support the effectiveness of manual therapy in the treatment of fibromyalgia.

Two new RCTs not included in any systematic reviews were identified (Castro-Sánchez 2011a, Castro-Sánchez 2011b).[170;171] One RCT, with a medium quality rating, assessed the effects of cranio-sacral therapy in 92 women with fibromyalgia. After 20 weeks of treatment, there was a significant improvement in the clinical global impression of improvement and the clinical global impression of severity and a significant reduction in pain at 13 of 18 tender points. However, most of these differences were not maintained one year after the treatment. The other RCT, with a low quality rating, assessed the effects of massage-myofascial release therapy in 59 patients with fibromyalgia. After 20 weeks of treatment, there was a significant improvement in pain (VAS), pain at 8 of 18 tender points, and four of eight quality of life domains (SF-36). Most of these changes were not maintained six months after the intervention.

Evidence summary. Evidence for the use of chiropractic spinal manipulation in fibromyalgia remains unclear. Due to the paucity and lack of study quality, evidence for the effectiveness of cranio-sacral therapy and massage-myofascial release therapy for fibromyalgia was inconclusive in a favourable direction.

RCTs

Study and Participants	Interventions	Outcomes
Castro-Sánchez 2011a[170] Spain **Focus:** RCT of the effects of cranio-sacral therapy on pain and heart rate variability in patients with fibromyalgia **Duration:** 20 weeks **Follow-up:** 1 year **Quality:** medium **PARTICIPANTS:** **N:** 92 (100% female) **Age:** 51.3 SD13.1 to 53.9 SD10.1 years **Inclusion:** patients with fibromyalgia, 16 to 65 years	**Intervention type:** cranio-sacral therapy **Intervention (n=46):** cranio-sacral therapy; sequence of manipulative therapy: still point (in feet), pelvic diaphragm release, scapular girdle release, frontal lift, parietal lift, compression–decompression of sphenobasilar fascia, decompression of temporal fascia, compression–decompression of temporomandibular joint and evaluation of dural tube (balance of dura mater) **Comparison (n=46):** sham therapy with disconnected magnetotherapy equipment **Dose:** twice a week 1 h sessions for 20 weeks **Providers:** cranio-sacral and magnetotherapists **Further information available on:** heart rate, heart rate variability, body composition	**Results** • *Clinical global impression of improvement (Likert scale):* significantly better in intervention group than control group after treatment and 2 months post-treatment but not 1 year post-treatment • *Clinical global impression of severity (Likert scale):* significantly better in intervention group than control group after treatment but not at 2 months or 1 year post-treatment • *Pain:* 20 weeks: significant reduction in pain at 13 of 18 tender points in intervention group, no reduction in control group, significant difference between groups; 1 year: reduction remained significant for 4 tender points ***Specific adverse effects:*** not reported
Castro-Sánchez 2011a[171] Spain **Focus:** RCT of the effects of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia **Duration:** 20 weeks **Follow-up:** 6 months post-intervention **Quality:** low **PARTICIPANTS:** **N:** 59 (95% female) **Age:** 49.3 SD11.6 to 46.3 SD12.3 year **Inclusion:** patients with fibromyalgia syndrome, age 18 to 65 years, no regular physical activity	**Intervention type:** physiotherapy **Intervention (n=30):** massage-myofascial release protocol: massage-myofascial release at insertion of the temporal muscle, release of falx cerebri by frontal lift, release of tentorium cerebella by synchronization of temporal, assisted release of cervical fascia, release of anterior thoracic wall, release of pectoral region, lumbosacral decompression, release of gluteal fascia, transversal sliding of wrist flexors and fingers, and release of quadriceps fascia **Comparison (n=29):** sham therapy with disconnected magnetotherapy equipment **Dose:** *intervention:* weekly 90 min session for 20 weeks; *control:* **Providers:** physiotherapist specialised in massage-myofascial therapy **Further information available on:** sleep parameters, state and trait anxiety	**Results** • *Pain:* 20 weeks: VAS pain score significantly reduced versus baseline and control ($p<0.043$); significantly greater reduction in pain at 8of 18 tender points in intervention compared to control group; 6 months: reduction remained significant for 3 tender points; no significant difference in VAS score • *Quality of life (SF-36):* significantly better for 4 of 8 domains than placebo at 20 weeks (physical function, physical role, body pain, social function) but not at 6 months • *Beck depression inventory:* no significant difference between groups ***Specific adverse effects:*** not reported

Myofascial pain syndrome

Two additional medium quality systematic reviews assessing the effectiveness of manual therapy in myofascial pain syndrome were identified (de las Peñas 2005 and Rickards 2006).[172;173] However, none of them included any trials over and above those mentioned in the Bronfort report. Rickards 2006[173] concluded that there was no conclusive evidence about the effectiveness of manual therapy (including ischaemic compression and deep friction massage) in myofascial pain syndrome and a lack of information on longer term effects. Similarly, de las Peñas 2005[172] concluded that there was no rigorous evidence that some manual treatments have an effect beyond placebo in the treatment of myofascial trigger points.

Three additional medium quality RCTs were identified on the effects of manual therapy in people with myofascial pain (Gemmell 2008a, Gemmell 2008b, Nagrale 2010).[174-176] The two trials by Gemmell 2008a and 2008b only assessed outcomes immediately after a single treatment and therefore longer term effects are unclear. In the first trial, Gemmell 2008a[174] compared the effects of ischaemic compression therapy with trigger point therapy using the Activator instrument in 52 participants with active upper trapezius trigger points. Improvements were seen in both groups on pain, pressure pain threshold and a global impression of improvement, but there was no significant difference between the two intervention groups. In the second trial, Gemmell 2008b[175] compared the effects of ischaemic compression, trigger point pressure release, and sham treatment in 45 patients with subacute mechanical neck pain and active upper trapezius trigger points. After the intervention, there was no significant difference between the three groups in neck pain, pressure pain threshold or lateral cervical flexion. However, there were significantly more participants in the ischaemic compression group who reported an improvement (pain reduction of at least 20 mm (VAS)) than in the sham group. None of the two trials reported on adverse events.

In the trial by Nagrale 2010,[176] 60 patients with non-specific subacute neck pain and active upper trapezius trigger points were treated 12 times over a period of four weeks using a muscle energy technique or an integrated neuromuscular inhibition technique (ischaemic compression plus strain-counterstrain plus muscle energy technique). After the intervention, participants in the integrated neuromuscular inhibition group had significantly better outcomes for pain, neck disability and lateral cervical flexion than participants in the muscle energy group. The authors did not report on adverse events.

Evidence summary. There is inconclusive evidence in a favourable direction for ischaemic compression (manual or using an Activator instrument) in the deactivation of upper trapezius trigger points. There is inconclusive negative evidence indicating that trigger point release is not as effective as ischaemic compression in deactivating active upper trapezius trigger points and improving associated neck pain. There is inconclusive evidence in a favourable direction for an integrated neuromuscular inhibition technique in the management of neck pain with active upper trapezius trigger points.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Gemmell 2008a[174]
UK

Focus: RCT of the immediate effect of a ischaemic compression and activator trigger point therapy on active upper trapezius trigger points
Duration: single treatment
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 52 (67 to 72% female)
Age: 28 SD9.1 to 29 SD8.5 years
Inclusion: patients with active upper trapezius trigger points of more than 12 weeks’ duration rated at least 4 on an 11-point numerical rating scale, male and female between 18 and 55 years</td>
<td>Intervention type: chiropractic
Intervention 1 (n=25): ischaemic compression therapy: continuous, perpendicular deep thumb pressure to the identified upper trapezius trigger point for 30 to 60 s; pressure was released according to which of the following occurred first: a palpable decrease in trigger point tension or once 60 s had passed
Intervention 2 (n=27): Activator trigger point therapy: a force setting of 3 was used (170 N); to treat the trigger point, the Activator instrument was placed perpendicular over the identified TrP and 10 thrusts were delivered, with a rate of one thrust per second
Dose: single treatment
Providers: chiropractor

<u>Further information available on:</u> demographic details</td>
<td><u>Results</u>
• Patient Global Impression of Change (PGIC, 7 point scale, ‘very much improved’ to ‘very much worse’)
• Pain numeric rating scale (NRS)
• Pressure pain threshold (PPT)

Results reported as % participants undergoing a meaningful clinical improvement
<table><tr><th></th><th>Ischaemic compression</th><th>Activator</th><th>p</th></tr><tr><td>PCIC</td><td>78%</td><td>72%</td><td>NS</td></tr><tr><td>NRS</td><td>41%</td><td>36%</td><td>NS</td></tr><tr><td>PPT</td><td>30%</td><td>32%</td><td>NS</td></tr></table>
Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Gemmell 2008b[175]
UK

Focus: RCT of the immediate effect of a ischaemic compression and trigger point pressure release on neck pain and upper trapezius trigger points
Duration: single treatment
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 45 (% female not stated)
Age: 23 SD1.5 to 24 SD4.6 years
Inclusion: participants with mechanical neck pain for <3 months; active upper trapezius trigger point; pain of at least 30 mm on VAS; decreased lateral flexion to the opposite side of the active upper trapezius trigger point, 18 to 55 years</td>
<td>Intervention type: chiropractic
Intervention 1 (n=15): ischaemic compression therapy: continuous, perpendicular deep thumb pressure to the identified upper trapezius trigger point for 30 to 60 s; pressure was released according to which of the following occurred first: a palpable decrease in trigger point tension or once 60 s had passed
Intervention 2 (n=15): trigger point (TrP) pressure release: clinician applied non-painful slowly increasing pressure with the thumb over the trigger point until a tissue resistance barrier was felt; level of pressure was maintained until release of the tissue barrier was felt, at which time pressure was increased until a new barrier was reached; process was repeated until there was no trigger point tension / tenderness or 90 s had elapsed, whichever occurred first
Control (n=15): sham procedure (detuned ultrasound)
Dose: single treatment
Providers: chiropractor

<u>Further information available on:</u> demographic details</td>
<td><u>Results</u>
• % improved: pain reduction of at least 20 mm on VAS

<table>
<tr><th></th><th>Ischaemic compression (IC)</th><th>TrP pressure release</th><th>Sham</th><th>p</th></tr>
<tr><td>% improved (VAS)</td><td>60.0%</td><td>46.7%</td><td>26.7%</td><td>IC versus sham <0.05</td></tr>
<tr><td>Neck pain (VAS, mm)</td><td>22.93 SD12.76</td><td>27.13 SD16.40</td><td>22.67 SD8.21</td><td>NS</td></tr>
<tr><td>PPT (kg/m^2)</td><td>4.45 SD1.69</td><td>3.77 SD1.76</td><td>3.37 SD1.62</td><td>NS</td></tr>
<tr><td>Lateral cervical flexion (°)</td><td>50.5 SD8.6</td><td>49.1 SD10.4</td><td>49.1 SD8.3</td><td>NS</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Nagrale 2010[176]
India

Focus: RCT comparing the effects of muscle energy techniques versus an integrated neuromuscular inhibition technique in deactivating upper trapezius trigger points (improvement in pain, range of motion, disability)
Duration: 4 weeks
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 60 (58% female)
Age: 27.6 SD4.3 to 28.2 SD4.8 years
Inclusion: 18 to 55 years, non-specific neck pain of <3 months’ duration, active upper trapezius trigger points</td>
<td>Intervention type: physiotherapy
Intervention 1 (n=30): muscle energy (MET) treatment as per Lewit’s post-isometric relaxation approach
Intervention 2 (n=30): integrated neuromuscular inhibition technique (INIT): ischaemic compression plus strain-counterstrain plus muscle energy technique
Dose: 3 times per week for 4 consecutive weeks
Providers: not stated</td>
<td><u>Results</u> (4 weeks)

<table>
<tr><th></th><th>MET</th><th>INIT</th><th>p</th></tr>
<tr><td>Pain (VAS)</td><td>6.10 SD0.68</td><td>5.28 SD0.47</td><td><0.01</td></tr>
<tr><td>Neck disability index</td><td>31.88 SD4.4</td><td>27.19 SD3.7</td><td><0.01</td></tr>
<tr><td>Lateral cervical flexion (°)</td><td>29.33 SD1.72</td><td>34.44 SD1.2</td><td><0.01</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Non-musculoskeletal conditions

Asthma

We identified one additional medium quality systematic review on chiropractic treatment for asthma (Kaminskyj 2010),[177] one additional medium quality RCT of cranio-sacral therapy for asthma in adults (Mehl-Madrona 2007),[178] as well as one qualitative study on complementary therapy use in patients with asthma (Shaw 2006).[179]

The systematic review by Kaminskyj 2010[177] included eight studies, of which three were RCTs and one was a CCT, while the rest were uncontrolled studies. Three of the included studies were in children. In the comparative studies, no significant differences between comparison groups were seen in respiratory parameters, symptoms or subjective measures. In the uncontrolled studies, improvements were generally seen in subjective measures – however, improvements in subjective measures were also seen in the control groups of comparative studies. Only one study reported on adverse events (none reported). The review authors concluded that some patients may experience chiropractic care as beneficial, but overall no significant effect in any outcomes versus sham treatment. However, the quality of the evidence was generally poor and more evidence is required using valid and reliable outcome measurement.

The RCT by Mehl-Madrona 2007[178] included 89 adults with asthma subdivided into five comparison groups. These included cranio-sacral therapy only (12 sessions), acupuncture (12 sessions) only, combined cranio-sacral therapy and acupuncture (6 sessions each), attention control and waiting list control. The study was underpowered for this number of comparison groups and as no significant difference could be found between the intervention groups and between the control groups, intervention groups and control groups were lumped together (i.e. no results were presented for cranio-sacral therapy alone). The intervention groups (acupuncture and/or cranio-sacral therapy) showed no significant difference to the control groups in pulmonary function measures or depression (Beck Depression Scale), however, medication use was significantly reduced both post-intervention and at six months follow-up in the intervention groups (i.e. the same lung function could be maintained at a lower level of medication use), and the Asthma Quality of Life score was significantly more improved post-intervention (not at six months follow-up) than in the control groups. An effect of provider continuity was also found, with the effects on quality of life being stronger in the groups having had 12 treatment sessions with a single provider, and with these groups also having a significantly reduced anxiety level (Beck Anxiety Interventory). No adverse effects were seen.

In the qualitative study by Shaw 2006,[179] 50 patients with asthma (21 adults and 29 children with their parents) were interviewed about their use of complementary therapies. Of these, 13 did not use complementary therapies. Reasons for non-use of complementary therapies included general scepticism, trust in conventional doctors, and not having tried any complementary therapies yet, despite being interested and open. The main complementary therapies used by the rest were breathing techniques (e.g. the Buteyko Method) and homeopathy, with some reported use of chiropractics, osteopathy and cranial osteopathy. Reasons for using complementary therapies included concerns about side effects of conventional medications, about medication dependency, and about medication escalation (push factors). Pull factors included the desire for more natural or non-invasive treatments, the quality of the consultation (holistic approach, time taken, listening), a commitment to alternative philosophies of health, and experience of effectiveness. Other important factors included the fact that

complementary therapy use provided a greater scope for self-help and taking control, and that it allowed an exploration of a broader range of causes of asthma than conventional approaches. No specific statements on the views of manual therapy were offered.

Evidence summary. Bronfort considered the evidence for spinal manipulation to be negative, whereas the evidence from the Kaminskyj 2010 review could be rated as inconclusive in an unclear direction. The evidence from the additional RCT can be rated as inconclusive in a favourable direction.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Kaminskyj 2010[177;180] **Focus:** SR of chiropractic treatment for asthma **Quality:** medium	**INCLUSION CRITERIA** **Study design:** prospective and retrospective studies including RCTs, controlled clinical/quasi-experimental trials; cohort, case-control, case series and survey designs **Participants:** patients diagnosed with asthma **Interventions:** chiropractic treatment **Outcomes:** any outcome relevant to asthma or breathing **METHODOLOGY** 7 databases searched, hand-searching of conference proceedings, bibliographies of relevant articles; search terms not shown; unclear if duplicate study selection; description of quality assessment; unclear if duplicate validity assessment and data extraction **Limitations:** English language, published 1980 to March 2009 **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 8 (3 RCTs (Balon 1998, Bronfort 2001, Nielson 1995), 1 CCT (McKelvey 1999), 1 case study, 1 case series, 2 surveys) **N participants:** 275 plus 5607 from one survey **Trial quality:** four studies <10/27 on Down's and Black checklist, four studies ≥15/27 **Study characteristics:** 3 studies in children (1 to 17 years); in all comparative trials the comparator was sham treatment; treatment in comparative studies up to 4 months **Excluded studies eligible for current review:** none **Further information available on:** study characteristics, individual study results, study quality	**RESULTS** • in comparative studies, no significant differences between comparison groups in respiratory parameters, symptoms or subjective measures • in uncontrolled studies, improvements were generally seen in subjective measures (symptoms), but some improvement in peak flow was also seen; subjective improvements were also in control groups of comparative studies • no adverse effects seen (but only reported by one study) **CONCLUSIONS** Some patients may experience chiropractic care as beneficial, but overall no significant effect in any outcomes versus sham treatment; low quality evidence **Research recommendations** More evidence required using valid and reliable outcome measurement

RCTs

Study and Participants	Interventions	Outcomes
Mehl-Madrona 2007[178] USA **Focus:** RCT of acupuncture, cranio-sacral therapy, a combination of the two, attention control, waiting list control in adults with asthma **Duration:** 12 weeks **Follow-up:** 6 months **Quality:** medium **PARTICIPANTS:** **N:** 89 (73.5% female) **Age:** median 37 years **Inclusion:** adults with asthma (definition National Heart, Lung and Blood Institute), class II to IV asthma sufferers	**Intervention type:** osteopathy 10 to 16 participants per group **Intervention 1:** 12 treatments of acupuncture (45 min sessions, twice weekly) **Intervention 2:** 12 treatments of cranio-sacral therapy (45 min sessions, twice weekly) **Intervention 3:** combination of cranio-sacral therapy with acupuncture (6 sessions each, 45 mins, one each weekly) **Control 1:** attention control (6 sham cranio-sacral therapy and 6 educational classes) **Control 2:** waiting list control (instructed to maintain normal asthma care regimens) **Dose:** see above **Providers:** acupuncturists, trained cranio-sacral therapists	**Results** • Due to small numbers and no significant differences between intervention groups or control groups, groups were collapsed into 'intervention' and 'control' • No change in pulmonary function measures • Asthma Quality of Life score significantly more improved in intervention groups than control groups post-treatment (p=0.004), difference not significant any more at 6 months; QoL was improved significantly more post-treatment in groups with a single practitioner (i.e. not combination treatment, p=0.016) • Medication use was significantly reduced in the intervention groups compared to control, both post-treatment (p<0.001) and at 6 months follow-up (p=0.043) • No changes in the Beck Depression Scale • Overall no difference in Beck Anxiety Inventory intervention versus control, but there was a tendency for the groups with a single practitioner (i.e. longer treatment) to have reduced anxiety levels (p=0.031 at 3 months post-intervention) ***Specific adverse effects:*** no adverse effects seen

Qualitative studies

Study	Interventions	Outcomes
Shaw 2006[179] UK **Focus:** qualitative study of complementary therapy use in patients with asthma **Duration:** single interviews **Quality:** high **PARTICIPANTS:** **N:** 50 (54% female) **Age:** age not reported, 21 adults, 29 children (with parents) **Inclusion:** children and adults with asthma, variety of healthcare settings and socio-demographic backgrounds	**Intervention type:** various (chiropractic, osteopathy) **Intervention:** complementary therapies including chiropractic, osteopathy, cranial osteopathy; of the participants, 31 used complementary therapy for asthma, 6 for other problems, 13 were non-users **Dose:** not reported **Providers:** settings: GP practice in affluent suburb, GP practice in deprived inner city area, NHS outpatient respiratory clinic, NHS outpatient homeopathic hospital, private complementary therapists	**OUTCOME ASSESSMENT** ***Interviews:*** interviews with adults 25 mins to 1 h; paired interviews with children and parents 30 mins to 1.5 h (first half focussing on child, second on parent); interviews recorded and transcribed, thematic analysis **RESULTS** **Interviews:** ***Reasons for non-use:*** • Scepticism about complementary therapies: lack of scientific evidence, strong belief in "scientific medicine" • Trusted and wanted to follow advice from conventional doctors • Interested and open to trying complementary therapies but had not yet done so (no perceived need, not got round to it, financial cost, certain trigger factors could prompt use) ***Complementary therapy use:*** • Mainly breathing techniques (e.g. Buteyko Method) and homeopathy • *Types:* last resort users (tried all conventional treatments first, escalation of medication with lack of benefit); pragmatic users ("shop around" to see whatever treatments will help in parallel to conventional medicine); committed users: complementary therapies are preferred first port-of-call; but all still using conventional medication • *Conventional medicine (push factors):* concerns about side effects, steroids, dislike of dependence on medication, concerns of escalation of medication • *Complementary therapy (pull factors):* desire for "natural" or "non-invasive" treatments, quality of complementary therapy consultations (holistic approach, listening, time), personal commitment to alternative philosophies of health, experience of effectiveness of complementary therapies • Benefits of self-help and taking control • Exploring a broader range of causes of asthma

Attention Deficit / Hyperactivity Disorder (ADHD) / Learning disabilities

One medium quality systematic review (Karpouzis 2010)[181] and two low quality RCTs (Bierent-Vass 2005 and Hubmann 2006)[182;183] were identified on the use of manual therapy in children or adolescents with attention deficit / hyperactivity disorder (ADHD).

The systematic review by Karpouzis 2010[181] sought to assess the effects of chiropractic treatment in children or adolescents with ADHD. However, the authors found no studies fulfilling their inclusion criteria.

The two low quality RCTs – that had very limited description of study methodology and the study population – both assessed the effects of osteopathic treatment of children with ADHD. Children had three (Hubmann 2006) and four (Bierent-Vass 2005)[182] osteopathic treatments separated by several weeks. Both trial reported improved outcomes on the ADHD Connors scale for the intervention group compared to the control group, however, no statistical analyses were reported.

Evidence summary. Given the severe methodological limitations of the studies, there is inconclusive evidence in an unclear direction regarding the effectiveness of osteopathic treatment for ADHD.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Karpouzis 2010[181] **Focus:** systematic review of chiropractic treatment for attention deficit / hyperactivity disorder in children or adolescents **Quality:** medium	**INCLUSION CRITERIA** **Study design:** systematic reviews, randomised or quasi-randomised controlled trials, comparative studies with or without concurrent controls **Participants:** children aged 0 to 17 years; diagnosis of attention deficit / hyperactivity disorder (AD/HD) consistent with DSM-III, DSM-IV, DSM-IV-TR or ICD-10 criteria; diagnosis by paediatrician, psychiatrist, medical doctor, clinical or educational psychologist **Interventions:** chiropractic treatment **Outcomes:** validated psychometric outcome measure as recommended by the American Academy of Child and Adolescent Psychiatry **METHODOLOGY** 9 databases searched, hand-searching of 2 journals; partial duplicate study selection; description of quality assessment (Jadad and 15-item checklist by Hawk); list of excluded studies **Limitations:** full text, English language **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**Number of included trials:** none **Number of participants:** none **Trial quality:** only low quality studies identified that did not fulfil inclusion criteria **Study characteristics:** NA **Excluded studies eligible for current review:** none **Further information available on:** AD/HD rating scales, characteristics of excluded studies	**RESULTS** None of the identified studies fulfilled the inclusion criteria **CONCLUSIONS** There is no high quality evidence to evaluate the efficacy of chiropractic care for paediatric and adolescent AD/HD; the claims made by chiropractors that chiropractic care improved AD/HD symptomatology for young people is only supported by low levels of scientific evidence (e.g. case reports, case series) **Research recommendations** Adequately-sized RCTs using clinically relevant outcomes and standardised measures to examine the effectiveness of chiropractic care versus non-treatment/placebo control or standard care are needed

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr><td>Bierent-Vass 2005[182]
Germany

Focus: RCT of the effects of osteopathic treatment for children with ADHD
Duration: 6 weeks
Follow-up: 4 weeks after the last treatment
Quality: low

PARTICIPANTS:
N: 77 (% female not reported)
Age: 6 to 14 years (details not reported)
Inclusion: children with attention deficit with or without hyperactivity (ADD / ADHD)</td><td>Intervention type: osteopathy
Intervention (n=50): osteopathic treatment; 4 treatments with intervals of 2 weeks
Comparison (n=27): no osteopathic treatment
Dose: see above
Providers: osteopath</td><td><u>Results</u>
• Connor’s Scale (-3 – ‘severe worsening’ to +3 – ‘significant improvement’), p-values not reported
<table><tr><th></th><th>Osteopathic (n=50)</th><th>Control (n=27)</th></tr><tr><td>-3</td><td>0.4%</td><td>0%</td></tr><tr><td>-2</td><td>0.6%</td><td>1.1%</td></tr><tr><td>-1</td><td>4.4%</td><td>11.1%</td></tr><tr><td>0</td><td>45.1%</td><td>78.5%</td></tr><tr><td>+1</td><td>35.6%</td><td>9.3%</td></tr><tr><td>+2</td><td>12.8%</td><td>0</td></tr><tr><td>+3</td><td>1.2%</td><td>0</td></tr></table>
Specific adverse effects: not reported</td></tr>
<tr><td>Hubmann 2006[183]
Austria

Focus: RCT of the effects of osteopathic treatment for children with ADHD
Duration: 2 months
Follow-up: no post-intervention follow-up
Quality: low

PARTICIPANTS:
N: 30 (% female not reported)
Age: 6 to 10 years (details not reported)
Inclusion: ADHD, treated with ritalin or other ADHD-specific drugs</td><td>Intervention type: osteopathy
Intervention (n=15): osteopathic treatment; 3 treatments with intervals of 4 weeks
Comparison (n=15): no osteopathic treatment
Dose: see above
Providers: osteopath

<u>Further information available on:</u>
behavioural details</td><td><u>Results</u>
• Connor’s Scale (0 – ‘not at all’ to 3 – ‘very much’); p-values not reported
<table><tr><th></th><th>Osteopathic (n=15)</th><th>Control (n=15)</th></tr><tr><td>Restless or overactive</td><td>-21.43%</td><td>-8.00%</td></tr><tr><td>Excitable, impulsive</td><td>-31.03%</td><td>-7.69%</td></tr><tr><td>Disturbs other children</td><td>-13.04%</td><td>+16.67%</td></tr><tr><td>Fails to finish things – short attention span</td><td>-32.14%</td><td>-3.57%</td></tr><tr><td>Constantly fidgeting</td><td>-14.81%</td><td>0</td></tr><tr><td>Inattentive, easily distracted</td><td>-31.43%</td><td>-10.00%</td></tr><tr><td>Demands must be met immediately, easily frustrated</td><td>-14.29%</td><td>+7.41%</td></tr><tr><td>Cries often and easily</td><td>-24.14%</td><td>-4.35%</td></tr><tr><td>Mood changes quickly and drastically</td><td>-12.00%</td><td>+13.04%</td></tr><tr><td>Temper outburst, explosive and unpredictable behaviour</td><td>-8.00%</td><td>+4.00%</td></tr></table>
Specific adverse effects: not reported</td></tr>
</table>

Cancer care

One low quality systematic review (Alcantara 2011)[184] assessed chiropractic care of patients with cancer. No comparative studies were identified. While the review reports evidence that patients with cancer frequently consult chiropractors, no evidence regarding the effects of the chiropractic treatment were reported.

With respect to adverse events, one moderate quality controlled cohort study (Wu 2010)[185] assessed the prognosis of patients with osteosarcoma who had or had not had manipulative therapy (patients had sought manipulative therapy because of non-specific symptoms, not for cancer treatment). Tumour characteristics and demographic characteristics were similar between the two groups, however, the patients who had received manipulative therapy had a significantly worse prognosis over the 42 to 50 month follow-up period than the non-manipulation group (lower survival rate, more lung metastases, more local recurrence).

Evidence summary. No data are available on benefits of manual therapy in cancer patients. In some types of cancer such as osteosarcoma, manipulative therapy may have significant adverse effects and is contraindicated.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Alcantara 2011[184] **Focus:** chiropractic care of patients with cancer **Quality:** low	**INCLUSION CRITERIA** **Study design:** any type of primary study **Participants:** patients with cancer **Interventions:** chiropractic care **Outcomes:** not specified **METHODOLOGY** 9 relevant databases searched, 4 journals hand searched, bibliographies searched, no date limit; studies selected independently by two authors, no details on data extraction; no quality assessment; excluded studies not listed; no systematic tabulation of studies. **Data analysis:** text **Subgroups / sensitivity analyses:** none	**N included trials:** 60 case reports, 2 case series, 21 commentaries, 2 survey studies, 2 reviews **Study quality:** not reported **Study characteristics:** no high quality studies included, no effects on patient outcomes reported **Excluded studies eligible for current review:** not reported	**RESULTS / CONCLUSIONS** Patients with cancer seek care from chiropractors but the effects of such care were not described

Non-randomised comparative studies

Study	Interventions	Outcomes
Wu 2010[185] Taiwan **Focus:** prognosis of patients with osteosarcoma who had prior manipulative therapy **Study design:** prospective controlled cohort study **Duration:** mean 2.8 weeks **Follow-up:** mean follow-up 50.2 months in the control group and 41.8 months in the manipulation group **Quality:** moderate **PARTICIPANTS:** **N:** 134 (31% female) **Age:** 18.2 to 21.5 years (range 5 to 67) **Inclusion:** osteosarcoma, 2 groups had similar symptom duration (4 months), tumour location, and tumour volume (276 to 285 ml)	**Intervention type:** various **Intervention:** providers: bone-setters (51%), Chinese medical practitioners (46%), physiotherapists (3%) **Comparison:** no manipulation **Dose:** 2.6 manipulative sessions over mean of 2.8 weeks **Providers:** see above **Further information available on:** demographic details, co-interventions	

	Manipulative therapy	No manipulative therapy	p
Skip lesions	11%	0	0.005
Primary lung metastasis	32%	3%	0.003
Lung metastasis rate	51.4%	18.8%	<0.001
Local recurrence	29%	6%	0.001
5-year survival rate	58%	92%	0.004

Cerebral palsy in children

Three RCTs were identified that assessed the effects of osteopathy in children with cerebral palsy (Duncan 2004, Duncan 2008, Wyatt 2011).[186-188] One of the trials was low quality and two were medium quality.

The low quality trial by Duncan 2004[186] assessed the effects of osteopathy (cranio-sacral and myofascial release techniques) versus acupuncture and attention control in 50 children with cerebral palsy. Outcomes were based on parents' perceptions only (and parents were not reported to have been blinded). Statistical differences between groups were not reported. Most improvements were seen in leg or hand use and in sleep, and these appeared similar between the two intervention groups. Improvements in speech / drooling and cognition appeared to be more for the acupuncture group than the osteopathy group, while there were similar improvements in mood. The sample number was small and the significance of any differences between groups remains unclear.

The second trial by Duncan 2008[187] was medium quality and again compared osteopathy with acupuncture or attention control in 55 children with cerebral palsy. Osteopathy consisted of direct or indirect techniques in the cranial field and / or myofascial release (10 sessions over 24 weeks), compared with 30 sessions of acupuncture (scalp, body and auricular acupuncture). No significant effects of acupuncture were seen for any of the gross motor function or disability outcomes, while osteopathy resulted in a significant effect for two of the six gross motor and disability outcomes assessed (Gross Motor Function Measurement percent and Functional Independence Measure for Children mobility).

The medium quality RCT by Wyatt 2011[188] compared the effects of six sessions of cranial osteopathy with an attention control group in 142 children with cerebral palsy. After six months, there were no significant differences between the two groups in gross motor function or quality of life. Similarly, there were no significant differences regarding sleep-related parameters, parental assessment of the child's pain and main carer's quality of life. However, significantly more parents in the osteopathy group rated their child's global health as 'better' after six months than in the control group (38% versus 18%, $p<0.05$) – but parents were not blinded to the intervention condition.

Evidence summary. There is inconsistent evidence in an unclear direction for the effectiveness of osteopathic manual therapy in the treatment of cerebral palsy.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Duncan 2004[186]
USA

Focus: RCT of osteopathic manipulation or acupuncture as an adjunct to therapy for children with spastic cerebral palsy
Duration: 6 months
Follow-up: no post-intervention follow-up
Quality: low

PARTICIPANTS:
N: 50 (24% female)
Age: 11 months to 12 years
Inclusion: children with cerebral palsy; Gross Motor Functional Classification System 22% classified level I (mildest disturbance), 58% levels IV or V (most severe disturbance)</td>
<td>Intervention type: osteopathy
Intervention 1 (n=23): osteopathy: cranio-sacral and myofascial release techniques
Intervention 2 (n=19): acupuncture: combination of scalp, body and auricular acupuncture
Intervention 3 (n=8): combination of osteopathy and acupuncture
Comparison (n=19): non-therapeutic time with a volunteer (elected, not randomised)
Dose: unclear
Providers: acupuncture: Traditional Chinese Practitioner; osteopathy: osteopathic physician

<u>Further information available on:</u> anatomical lesions / restrictions</td>
<td><u>Results</u>
• No statistical evaluations reported, all results based on parents' reports
• Only 2 of 17 parents in control arm reported any improvement, compared with 21 of 23 parents in the osteopathic arm, all of the parents in the control arm, and all of the parents in the combination arm (parents presumably not blinded)

<table>
<tr><th>Improvement in…</th><th>Osteopathic (n=23)</th><th>Acupuncture (n=19)</th><th>Control (n=17)</th></tr>
<tr><td>Leg or hand use</td><td>61%</td><td>68%</td><td>0</td></tr>
<tr><td>Sleep</td><td>39%</td><td>53%</td><td>0</td></tr>
<tr><td>Improved mood</td><td>30%</td><td>32%</td><td>12%</td></tr>
<tr><td>Worsened mood</td><td></td><td></td><td>29%</td></tr>
<tr><td>Speech or drooling</td><td>4%</td><td>37%</td><td>6%</td></tr>
<tr><td>Bowel movements</td><td>26%</td><td>21%</td><td>0</td></tr>
<tr><td>Cognition</td><td>4%</td><td>21%</td><td>0</td></tr>
<tr><td>VAS muscle stiffness reduced >10</td><td>43%</td><td>61%</td><td>39%</td></tr>
<tr><td>VAS happiness increased >10</td><td>38%</td><td>17%</td><td>22%</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Duncan 2008[187]
USA

Focus: RCT of osteopathic manipulation or acupuncture as an adjunct to therapy for children with moderate to severe spastic cerebral palsy
Duration: 6 months
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 55 (24% female)
Age: 20 months to 12 years
Inclusion: children with moderate to severe spastic cerebral palsy; Gross Motor Functional Classification System (GMFCS) 20% classified level I (mildest disturbance), 62% levels IV or V (most severe disturbance)</td>
<td>Intervention type: osteopathy
Intervention 1 (n=26): osteopathy: use of direct or indirect techniques in the cranial field, myofascial release, or both; 10 sessions of 1 h over 24 weeks (once weekly weeks 1-4, once biweekly weeks 5-8, once monthly weeks 9 to 24)
Intervention 2 (n=27): acupuncture: combination of scalp, body and auricular acupuncture; 30 sessions of 30 min over 24 weeks (three times a week weeks 1-4, twice a week weeks 5-8, once a week weeks 9-12, once biweekly weeks 13-24)
Comparison (n=22): 11 h of non-specific non-therapeutic play time
Dose: see above
Providers: acupuncture: Traditional Chinese Practitioner; osteopathy: osteopathic physician

<u>Further information available on:</u> modified Ashworth Scale biceps and hamstring, parent / guardian rating of arched back, parent / guardian rating of startle reflex</td>
<td><u>Results</u>

<table>
<tr><th></th><th>Osteopathic</th><th>Acupuncture</th><th>Control</th><th>p</th></tr>
<tr><td>GMFCS</td><td>3.4 SD1.8</td><td>3.2 SD1.4</td><td>4.2 SD1.3</td><td>NS</td></tr>
<tr><td>GMFM percent</td><td>58.0 SD32.3</td><td>50.9 SD37.9</td><td>33.5 SD31.2</td><td>p<0.05 for OMT</td></tr>
<tr><td>PEDI mobility</td><td>28.7 SD21.0</td><td>27.7 SD22.3</td><td>18.6 SD20.2</td><td>NS</td></tr>
<tr><td>PEDI self-care</td><td>31.7 SD26.5</td><td>30.8 SD23.1</td><td>19.5 SD20.4</td><td>NS</td></tr>
<tr><td>WeeFIM mobility</td><td>15.9 SD10.1</td><td>14.6 SD11.2</td><td>10.7 SD9.3</td><td>p<0.05 for OMT</td></tr>
<tr><td>WeeFIM self-care</td><td>24.3 SD18.5</td><td>22.2 SD17.6</td><td>16.3 SD15.1</td><td>NS</td></tr>
<tr><td>Doctor rating of spasticity</td><td>48.8 SD25.7</td><td>57.1 SD24.8</td><td>69.5 SD21.6</td><td>NS</td></tr>
</table>
GMFM: Gross Motor Function Measurement; PEDI: Paediatric Evaluation Disability Inventory; WeeFIM: Functional Independence Measure for Children

Specific adverse effects: not reported</td>
</tr>
</table>

Study and Participants	Interventions	Outcomes
Wyatt 2011[188] UK **Focus:** RCT of cranial osteopathy in children cerebral palsy **Duration:** 6 months **Follow-up:** no post-intervention follow-up **Quality:** medium **PARTICIPANTS:** **N:** 142 (42% female) **Age:** 7.8 years (5 to 12) **Inclusion:** children aged 5 to 12 with varying levels of function (categories II to V of the Gross Motor Function Classification System)	**Intervention type:** osteopathy **Intervention (n=71):** cranial osteopathy; 6 sessions (3 in the first 10 weeks, remaining sessions within 6 months; average length of session 21 mins); each child was assigned to 1 of 37 osteopaths who planned the course of therapy according to child's individual needs **Comparison (n=71):** partial attention waiting list (parents taking part in 2 semistructured interviews) **Dose:** see above **Providers:** osteopaths **Further information available on:** modified Ashworth Scale biceps and hamstring, parent / guardian rating of arched back, parent / guardian rating of startle reflex	**Results** • No significant difference between groups after 6 months for gross motor function (GMFM-66) or child quality of life (CHQ) • No significant difference between groups after 6 months for time to sleep, time spent asleep, parental assessment of child's pain, main carer's quality of life • Significantly more parents in the intervention group rated their child's global health as 'better' after six months than in the control group (38% versus 18%,$p<0.05$, parents unblinded) ***Specific adverse effects:*** no serious side effects occurred

Cervicogenic dizziness / balance

One high quality systematic review was identified on the effects of manual therapy with or without vestibular rehabilitation in the management of cervicogenic dizziness (Lystad 2011),[189] as well as one low quality RCT on the effects of chiropractic care in elderly adults with impaired balance (Hawk 2009).[190]

The high quality systematic review by Lystad 2011[189] included five RCTs (three of these were Chinese studies) and eight non-controlled cohort studies. One of the RCTs was good quality, while the rest were moderate quality. Six of the studies (two RCTs) used manipulation / mobilisation only as an intervention, while the rest used a multimodal approach. None of the trials used a vestibular rehabilitation intervention. Twelve studies (including all RCTs) found an improvement in dizziness and associated symptoms after manual therapy, and two of the RCTs found an improvement in balance performance. Adverse events were only reported by three studies, but two of these found no adverse events and one only minor ones. The review authors concluded that there is moderate evidence in a favourable direction to support the use of manual therapy (spinal mobilisation and / or manipulation) for cervicogenic dizziness but that research is needed on combining manual therapy with vestibular rehabilitation.

The low quality RCT by Hawk 2009[190] compared the effect of a limited or extended course of chiropractic care on balance, chronic pain, and associated dizziness in 34 older adults with impaired balance. In the limited chiropractic care group, patients were treated twice a week for eight weeks using the diversified technique (manipulation, soft tissue treatments, hot packs), in the extended schedule group patients received additional monthly treatments for ten months. Outcome reporting of falls in this study were unreliable as patients were asked at each treatment / assessment visit and there were unequal numbers of visits between groups and patients with more visits reported more falls. There was no significant difference between groups in scores on the Berg Balance Scale, depression, the Pain Disability Index, or dizziness.

Evidence summary. There is moderate quality positive evidence for the effectiveness of self-mobilising apophyseal glides in the treatment of cervicogenic dizziness. There is inconclusive evidence in a favourable direction for the effectiveness of manipulation / mobilisation for cervicogenic dizziness. There is inconclusive evidence in an unclear direction for diversified chiropractic treatment in the improvement of balance in elderly people.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Lystad 2011[189] **Focus:** effects of manual therapy with or without vestibular rehabilitation in the management of cervicogenic dizziness **Quality:** high	**INCLUSION CRITERIA** **Study design:** prospective controlled or non-controlled intervention studies **Participants:** patients with cervicogenic dizziness **Interventions:** manual therapy (spinal manipulation or mobilisation) alone or manual therapy in combination with vestibular rehabilitation (exercise-based) **Outcomes:** as reported by the studies **METHODOLOGY** 4 relevant databases searched, website searches, bibliographies and relevant reviews searched, no language restriction, no date limit; studies selected independently by two authors; data extraction in a spreadsheet; quality assessment using the Maastricht-Amsterdam criteria (by two reviewers independently; excluded studies listed; systematic tabulation of studies. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 5 RCTs (Karlberg 1996 / Malmström 2007, Reid 2008, Kang 2008, Fang 2010, Du 2010), 8 non-controlled cohort studies **Study quality:** RCTs: 1 good quality (Reis 2008), 4 moderate quality; cohort studies: all poor quality **Study characteristics:** participants: sample sizes 12 to 168; interventions: 6 studies (2 RCTs) used only manipulation and /or mobilisation, self-mobilising apophyseal glides in 1 RCT (Reid 2008), 7 studies (3 RCTs) used multi-modal approach (several different interventions and home exercise programme), none used manual therapy in conjunction with vestibular rehabilitation **Excluded studies eligible for current review:** no	**RESULTS** • 12 studies (all 5 RCTs) found improvement in dizziness and associated symptoms after manual therapy • 2 RCTs found improvement in balance performance (posturography) • Only 3 studies reported adverse events: no adverse events in 2 RCTs, minor adverse events in one cohort study **CONCLUSIONS** There is moderate evidence in a favourable direction to support the use of manual therapy (spinal mobilisation and / or manipulation) for cervicogenic dizziness; research needed on combining manual therapy with vestibular rehabilitation

RCTs

Study and Participants	Interventions	Outcomes
Hawk 2009[190] USA **Focus:** pilot RCT to compare the effect of a limited and extended course of chiropractic care on balance, chronic pain, and associated dizziness in a sample of older adults with impaired balance **Duration:** 8 weeks to 12 months **Follow-up:** 12 months **Quality:** low **PARTICIPANTS:** **N:** 34 (59% female) **Age:** 80 years (65 to 93) **Inclusion:** ≥ 65 years, able to stand steadily without assistance on one leg for <5 seconds (averaging time for both legs), indicating increased risk of falls	**Intervention type:** chiropractic **Intervention 1 (n=13):** chiropractic care for 8 weeks with 2 visits per week (limited schedule); spinal manipulative therapy using diversified technique (incl. extravertebral manipulation to the hip, knee, ankle and foot; soft tissue treatments such as massage and trigger point therapy; hot packs) **Intervention 2 (n=15):** chiropractic care for 8 weeks with 2 visits per week, followed by 10 months with one visit per month (extended schedule) **Comparison (n=6):** instructed on doing home exercises **All groups:** lifestyle advice (brochure with health recommendations, home hazard checklist, pamphlet on balance exercises) **Dose:** see above **Providers:** chiropractors **Further information available on:** demographic details	**Results (after 12 months)** • Unequal reporting of falls as patients were asked at each treatment / assessment visit and there were unequal numbers of visits between groups: 6 patients with falls in intervention 1, 9 in intervention 2, none in the comparison group) • No significant difference between groups in scores on Berg Balance Scale, depression, Pain Disability Index, dizziness ***Specific adverse effects:*** 3 patients reported minor treatment-related effects (lightheadedness, stiffness, joint popping sound) but none lasted longer than 24 h

Chronic fatigue syndrome / myalgic encephalomyelitis

One high quality systematic review was identified that studied the effects of alternative medical interventions (including manual therapy) on patients with chronic fatigue syndrome or fibromyalgia (Porter 2010).[169] The authors identified one low quality RCT assessing the effects of osteopathic manual therapy in 58 patients with myalgic encephalomyelitis (Perrin 1998). In that trial there was a significant improvement in symptoms in the intervention group but not in the control group (significant difference between groups).

Evidence summary. There is inconclusive evidence in a favourable direction for osteopathic manual therapy improving symptoms of myalgic encephalomyelitis.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Porter 2010[169] **Focus:** alternative medical interventions in the treatment / management of myalgic encephalomyelitis and fibromyalgia (emphasis in this table on the former) **Quality:** high	**INCLUSION CRITERIA** **Study design:** RCTs and CCTs **Participants:** patients with myalgic encephalitis / chronic fatigue syndrome according to established case definitions **Interventions:** CAM interventions as defined by the National Center for Complementary and Alternative Medicine **Outcomes:** laboratory test results, physical functioning, psychologic functioning, quality of life **METHODOLOGY** 5 relevant databases searched, website searches, 2 journals hand searched, bibliographies searched, no date limit; studies selected independently by four authors; data extraction conducted by one reviewer and checked by another; quality assessment using the Jadad scale; excluded studies listed; systematic tabulation of studies. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 1 RCT for manual therapy in myalgic encephalomyelitis **Study quality:** low **Study characteristics:** osteopathic manual therapy in 58 patients with myalgic encephalomyelitis compared to no treatment **Excluded studies eligible for current review:** no	**RESULTS** Trial showed overall beneficial effects and improvement in symptoms **CONCLUSIONS** Osteopathic manual therapy may have potential for future high quality clinical research

Chronic pelvic pain

Three RCTs were identified that assessed the effects of manual therapy in chronic pelvic pain (FitzGerald 2009, Heyman 2006, Marx 2009).[191-193]

One medium quality RCT (FitzGerald 2009)[191] compared the effects of 10 weeks of myofascial physical therapy or general full body Western massage in 47 adults with interstitial cystitis / painful bladder syndrome or men with chronic prostatitis / chronic pelvic pain. Overall, significantly more patients had moderate or marked symptom improvement with myofascial therapy than with massage therapy (57% versus 21%, 'responders'). When considering the subgroups with interstitial cystitis / painful bladder syndrome or with chronic prostatitis / chronic pelvic pain, a significant difference between groups was only seen for the former (50% versus 7%, p=0.03), while a substantial proportion of the latter were also 'responders' to massage therapy (64% myofascial therapy, 40% massage therapy). Significantly more improvement seen for both the Interstitial Cystitis Symptom and Problem Index for the myofascial therapy group than the massage group, while there was no difference in urinary frequency or urgency, sexual function, pain, or quality of life (SF-12).

A low quality RCT (Heyman 2006)[192] compared the effects of distension of painful pelvic structure (two sessions) in 50 women with chronic pelvic pain with a counselling control group. At the end of the treatment, the intervention group had significantly reduced pelvic pain, painful intercourse, low back pain, sleep disturbance, sleep quality, mental fatigue, and anger than the control group. There was no significant difference in depression or mood.

Another low quality RCT (Marx 2009)[193] compared the effects of eight weeks of osteopathic care with a simple exercise control group in 35 men with chronic prostatitis / chronic pelvic pain syndrome. Six weeks after the last treatment, the osteopathy group had had a significantly improved International Prostate Symptom Score, Chronic Prostatitis Symptom Index, and quality of life score compared to the control group.

Evidence summary. There is inconclusive evidence in a favourable direction for the use of myofascial therapy in interstitial cystitis / painful bladder syndrome or chronic prostatitis / chronic pelvic pain. There is inconclusive evidence in a favourable direction for distension of painful pelvic structures in chronic pelvic pain in women and for osteopathic manual therapy in men with chronic prostatitis / chronic pelvic pain.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>FitzGerald 2009[191]
USA

Focus: determining the feasibility of an RCT to compare myofascial physical therapy and global therapeutic massage
Duration: 10 weeks
Follow-up: 12 weeks
Quality: medium

PARTICIPANTS:
N: 47 (51% female)
Age: 43 SD13 years
Inclusion: adults with a clinical diagnosis of interstitial cystitis / painful bladder syndrome (IC/PBS, men and women) and chronic prostatitis / chronic pelvic pain (CP/CPPS, men), pain / discomfort in the pelvic region for at least 3 months in the last 6 months, current symptoms present for <3 years</td>
<td>Intervention type: physiotherapy
Intervention (n=23): myofascial physical therapy; connective tissue manipulation, manual trigger point release techniques; home exercises offered
Comparison (n=24): general massage therapy: full body Western massage
Dose: 10 weekly treatments lasting of 1 h each
Providers: physical therapists, massage therapists

<u>Further information available on:</u> details of adverse events, demographic details, details of global response assessment</td>
<td><u>Results</u>
• Global response assessment (GRA, “Compared to before therapy, how would you rate you symptoms?”: 1 – ‘markedly worse’ to 7 ‘markedly improved’); responders: scores 6 and 7, rest nonresponders
• IC symptom and problem index (ICSI, ICPI), sexual function index (FSFI, gender-specific), quality of life (SF-12)

<table>
<tr><th></th><th>Myofascial therapy</th><th>Massage</th><th>p</th></tr>
<tr><td>GRA responders</td><td>57%</td><td>21%</td><td>0.03</td></tr>
<tr><td>GRA responders IC/PBS</td><td>50%</td><td>7%</td><td>0.03</td></tr>
<tr><td>GRA responders CP/CPPS</td><td>64%</td><td>40%</td><td>NS</td></tr>
<tr><td>Pain (0-10)</td><td>-2.5</td><td>-0.9</td><td>NS</td></tr>
<tr><td>Urinary urgency</td><td>-2.7</td><td>-0.8</td><td>NS</td></tr>
<tr><td>Urinary frequency</td><td>-3.6</td><td>-1.2</td><td>NS</td></tr>
<tr><td>ICSI</td><td>-4.6</td><td>0</td><td>0.01</td></tr>
<tr><td>ICPI</td><td>-4.7</td><td>-1.3</td><td>0.04</td></tr>
<tr><td>FSFI</td><td>+5.0</td><td>+1.4</td><td>NS</td></tr>
<tr><td>SF-12 physical</td><td>+1.3</td><td>-4.4</td><td>NS</td></tr>
<tr><td>SF-12 mental</td><td>+6.2</td><td>+1.8</td><td>NS</td></tr>
</table>

Specific adverse effects: adverse events reported by 5 patients in the massage group and 12 patients in the myofascial therapy group, pain was most commonly reported, adverse events mostly mild</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Heyman 2006[192]
Sweden

Focus: RCT of the effects of distension of painful pelvic structures for chronic pelvic pain in women
Duration: 2 to 3 weeks
Follow-up: no post-intervention follow-up
Quality: low

PARTICIPANTS:
N: 50 women
Age: median 33 years (range 19 to 54)
Inclusion: >19 years, women with chronic pelvic pain of at least 6 months' duration with continuous or intermittent pain at least 2 days per week</td>
<td>Intervention type: physiotherapy
Intervention (n=10): treatment procedure: patient lay in a prone position and the physician placed his index finger deep in the patient's rectum and previously identified painful structures were treated as follows in the given order: At a point two fingerwidths lateral of the sacrum, the physician used his index finger to exert strong pressure against the sacrotuberous/spinal ligaments for 15 s to elicit pain. Thereafter, the musculature of the pelvic floor and the joint between the coccyx and sacrum were concurrently forcefully distended dorsally for 60 s using the index finger. This procedure was repeated after 2 to 3 weeks
Comparison (n=10): counselling
Dose: see above
Providers: physicians</td>
<td><u>Results</u>
VAS symptom scales (0 – no complaints, 100 – worst complaints)
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>Pelvic pain</td><td>-35 SD31</td><td>+0.8 SD9.2</td><td>0.001</td></tr>
<tr><td>Painful intercourse</td><td>-19 SD38</td><td>+0.13 SD10.7</td><td>0.035</td></tr>
<tr><td>Low back pain</td><td>-21 SD39</td><td>+5 SD32.2</td><td>0.018</td></tr>
<tr><td>Sleep disturbance</td><td>-6 SD21</td><td>+11 SD25.2</td><td>0.019</td></tr>
<tr><td>Quality of sleep</td><td>-11 SD23</td><td>+4.0 SD21.7</td><td>0.029</td></tr>
<tr><td>Mental fatigue</td><td>-11 SD27</td><td>+15.2 SD25</td><td>0.001</td></tr>
<tr><td>Depression</td><td>-11 SD18</td><td>-0.8 SD17.7</td><td>NS</td></tr>
<tr><td>Mood</td><td>-9 SD22</td><td>+2.1 SD25.6</td><td>NS</td></tr>
<tr><td>Anger</td><td>-10 SD23</td><td>-5.9 SD27.9</td><td>0.05</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
<tr>
<td>Marx 2009[193]
Germany

Focus: RCT of the effects of osteopathic treatment in men with chronic prostatitis / chronic pelvic pain syndrome
Duration: 8 weeks
Follow-up: 6 weeks after the end of therapy, 1.5 years for intervention patients only
Quality: low

PARTICIPANTS:
N: 35 men
Age: 47 years (range 29 to 70)
Inclusion: men with chronic prostatitis / chronic pelvic pain syndrome, significant symptoms without significant urological abnormalities (no sonographic abnormalities, prostate size <45 cm^3, negative bacteriology of urine or ejaculate, PSA <4 µg/L, residual urine <100 ml)</td>
<td>Intervention type: osteopathy
Intervention (n=20): osteopathic care; osteopathic examination and treatment at the therapist's discretion (could include manipulation, mobilisation, muscle energy techniques, myofascial techniques, visceral and cranial techniques, "balanced ligamentous tension"); 5 treatments of 45 mins, weekly treatments in the first 3 weeks, then after 2 weeks and another 3 weeks
Comparison (n=15): simple exercise programme (warming up, pelvic floor exercises, breathing exercises)
Dose: 6 weekly treatments lasting up to 45 mins
Providers: osteopaths</td>
<td><u>Results</u>
• Outcomes: International Prostate Symptom Score (IPSS 0 to 35), Chronic Prostatitis Symptom Index (NIH-CPSI, 0 to 43), quality of life (0 to 6) (scores are for least to worst symptoms)

6 weeks after the last treatment:
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>p</th></tr>
<tr><td>IPPS</td><td>-9.50</td><td>+0.54</td><td><0.0005</td></tr>
<tr><td>NIH-CPSI</td><td>-15.65</td><td>+1.23</td><td><0.0005</td></tr>
<tr><td>QoL</td><td>-2.65</td><td>+0.16</td><td><0.0005</td></tr>
</table>

Specific adverse effects: no serious adverse effects seen (some reported tiredness on the day of the treatment)</td>
</tr>
</table>

Cystic fibrosis

One small medium quality RCT assessed the effects of musculoskeletal treatments including mobilisations to the rib cage and thoracic spine in 20 adults with cystic fibrosis (Sandsund 2011).[194] Patients in the intervention group received six treatment sessions, patients in the control group received usual care only. After 12 weeks, there were no significant differences between groups in pain or FEV1. However, quality of life had increased significantly more in the intervention than in the control group. The trial was exploratory in nature examining the sensitivity of outcome measures, the acceptability of methods and generating data for sample size calculations.

Evidence summary. There is inconclusive evidence in an unclear direction for the use of mobilisations (rib cage and thoracic spine) in patients with cystic fibrosis.

RCTs

Study and Participants	Interventions	Outcomes
Sandsund 2011[194] UK **Focus:** RCT of response of patients with cystic fibrosis to physiotherapy musculoskeletal techniques (designed as exploratory pilot study) **Duration:** 6 weeks **Follow-up:** 12 weeks **Quality:** medium **PARTICIPANTS:** **N:** 20 (50% female) **Age:** median age 27 years **Inclusion:** adults with cystic fibrosis; reported awareness of postural changes including stiffness, discomfort and/or pain of musculoskeletal origin in the thoracic spine or chest wall; stable clinical state	**Intervention type:** physiotherapy **Intervention (n=10):** usual care plus musculoskeletal treatments: specific mobilisations to the rib cage and thoracic spine; treatment of specific muscle dysfunction or tight muscle groups; and postural awareness, education and advice based on the principles of the Alexander technique **Comparison (n=10):** usual care **Dose:** 6 weekly treatments lasting up to 45 mins **Providers:** not reported **Further information available on:** anatomical lesions / restrictions	**Results** • No significant difference between groups after the end of the study in changes from baseline for pain (VAS), FEV1, thoracic index, modified shuttle test, chest wall excursion • Quality of life (Cystic Fibrosis Quality of Life questionnaire) significantly more increased in the intervention group than in the control group at 12 weeks (p=0.002) ***Specific adverse effects:*** no adverse effects seen

Dysfunctional voiding

One low quality RCT was identified that assessed manual therapy in paediatric dysfunctional voiding (Nemett 2008).[195] Children (n=21) with vesicoureteal reflux and / daytime incontinence were randomised to standard therapy or standard therapy plus four sessions of manual physical therapy based on an osteopathic approach. Outcome was assessed in terms of "clinically significant improvements" for vesicoureteal reflux, days wet, post-void residuals, urinary tract infections, and dyssynergic voiding; however, the "clinically significant improvement was not defined". Overall, children who received osteopathic manual therapy had significantly more (p=0.008) improvement of symptoms after 10 weeks of treatment than children in the control group, however, significance was not quite reached in subgroups with vesicoureteal reflux only or with daytime incontinence only (possibly partially due to small numbers). Adverse effects were not assessed.

Evidence summary. There is inconclusive evidence in a favourable direction for osteopathic manual therapy improving symptoms of paediatric dysfunctional voiding.

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Nemett 2008[195]
USA

Focus: RCT of effect of manual physical therapy based on an osteopathic approach added to standard therapy on dysfunctional voiding in children
Duration: 10 weeks
Follow-up: ≥3 months
Quality: low

PARTICIPANTS:
N: 21 (67% female)
Age: 6.8 years SD 2.2
Inclusion: children with post-void residuals (PVR), daytime urinary incontinence (DI), recurrent urinary tract infections (UTI), dyssynergic voiding (DYS) or vesicoureteal reflux (VUR); 41% had VUR, 64% had DI, 9% had both VUR and DI, 59% had recurrent UTIs, 77% had DYS</td>
<td>Intervention type: osteopathy
Intervention (n=10): manual physical therapy based on an osteopathic approach (MPT-OA), customised to each child, included gentle mobilisation of body tissues to relieve movement restrictions, and thereby achieve balanced alignment and mobility and postural symmetry, with particular attention to the thoracolumbar spine, thoracic and pelvic diaphragms, pelvis, pelvic organs, and lower extremities; plus standard therapy as below
Comparison (n=11): standard care as appropriate (could include medications, establishment of timed voiding and evacuation schedules, dietary modifications, behaviour modification, pelvic floor muscle retraining, biofeedback training, and treatment of constipation)
Dose: standard treatment: four clinic appointments lasting 1 h at 2-week intervals; osteopathy: four 1 h treatment sessions coinciding with clinic appointments
Providers: not reported

<u>Further information available on:</u> anatomical lesions / restrictions</td>
<td><u>Primary</u>
Proportion of outcomes improved (of VUR, days wet, PVR, UTI, DYS) by diagnosis:
<table>
<tr><th>Diagnosis</th><th>MPT-OA</th><th>Control</th><th>p</th></tr>
<tr><td>all together</td><td>60%</td><td>31%</td><td>0.008</td></tr>
<tr><td>VUR (no DI)</td><td>62.5%</td><td>33.3%</td><td>NS</td></tr>
<tr><td>DI (no VUR)</td><td>58.3%</td><td>31.8%</td><td>0.065</td></tr>
<tr><td>VUR and DI</td><td>-</td><td>25%</td><td>-</td></tr>
</table>
NR=not reported

Specific adverse effects: not reported</td>
</tr>
</table>

Paediatric nocturnal enuresis

One high quality new systematic (Cochrane) review was identified that assessed the effects of complementary and miscellaneous interventions (including chiropractic) for nocturnal enuresis in children (Huang 2011).[196] However, the review did not include any new trials fulfilling our inclusion criteria that were not already considered by the Bronfort report. One small (n=70) new study in Chinese language of pinching massage versus desmopressin (Feng 2008) was included, however, the study was low quality. Pinching massage seemed to be as good as desmopressin, but confidence interval were wide and there was no information on bedwetting after the end of the treatment.

Evidence summary. No substantial change from the Bronfort report (inconclusive evidence in a favourable direction for spinal manipulation and pinching massage).

Infantile colic

Two potentially relevant new systematic reviews (Alcantara 2011 and Perry 2011)[197;198] including manual treatments for infant colic were identified. The review by Alcantara 2011[197] was judged to be low quality, the review by Perry 2011[198] was judged to be of moderate quality. None of the systematic reviews included any new studies not already considered by the Bronfort report or eligible according to the inclusion criteria of the current review. The results of the reviews suggested that there is no conclusive evidence regarding the effectiveness of chiropractic care for infantile colic.

One additional comparative cohort study regarding the long term effects of infantile colic in children with our without chiropractic treatment was identified (Miller 2009).[199] However, the study only included children in whom chiropractic manual therapy was associated with a remission of symptoms and can therefore not be regarded as an unbiased assessment of the effect of chiropractic therapy on infantile colic – the study was therefore not considered any further.

Evidence summary. No change from the Bronfort report (inconclusive evidence in a favourable direction for cranial osteopathic manual therapy, moderate quality evidence that spinal manipulation is no more effective than sham spinal manipulation).

Dysmenorrhoea

No additional / new studies found.

Evidence summary. No change from the Bronfort report (moderate quality evidence that spinal manipulation is no more effective than sham manipulation in the treatment of primary dysmenorrhoea).

Premenstrual syndrome

No additional / new studies found.

Evidence summary. No change from the Bronfort report (inconclusive evidence in an unclear direction regarding the effectiveness of spinal manipulation in the treatment of premenstrual syndrome).

Menopausal symptoms

One small low quality RCT (Cleary 1994)[200] assessed the effects of Fox's low force osteopathic technique and cranial methods in the treatment of menopausal symptoms in 30 women aged between 50 and 60 years, compared to a placebo procedure. The treatment was applied once a week for 10 weeks and follow-up was at 15 weeks. Four of six menopausal symptoms were improved in the intervention group after the end of the intervention period compared to control, and three were reduced after the five week follow-up period. At the follow-up, there was also a significant reduction in neck pain compared to control in those patients who had had chronic neck pain at the start of the trial; the difference was nearly significant for back pain (small numbers).

Evidence summary. There is inconclusive evidence in a favourable direction for the effectiveness of combined use of Fox's low force osteopathic techniques and cranial techniques in the treatment of menopausal symptoms.

RCTs

Study and Participants	Interventions	Outcomes
Cleary 1994[200] UK **Focus:** RCT of the effects of "Fox's low force osteopathic techniques" on menopausal symptoms **Duration:** 10 weeks **Follow-up:** 5 weeks post-intervention **Quality:** low **PARTICIPANTS:** **N:** 30 women **Age:** 51.3 SD13.1 to 53.9 SD10.1 years **Inclusion:** women aged 50 to 60 years who had menstruated less than 4 times in the previous 12 months; exclusions: hormone replacement therapy	**Intervention type:** osteopathy **Intervention (n=15):** Fox's low force technique: spine, cranium and pelvis examined for areas of joint strain; treatment of spine and pelvis in the following manner: a finger or thumb was used to deliver the low-force to the spinous process in a direction thought to relieve the restriction, relaxing the joint's protective mechanism, via the muscle spindle, by increasing the resting length of the muscle, thereby improving mobility; the 'force' required to relax the muscle is so low that it does not extend to adjacent joints or surrounding tissues; patients are not required to assist the practitioner by adopting a particular position, or use their own muscle power; also use of cranial techniques **Comparison (n=15):** placebo: employing the same method, but with the force delivered to a joint adjacent to a restricted joint, where it will have no effect **Dose:** 30 min once a week for 10 consecutive weeks **Providers:** osteopaths **Further information available on:** hormone levels	**Results** • *Menopausal symptoms (questionnaire):* after the intervention, significant reduction in hot flushes, night sweats, urinary frequency, and depression compared to control, but not insomnia and irritability; at 5 weeks post-intervention, difference remained significant for hot flushes and night sweats and became significant for insomnia • *Back and neck pain:* at the 5 week follow-up, reduction in neck pain was significantly greater for the intervention group (p=0.04) (n=8 and n=6 with neck pain in intervention and control groups respectively), and nearly so for back pain (p=0.06) (n=8 and n=4 with back pain in intervention and control groups respectively) ***Specific adverse effects:*** not reported

Gastrointestinal disorders

One additional medium quality systematic review (Ernst 2011)[201] and one additional low quality RCT (Hundscheid 2006)[202] were identified that investigated manual treatment for gastrointestinal disorders.

The systematic review included one randomised trial (Hains 2007) and one CCT (Pikalov 1994) that reported the effects of chiropractic spinal manipulation in patients with gastroesophageal reflux disease (Hains 2007) and duodenal ulcer (Pikalov 1994). Given the paucity and low quality of the reviewed evidence, the review could not draw any definitive conclusions regarding the effects of spinal manipulation versus ischaemic compression (Hains 2007) or conventional treatment (Pikalov 1994).

One additional low quality randomised pilot trial assessed the benefits and harms of osteopathy compared to standard care at 1, 3, and 6 months of post-baseline follow-up for 39 patients with irritable bowel syndrome (Hundscheid 2006).[202] The primary outcomes were patient-based responses for changes in overall/global assessment, symptom score (range: 0-36), quality of life (the IBSQOL 2000 questionnaire), and Functional Bowel Disorder Severity Index (FBDSI). The post-treatment change at 6 months was in statistically significant favour of osteopathy versus standard care for overall/global assessment, FBDSI score, and quality of life. Similarly, the end-point mean symptom score was significantly reduced in favour of the osteopathy over standard care group. There was no occurrence of adverse events.

Evidence summary. No relevant evidence pertaining to gastrointestinal disorders was found in the Bronfort report. Due to the paucity and low quality of the reviewed evidence, results regarding comparative effectiveness/safety of manual therapy in patients with gastrointestinal disorders remain inconclusive.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Ernst 2011[201] **Focus:** effectiveness of spinal manipulation in patients with gastrointestinal disorders **Quality:** medium	**INCLUSION CRITERIA** **Study design:** controlled studies **Participants:** studies concerning any gastrointestinal disorders **Interventions**: manual procedures **Outcomes:** pain relief, symptom severity, clinical remission **METHODOLOGY** 6 relevant databases searched; no language limit; some details on study selection and data extraction; studies of infant colic were excluded; excluded studies not listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** none	**N included trials:** 2 controlled trials: 1 RCT (Hains 2007) and 1 non-RCT (Pikalov 1994) **Study quality:** Jadad score (0-1); Hains 2007 low quality (Jadad score 1), Pikalov 1994 low quality (Jadad score 0) **Study characteristics:** Hains 2007: 62 adults with gastro-oesophageal reflux disease treated with spinal manipulation versus ischaemic compression for 7 weeks (20 sessions); Pikalov 1994: 35 adults with duodenal ulcer treated with spinal manipulation (3-14 sessions; duration: not reported) plus conventional treatment versus conventional treatment only **Excluded studies eligible for current review:** not reported	**RESULTS** No significant differences in outcome measures (symptom severity score, clinical parameters) between the manual therapy and control groups **CONCLUSIONS** Evidence is inconclusive based on two low quality studies; it cannot be established whether manual therapy is more effective than ischaemic compression or conventional treatment in patients with gastrointestinal disorders

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Hundscheid 2006[202]
The Netherlands

Focus: RCT of osteopathic treatment effects compared to standard therapy in adults with irritable bowel syndrome
Duration: 6 months
Follow-up: 6 months
Quality: low

PARTICIPANTS:
N: 39 (59% female)
Age: 44 years
Inclusion: adults with diagnosis of irritable bowel syndrome (Rome II criteria) with abdominal complaints (moderate severity) of at least 3 days of the week prior to trial entry. Patients with somatic pathology or conditions explaining abdominal complaints were excluded</td>
<td>Intervention type: osteopathy
Intervention (n=20): osteopathy using individual black box method; 5 sessions once per 2-3 weeks for 6 months; no use of medications
Comparison (n=19): standard care of 6 months consisted of fibre rich diet; in cases of constipation and diarrhoea, laxative and loperamide were added respectively; in case of cramps, mebeverine was prescribed
Dose: see above
Providers: an osteopath</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Osteopathy</th><th>Control</th><th>p-value</th></tr>
<tr><td>Overall assessment</td><td>68%</td><td>18%</td><td><0.006</td></tr>
<tr><td>FBDSI score</td><td>100</td><td>52</td><td>0.02</td></tr>
<tr><td>Quality of life</td><td>18</td><td>12</td><td><0.05</td></tr>
<tr><td>Symptom score [endpoint]</td><td>6.8</td><td>10</td><td>0.02</td></tr>
</table>

Specific adverse effects: not observed</td>
</tr>
</table>

Hypertension

We identified one new medium quality systematic review (Mangum 2012)[203] and one additional medium quality non-randomised clinical trial not included in any systematic review (Cerretelli 2011)[204] on the use of manual therapy in the treatment of hypertension.

The systematic review by Mangum 2012 examined the effects of spinal manipulative therapy on hypertension. Results of five RCTs using a variety of spinal techniques were reported (Gonstead chiropractic adjusting, NUCCA technique, "diversified adjustments", Activator instrument, and osteopathic manipulative therapy). The two included trials with a low risk of bias (Goertz 2002, Plaugher 2002) both found no significant differences for diversified adjustments plus diet versus diet only or of Gonstead chiropractic adjusting versus brief massage or control on systolic or diastolic blood pressure (however, the trial of Gonstead chiropractic care had a very small sample size). Of the three trials with unclear risk of bias, two (both using largely only a single adjustment) found a significantly greater reduction of both systolic and diastolic blood pressure with spinal manipulation using the Activator instrument (Abram 1988) or the NUCCA technique (Bakris 2007) versus control, while one trial (Morgan 1985) found no significant difference in a cross-over trial between the effects of osteopathic manipulative therapy and sham massage on blood pressure.

The non-randomised clinical trial by Cerritelli 2011[204] examined the effects of biweekly osteopathic manipulative therapy plus pharmacological treatment versus pharmacological treatment only on blood pressure and intima media thickness (femoral and carotid bifurcation) over 12 months in 63 patients with hypertension. After adjusting for a range of confounding factors, osteopathic treatment was significantly associated with both a larger decrease in systolic blood pressure and in intima media thickness than pharmacological treatment alone.

Evidence summary. There is moderate quality evidence that diversified spinal manipulation is not effective when added to diet in stage 1 hypertension (no change from Bronfort). There is inconclusive evidence in a favourable direction for upper cervical NUCCA manipulation for stage 1 hypertension and inconclusive evidence in an unclear direction for instrument assisted spinal manipulation for hypertension (no change from Bronfort). There is inconclusive evidence in an unclear direction regarding the effectiveness of Gonstead full spine chiropractic care or osteopathic manipulative therapy for hypertension.

Systematic reviews

<table>
<tr><th>Study</th><th>Inclusion criteria and methodology</th><th>Included studies</th><th>Results and Conclusions</th></tr>
<tr>
<td>Mangum 2012[203]

Focus: effects of spinal manipulative therapy for hypertension
Quality: medium</td>
<td>INCLUSION CRITERIA
Study design: observational or therapy trial
Participants : patients with hypertension
Interventions: spinal manipulative therapy
Outcomes: blood pressure

METHODOLOGY
5 relevant databases searched, non-English studies and abstracts excluded; studies selected by three authors; quality rated by all authors, data extraction unclear; quality assessment using the Cochrane Risk of Bias tool; excluded studies not listed; systematic tabulation of studies.
Data analysis: text and tables
Subgroups / sensitivity analyses: none</td>
<td>N included trials: 10 studies, but only results for 5 studies with low or unclear risk of bias reported (5 RCTs (Goertz 2002, Plaugher 2002, Bakris 2007, Abram 1988, Morgan 1985), 2 non-randomised CCTs, 3 case reports)
Study quality: of RCTs, 2 low risk of bias, 3 unclear risk of bias
Study characteristics: 21 to 128 patients included; spinal manipulative treatment (SMT) single session to up to 20 treatments over 2 months; types of SMT: Gonstead chiropractic adjusting, NUCCA technique, “diversified adjustments”, Activator instrument, osteopathic manipulative therapy

Excluded studies eligible for current review: not reported</td>
<td>RESULTS
• Goertz 2002, low risk of bias, 12 sessions of “diversified adjustments” plus diet versus diet only
• Plaugher 2002, low risk of bias, Gonstead chiropractic adjusting (up to 20 treatments), versus brief massage or control
• Bakris 2007, unclear risk of bias, SMT NUCCA technique weekly for 8 weeks (but 85% had only one adjustment)
• Abram 1988, unclear risk of bias, single Activator SMT versus placebo and no treatment
• Morgan 1985, unclear risk of bias, cross-over, 6 weeks osteopathic manipulative therapy versus sham massage
<table>
<tr><th>Study</th><th>Intervention BP, study end (mmHg, 95% CI)</th><th>Control BP, study end (mmHg, 95% CI)</th><th>p</th></tr>
<tr><td>Goertz 2002</td><td>SP -3.5 (-5.7 to -1.3)
DP -4.0 (-5.3 to -2.7)</td><td>SP -4.9 (-6.7 to -3.1)
DP -5.6 (-6.8 to -4.4)</td><td>NS</td></tr>
<tr><td>Plaugher 2002</td><td>SP -2.3 (-6.4 to +1.8)
DP -4.8 (-12.6 to +3.0)</td><td>No treatment
SP -7.7 (-14.5 to -0.9)
DP -9.0 (-16.8 to -1.2)
Brief massage
SP -1.3 (-9.4 to +11.9)
DP -1.7 (-6.2 to +2.9)</td><td>NS</td></tr>
<tr><td>Bakris 2007</td><td>SP -17.2 (-20.7 to -13.7)
DP -10.3 (-14.6 to -6.0)</td><td>SP -3.2 (-7.5 to +1.1)
DP -1.8 (-4.5 to +0.9)</td><td><0.05</td></tr>
<tr><td>Abram 1988</td><td>SP -14.7 (-17.3 to -12.1)
DP -13.0 (-15.4 to -10.6)</td><td>Placebo
SP +1.4 (-3.2 to +6.0)
DP -1.4 (-3.3 to +0.5)</td><td><0.05</td></tr>
<tr><td>Morgan 1985</td><td>First half of cross-over
SP -6.3 (-12.2 to -0.4)
DP -3.6 (-8.5 to +1.3)</td><td>First half of cross-over
SP -0.2 (-2.4 to +2.0)
DP -0.5 (-3.2 to +2.2)</td><td>NS</td></tr>
</table>
SP: systolic blood pressure, DP: diastolic blood pressure

CONCLUSIONS
There is lack of low bias evidence to support the use of spinal manipulative therapy for the treatment of hypertension; further high quality evidence is needed</td>
</tr>
</table>

Non-randomised comparative studies

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Cerritelli 2011[204]
Italy

Focus: effects of osteopathic manipulative treatment on hypertension
Study design: CCT
Duration: 12 months
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 63 (51% female)
Age: 50 SD6 years
Inclusion: grade 1+ hypertension and vascular abnormalities (B-ultrasound morphology classified as II, III, IV)</td>
<td>Intervention type: osteopathy
Intervention (n=31): osteopathic manipulative treatment (OMT) plus standard pharmacological therapy (calcium channel blockers, ACE-inhibitors, beta-blockers, diuretics, combination); OMT techniques: fascial, cranial and balanced ligamentous techniques
Comparison (n=32): standard pharmacological therapy only
Dose: OMT treatment every 2 weeks
Providers: osteopath

<u>Further information available on:</u> blood lipids, endothelial parameters</td>
<td><u>Results</u> (12 months)
<table>
<tr><th></th><th>OMT</th><th>Control</th><th>p</th></tr>
<tr><td>Systolic BP (mmHg)</td><td>-26.48
SD3.71</td><td>-21.69
SD2.57</td><td><0.0001</td></tr>
<tr><td>Diastolic BP</td><td>-11.65
SD3.84</td><td>-9.16
SD2.41</td><td>0.003</td></tr>
<tr><td>Intima media thickness (carotid / femoral bifurcations)</td><td>-0.53
SD0.30</td><td>-0.00
SD0.10</td><td><0.001</td></tr>
</table>
• After adjustment for BMI and baseline systolic blood pressure, OMT was significantly related to decreases in intima media thickness and systolic blood pressure, but not diastolic blood pressure

Specific adverse effects: not reported</td>
</tr>
</table>

Peripheral arterial disease

One medium quality non-randomised controlled trial was identified of osteopathic manipulative therapy in patients with intermittent claudication (Lombardini 2009).[205] Thirty male patients were treated for six months with a variety of osteopathic manual techniques plus standard pharmacological treatment or standard pharmacological treatment only. After the six months, patients in the intervention group had significantly improved values for the ankle-brachial pressure index at rest and after exercise, claudication pain time and total walking time on a treadmill, with no significant changes occurring in the control group (difference between groups not reported – presumably insignificant?). Four of eight quality of life measures were significantly more improved in the intervention group than in the control group (physical function, role limitations / physical, bodily pain, general health); there were no significant differences in mental health, role limitations / emotional, social function or vitality.

Evidence summary. There is inconsistent evidence in a favourable direction for the effectiveness of osteopathic manual therapy in the treatment of intermittent claudication.

Non-randomised comparative studies

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Lombardini 2009[205]
Italy

Focus: effects of osteopathic manipulative treatment in combination with lifestyle modification and pharmacological therapy in patients with intermittent claudication
Study design: CCT
Duration: 6 months
Follow-up: no post-intervention follow-up
Quality: medium

PARTICIPANTS:
N: 30 men
Age: 69 SD8 years
Inclusion: Fontaine stage II monolateral intermittent claudication, male, clinical onset of peripheral arterial disease less than 1 year, low compliance with physical training programme, ankle/brachial pressure index <0.90 at rest, stable maximum walking time of 170-250 s during standard treadmill test</td>
<td>Intervention type: osteopathy
Intervention (n=15): osteopathic manipulative treatment (OMT) plus standard pharmacological therapy; OMT techniques: myofascial release, strain/counterstrain, muscle energy, soft tissue techniques, high velocity low amplitude (thoracolumbar region), lymphatic pump, craniosacral manipulation; 30 min sessions
Comparison (n=15): standard pharmacological therapy only
Dose: months 1 and 2: one OMT session every 2 weeks, month 3: assessment of response and adjustment of OMT techniques if necessary, months 4 to 6: one OMT session every 3 weeks
Providers: osteopath

<u>Further information available on:</u> blood lipids, endothelial parameters</td>
<td><u>Results</u> (6 months)
<table>
<tr><th></th><th>OMT</th><th>Control</th><th>p</th></tr>
<tr><td>ABPI rest</td><td>0.87 SD0.05</td><td>0.78 SD0.05</td><td>OMT <0.05 vs BL</td></tr>
<tr><td>ABPI exercise</td><td>0.79 SD0.06</td><td>0.57 SD0.04</td><td>OMT <0.05 vs BL</td></tr>
<tr><td>CPT (min)</td><td>3.7 SD0.4</td><td>2.9 SD0.3</td><td>OMT <0.05 vs BL</td></tr>
<tr><td>TWT (min)</td><td>4.7 SD0.4</td><td>4.5 SD0.8</td><td>OMT <0.05 vs BL</td></tr>
<tr><td>Physical function</td><td>72.8 SD3.7</td><td>37.5 SD4.7</td><td><0.05</td></tr>
<tr><td>Role limitations / physical</td><td>60.5 SD22.6</td><td>29.3 SD16.5</td><td><0.05</td></tr>
<tr><td>Bodily pain</td><td>86.5 SD19.7</td><td>66.5 SD15.8</td><td><0.05</td></tr>
<tr><td>General health</td><td>67.8 SD7.6</td><td>53.2 SD12.0</td><td><0.05</td></tr>
<tr><td>Mental health</td><td>75.9 SD9.6</td><td>73.5 SD11.3</td><td>NS</td></tr>
<tr><td>Role limitations / emotional</td><td>86.4 SD8.7</td><td>83.5 SD11.0</td><td>NS</td></tr>
<tr><td>Social function</td><td>82.7 SD10.4</td><td>79.0 SD8.5</td><td>NS</td></tr>
<tr><td>Vitality</td><td>65.7 SD10.2</td><td>60.8 SD10.6</td><td>NS</td></tr>
</table>
ABPI: ankle-brachial pressure index, BL: baseline; CPT: claudication time pain, TWT: total walking time

Specific adverse effects: transient muscle tenderness in 3 patients</td>
</tr>
</table>

Insomnia

One low quality systematic review (Kingston 2010)[206] assessed the effects of chiropractic spinal manipulative therapy on primary insomnia. No relevant controlled studies were identified (the only controlled study mentioned was in fact of healthy volunteers (not mentioned by the reviewers) and thus no relevant outcomes were reported).

Evidence summary. No comparative data are available on the benefits of manual therapy in people with primary insomnia.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Kingston 2010[206] **Focus:** chiropractic as a treatment for primary insomnia **Quality:** low	**INCLUSION CRITERIA** **Study design:** RCTs and case studies **Participants:** primary insomnia **Interventions:** chiropractic spinal manipulative therapy **Outcomes:** at least one patient outcome measure (e.g. sleep diaries, Pittsburgh Sleep Quality index) **METHODOLOGY** 4 relevant databases searched, up to 2006; obviously no systematic development of search strategy; hand searching of potentially relevant journals (not specified); independent study selection by two reviewers; no details on data extraction; no details on quality assessment; excluded studies not listed. **Data analysis:** text **Subgroups / sensitivity analyses:** none	**N included trials:** 15 studies meeting the selection criteria mentioned (but they do not all seem to have been relevant), none of the studies was an RCT and only one had a control group (Cutler 2005) **Study quality:** not reported but obviously low **Study characteristics:** no systematic reporting or tabulation; Cutler 2005 investigated cranial osteopathic manipulation but outcome reporting appears not to have been consistent **Excluded studies eligible for current review:** not reported	**RESULTS / CONCLUSIONS** There is minimal evidence to support chiropractic treatment for primary insomnia; high quality trials are needed

Otitis media

No new evidence was identified for use of manual therapy in otitis media. One ongoing trial was identified on a five week standardised osteopathic manipulative medicine protocol plus standard care compared to standard care only in children between six months and two years with acute otitis media (Steele 2010).[207]

Evidence summary. No change from Bronfort report (inconclusive evidence in an unclear direction for osteopathic manual therapy).

Parkinson's disease

One small low quality controlled trial (Wells 1999)[208] assessed the effect of a single 30 minute session of osteopathic manual therapy on gait performance in patients with Parkinson's disease. Gait parameters were significantly improved in comparison to the control group, but no other patient-relevant outcomes were assessed and long term effects of osteopathic manipulation in Parkinson's disease remain unclear. Adverse effects were not assessed.

Evidence summary. Inconclusive evidence in a favourable direction for the effectiveness of osteopathic manual therapy in Parkinson's disease.

Non-randomised comparative studies

Study and Participants	Interventions	Outcomes
Wells 1999[208] USA **Focus:** effect of osteopathic manipulative treatment on gait in patients with Parkinson's disease **Study design:** CCT **Duration:** single session **Follow-up:** immediately after treatment **Quality:** low, unclear if randomised **PARTICIPANTS:** **N:** 20 (% female not reported) **Age:** 45 to 68 years **Inclusion:** Parkinson's disease (mild to moderate; Unified Parkinson's Rating Scale motor score average 14.3)	**Intervention type:** osteopathy **Intervention (n=10):** 30 minute standardised protocol of osteopathic manual therapy (1. Lateral (and anteroposterior) translation of vertebrae in the thoracic/lumbar spine performed with the patient in a seated position; 2. Active myofascial stretch to the thoracic spine with the patient in a seated position; 3. Occipito-atlanto (OA) release; 4. Translation of cervical spine performed with the patient in a supine position; 5. Muscle energy techniques of the cervical spine; 6. Spencer technique applied to the shoulder bilaterally; 7. Supination/pronation of the forearm bilaterally; 8. Circumduction of the wrist bilaterally; 9. Sacroiliac joint gapping bilaterally; 10. Muscle energy technique applied to adductor muscles of lower extremity bilaterally; 11. Psoas muscle energy technique applied bilaterally; 12. Hamstring muscle energy technique applied bilaterally; 13. Articulatory technique applied to the ankle bilaterally; and 14. Muscle energy technique applied to the ankle in dorsi and plantar flexion bilaterally) **Comparison (n=10):** sham procedure (examination of the patient's voluntary range of motion in each joint to which manipulation would have been applied without the manipulation procedure, some passive motion of limbs without reaching patient's range of motion limit) **Dose:** single 30 min session **Providers:** student physician with special training in osteopathic manipulative technique under the direction of an osteopathic physician	***Gait parameters*** • significant improvement in the following gait parameters in comparison to control: stride length difference, cadence difference, upper limb velocities (shoulder, wrist), lower limb velocities (hip, knee, ankle) ***Specific adverse effects:*** not reported

Pneumonia and other respiratory disorders

One high quality Cochrane review (Yang 2010)[209] was identified that assessed the effects of chest physiotherapy in adults with pneumonia, as well as one ongoing RCT of osteopathic manipulative treatment in elderly patients with pneumonia (Noll 2008a)[210] and on completed medium quality RCT of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease (Noll 2008b)[211].

The Cochrane review by Yang 2010[209] included two RCTs of osteopathic manipulative therapy for adults with pneumonia (Noll 1999 and Noll 2000 (the latter was already included in the Bronfort report)). Both included a standardised osteopathic manipulative treatment protocol versus sham (light touch) treatment which was applied twice a day for 10 to 15 minutes during the hospital stay in 21 and 58 patients with a mean age of 77 to 82 years. There was no significant effect of osteopathic treatment on mortality, cure rate, duration of fever, rate of improvement of chest X-ray, or duration of oral antibiotic therapy. Hospital stay in the osteopathy group was significantly reduced by two days (p=0.006) compared to control and both the duration of total antibiotic therapy and intravenous therapy were reduced by about two days in the osteopathy versus control groups (p=0.001 and 0.0009). The review authors concluded that osteopathic manipulative therapy may reduce the mean duration of hospital stay and antibiotic treatment but that further high quality evidence is needed before chest physiotherapy can be recommended as an adjunct to conventional therapy in pneumonia in adults.

The ongoing RCT (Noll 2008a, the MOPSE trial)[210] uses a similar protocol to the two smaller RCTs reported in the Yang 2010 review but adds a second control group on conventional therapy only.

In the RCT on the use of osteopathic manipulative treatment in the treatment of COPD (Noll 2008b),[211] the authors assessed the effects of a single standardised 20 minute session of osteopathic manipulative treatment (involving a range of techniques) on pulmonary function parameters. Of the 21 pulmonary function parameters assessed, a significant beneficial effect of osteopathic treatment compared to control was found for eight parameters when considering absolute end of study values and for six when considering percent changes from baseline. A majority of patients in both the intervention and the light touch control groups found the treatment for be beneficial. A similar small number of patients (two in the intervention and four in the control group) reported minor adverse effects after the treatment. No evidence is available on longer term effects of more extensive treatment.

Evidence summary. For pneumonia in older adults, there is no change from the Bronfort report (inconclusive evidence in a favourable direction for osteopathic manipulative treatment). For COPD, there is inconclusive evidence in an unclear direction.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Yang 2010[209] **Focus:** Cochrane review of chest physiotherapy for pneumonia in adults **Quality:** high	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** adults with any type of pneumonia **Interventions:** chest physiotherapy (including osteopathy) **Outcomes:** mortality, cure rate, duration of hospital stay, healing time, rate of improvement of chest X-ray, and various other secondary outcomes **METHODOLOGY** 6 relevant databases searched, journals hand searched, no language or publication restrictions; studies selected and data extracted independently by two authors; quality assessment using the Cochrane risk of bias instrument; excluded studies listed; systematic tabulation of studies. **Data analysis:** meta-analyses; text and tables **Subgroups / sensitivity analyses:** different types of chest physiotherapies	**N included trials:** 6 RCTs, including 2 RCTs on osteopathic manipulative treatment (Noll 1999, Noll 2000) **Study quality:** 2 osteopathic RCTs rated 'moderate risk of bias' **Study characteristics:** standardised osteopathic manipulative treatment protocols versus sham (light touch) treatment (twice a day 10 to 15 mins); 21 to 58 patients, mean age 77 to 82 years **Excluded studies eligible for current review:** no **Further information available on:** duration of leukocytosis, leukocyte count	**RESULTS** • No significant effect of osteopathic treatment on: mortality, cure rate, duration of fever, rate of improvement of chest X-ray, duration of oral antibiotic therapy • Hospital stay in the osteopathy group was significantly reduced by 2 days (p=0.006) compared to control • Both duration of total antibiotic therapy and intravenous therapy were reduced by about 2 days in the osteopathy versus control groups (p=0.001 and 0.0009) **CONCLUSIONS** Osteopathic manipulative therapy may reduce the mean duration of hospital stay and antibiotic treatment but the authors suggest that further high quality evidence is needed before chest physiotherapy can be recommended as an adjunct to conventional therapy in pneumonia in adults

RCTs

Study and Participants	Interventions	Outcomes
Noll 2008b[211] USA **Focus:** RCT of the effects of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease (COPD) **Duration:** single session **Follow-up:** 1 day after the intervention **Quality:** medium **PARTICIPANTS:** **N:** 35 (49% women) **Age:** 69.6 SD6.6 to 72.2 SD7.1 years **Inclusion:** known history of COPD, ≥65 years, airflow obstruction	**Intervention type:** osteopathy **Intervention (n=18):** standardised osteopathic manipulative medicine protocol (massage of paraspinal muscles, rib raising, doming the abdominal diaphragm, suboccipital decompression, myofascial release to the thoracic inlet, pectoral traction, thoracic lymphatic pump with activation) **Comparison (n=17):** sham light touch protocol **Dose:** single 20 min session **Providers:** osteopaths **Further information available on:** 21 lung function parameters	**Results** • *Absolute pulmonary function parameters:* statistically significant differences in 8 of 21 lung function parameters in the OMT group compared to control (forced expiratory flow after 25% and 50% of FEV had been exhaled ($FEF_{25\%}$, $FEF_{50\%}$) , forced expiratory flow at the midexpiratory phase ($FEF_{25\%\ 75\%}$) and expiratory reserve volume (ERV) significantly lower and lung volume parameters significantly higher, airway resistance decreased) • *Percent change in lung function parameters from baseline to post-treatment:* $FEF_{50\%}$ and $FEF_{25\%\ 75\%}$ significantly lower, lung volume parameters significantly higher • Patients in both groups felt that they had benefitted from the manipulative treatment, that they breathed better, enjoyed the treatment and would recommend it to others (71 to 94% in the intervention group, 59 to 82% in the sham group) ***Specific adverse effects:*** only minor adverse events, no difference between groups (n=2 intervention, n=4 control)

Pregnancy/obstetric care/neonatal care

This sub-section includes three publications, one systematic review (Khorsan 2009)[212] and two primary controlled studies (Cameron 2005, Pizzolorusso 2011)[213;214] that reported on the effectiveness of manipulative therapy used in pregnancy, obstetric and/or neonatal care settings.

One systematic review of medium quality (Khorsan 2009)[212] evaluated the evidence on the effects of spinal manipulative therapy (SMT) on back pain and other symptoms related to pregnancy. This review searched seven relevant databases and included studies published in English. Unpublished or non-English literature was not considered in the review. The review identified 32 relevant publications including the following: one randomised trial, two systematic reviews, one cohort study, two case-control studies, six case reports, six case series, four narrative reviews, and nine descriptive surveys. The study quality of controlled studies and systematic reviews was assessed using Intercollegiate Guidelines Network (SIGN) checklist. Most of the included studies were non-randomised and uncontrolled and their results supported that the use of SMT during pregnancy was associated with reduced back pain. Evidence regarding other related symptoms such as labour and delivery and adverse events was insufficient to be conclusive. The authors concluded that since there is limited number of effective treatments for pregnancy-related back pain, clinicians might consider SMT as a treatment option, if no contraindications are present.

In an RCT of medium quality (Cameron 2005),[213] 72 very preterm (gestational age < 32 weeks) infants born with very low birth weight (VLBW; < 1500 g) were randomised to receive developmental physical therapy (PT; 34 infants) or no PT (38 infants) for 4 months. The Alberta Infant Motor Scale (AIMS) was used to assess the effects of PT on motor development in the infants at 4 months post-randomisation. At the 4-month assessment, there were no significant differences on AIMS between the treatment and no treatment groups (the median percentile rank: 65 versus 72.5, p=0.191).

In a cohort study of 350 preterm infants (Pizzolorusso 2011)[214], the authors investigated the effect of osteopathic manipulative treatment (OMT) on gastrointestinal (GI) function and length of hospital stay (LOS). The treatment group consisted of 162 infants treated with OMT on top of conventional care and the control (no OMT) group included 188 infants receiving conventional care but without OMT. The treatment (OMT) and control (no OMT) post-surgery groups were compared with respect to average daily occurrence of gut symptoms (> 0.44 GI occurrences) and LOS (≥ 28 days). This study was judged to be of medium quality. The results indicated that the infants who had received OMT were at lower risk for having daily gut symptoms (odds ratio: 0.45, 95% CI 0.26, 0.74) as well as reduced rates of LOS (odds ratio: 0.22, 95% CI 0.09, 0.51) compared to infants who had not received OMT.

Evidence summary. No relevant evidence was found in the Bronfort report. Due to the absence of good quality evidence, results regarding comparative effectiveness/safety of manual therapy used in pregnancy, obstetric and/or neonatal care settings remain inconclusive.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Khorsan 2009[212] **Focus:** effectiveness/safety of spinal manipulation therapy (SMT) in pregnancy-related conditions **Quality of systematic review:** medium	**INCLUSION CRITERIA** **Study design:** systematic reviews, randomised, non-randomised controlled trials, cohort controlled studies, case-control studies, case series, case reports **Participants:** pregnant women with back pain and other pregnancy-related symptoms **Interventions**: manipulative procedures (chiropractic, osteopathy) **Outcomes:** back pain relief, pregnancy-related outcomes **METHODOLOGY** 7 relevant databases searched; no language limit; hand search of reference lists; some details on study selection; quality assessment of studies presented; studies not presenting original data, abstracts, conference proceedings, outcomes of interest not reported, those reporting non-manual or only soft tissue treatments were excluded; excluded studies not listed. **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 1 randomised trial (Guthrie 1982), 2 systematic reviews (Cooperstein 2001, Stuber 2008), 1 cohort study (Berg 1988), 2 case-control studies (Diakow 1991, King 2000), 6 case reports (Alcantara 2008, Fallon 1996, Kruse 2007, Schmitz 2005, Stern 1993, Thomas 2008), 6 case series (Lisi 2006, Daly 1991, Guadagnino 1999, Kunau 1998, Kunau 1999, McIntyre 1991) **Study quality:** Scottish Intercollegiate Guidelines Network (SIGN) checklist; 13 studies were assessed for quality using SIGN: low (n=4), neutral (n=7), and high (n=2) **Study characteristics:** studies differed in inclusion criteria, treatment protocols, and definition of outcomes. Most studies reported pain relief. Others reported pain medication use, length of labour and mode of delivery **Excluded studies eligible for current review:** not reported	**RESULTS** Limited evidence supported that use of SMT during pregnancy was associated with reduced back pain. Evidence regarding treatment during labour and delivery and regarding adverse events was insufficient **CONCLUSIONS** Since there is limited number of effective treatments for pregnancy-related back pain, clinicians may consider SMT as a treatment option, if no contraindications are present

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Cameron 2005[213]
UK

Focus: RCT of manual physical therapy (PT) effects compared to no PT in preterm infants with very low birth weight (VLBW)
Duration: each session of 60 minutes (PT) daily on weekdays for 4 months
Follow-up: 4 months
Quality: medium

PARTICIPANTS:
N: 60 (40% female)
Age: 29 weeks [gestational age]
Inclusion: infants with 24 weeks <gestational age < 32 weeks and birth weight < 1500 g; exclusions were cortical blindness or retinopathy causing blindness, musculoskeletal/congenital abnormality, oxygen dependency, severe hydrocephalus, signs of drug withdrawal, or family history of social problems.</td>
<td>Intervention type: physiotherapy
Intervention (n=34): neonatal developmental PT consisting of handling, positioning techniques to promote symmetry, muscle balance, and movement using postural support and facilitation techniques
Comparison (n=38): no PT
Dose: each session of 60 minutes (PT) daily on weekdays
Providers: paediatric physical therapists</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Physical therapy (interquartile range)</th><th>No physical therapy (interquartile range)</th><th>p-value</th></tr>
<tr><td>4-month median percentile rank on the AMIS</td><td>65.0
(42.0)</td><td>72.5
(32.5)</td><td>NS</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Non-randomised comparative studies

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Pizzolorusso 2011[214]
Italy

Focus: Effect of osteopathic manipulation treatment (OMT) on gastrointestinal (GI) function and length of hospital stay (LOS) in preterm infants
Design: CCT
Duration: 2 weeks
Follow-up: 2 months
Quality: medium

PARTICIPANTS:
N: 350 (49% female)
Age: 29-37 weeks [gestational age]
Inclusion: preterm infants with gestational age between 29 and 37 weeks; exclusions were infants with HIV, drug addicted mother, genetic disorders, congenital abnormalities, cardiovascular abnormalities, neurological disorders, enterocolitis, abdominal obstruction, pre-/post-surgery, atelectasis</td>
<td>Intervention type: osteopathy
Intervention (n=162): OMT consisting of indirect myofascial sutural spread, balanced membranous/ligamentous tension
Comparison (n=188): no OMT
Dose: session of 20-30 minutes twice per week
Providers: certified osteopaths</td>
<td>Results

<table>
<tr><th>Change in outcome</th><th>OMT</th><th>No OMT</th><th>OR (95% CI)</th></tr>
<tr><td>Average daily occurrence of gut symptoms

≤0.44 versus > 0.44</td><td>134 (82.7%) versus 28 (17.3%)</td><td>128 (68.1%) versus 60 (32%)</td><td>0.45 (0.26, 0.74)</td></tr>
<tr><td>Length of stay

< 28 days versus ≥ 28 days</td><td>134 (82.7%) versus 28 (17.3%)</td><td>133 (70.7%) versus 55 (29.3%)</td><td>0.22 (0.09, 0.51)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Rehabilitation

This sub-section includes six identified studies, of which three were randomised trials (Hunter 2011, Goldstein 2005, Sleszynski 1993)[215-217] and three were non-randomised studies (Jarski 2000, Yurvati 2005, Crow 2009).[218-220] Five studies enrolled post-surgery adults receiving manual therapy as part of rehabilitation process. In these studies, participants had undergone cholecystectomy (Sleszynski 1993),[217] abdominal hysterectomy (Goldstein 2005),[215] abdominal surgery (Crow 2009),[218] knee/hip arthroplasty (Jarski 2000),[219] and coronary artery bypass graft (CABG) surgery (Yurvati 2005).[220] In one study, the participants received manual therapy as a post-stroke rehabilitation treatment (Hunter 2011).[216]

In one RCT (Hunter 2011)[216] of medium quality, 76 adults with stroke were randomised to receive conventional physiotherapy alone or with additional three different doses of 30, 60, or 120 minutes of manual therapy (joint/soft tissue mobilisation, massage, tactile stimulation, active-assisted movements, soft tissue stretch, and/or compression) for two weeks. The measures of muscle contraction – Motricity Index (MI) and the upper limb functional tasks – Action Research Arm Test (ARAT) were ascertained at end of treatment. No statistically significant differences in either post-treatment MI or ARAT were observed across the control (conventional physiotherapy alone) and three treatment groups (30, 60, or 120 minutes of manual therapy additional to conventional physiotherapy). There was no occurrence of adverse events.

Sleszynski and colleagues (Sleszynski 1993)[217] randomised 42 adults who had had cholecystectomy to receive a form of spinal manual therapy (i.e., thoracic lymphatic pump) or incentive spirometry (IS) and compared the mean forced vital capacity (FVC), forced expiratory volume (FEV), and incidence of atelectasis (complication of abdominal surgery) between the two treatments. This trial was judged to be of medium quality. The 5-day post-treatment frequency of atelectasis was similar in the two treatment groups (5% versus 5%, $p>0.05$). There was a faster recovery of forced vital capacity (0.28 versus 0.39, $p<0.05$) and forced expiratory volume (0.29 versus 0.40, $p<0.05$) in participants receiving the manual therapy versus IS.

In the double-blind trial of low quality (Goldstein 2005),[215] 39 post-abdominal hysterectomy women were randomised to receive placebo (pre- and post-operative), osteopathic manual therapy (OMT; post-operative), morphine (pre-operative), or the combination of morphine (pre-operative) and OMT (post-operative). The study objective was to compare the analgesic effects across the study treatment groups. There were no significant between-group differences in pain, nausea, or vomiting mean scores at any time of the 48-hour follow-up post-surgery. Total 24-hour post-operative morphine dose was significantly lower ($p=0.02$) in the pre-operative morphine plus post-operative OMT group (0.17 mg/kg, 95% CI 0.06, 0.28) compared to the pre-operative morphine alone group (0.51 mg/kg, 95% CI 0.26, 0.77). The corresponding mean difference at 48 hours was also significant in favour of the OMT group ($p=0.011$).

One retrospective cohort study of low quality explored the effect of osteopathic manipulative treatment (OMT) on the length of hospital stay in adults who had developed ileus after abdominal surgery (Crow 2009).[218] Specifically, the records of 331 post-abdominal surgery participants with diagnosis of ileus were identified and divided into groups: a) patients who had received OMT (n=172) and b) patients who had not received OMT (n=139). Using the age-adjusted Analysis of Covariance (ANCOVA), the length of

hospital stay was computed for both groups. The results indicated a significantly shorter stay for the OMT recipient group versus the control (non-OMT) group (mean difference: 2.7 days, 95% CI -5.2, -0.28, p=0.029).

Yurvati and colleagues conducted a cohort study (Yurvati 2005)[220] to determine the effects of osteopathic manipulative treatment (OMT) on cardiac haemodynamics in 29 adults after coronary artery bypass graft (CABG) surgery. The treatment group consisted of 10 participants treated with OMT post-CABG surgery and the control group, identified through a chart review, consisted of 19 subjects who underwent CABG surgery but were not treated with post-surgery OMT. The treatment (OMT) and control (no OMT) post-surgery groups were compared with respect to changes in mixed venous oxygen saturation and cardiac index. This study was judged to be of low quality. The mean mixed venous oxygen saturation change in the OMT group was 3.7% (95% CI 2.69, 4.71) compared to –3.28% (95% CI -4.88, -1.68), indicating a statistically significant difference in favour of the OMT ($p \leq 0.005$). Although cardiac index increased (i.e., improved) in both groups, the OMT group (mean change: 0.51, 95% CI 0.38, 0.64) compared to the control group (mean change: 0.14, 95% CI 0.06, 0.22) experienced a significantly greater magnitude of improvement ($p \leq 0.02$).

In another cohort study of medium quality (Jarski 2000),[219] the authors assessed the effects of osteopathic manipulative treatment (OMT) on distance ambulated, days to independent negotiation of stairs, length of hospital stay, need for supplemental analgesics, and perception of pain in 76 adult participants who had knee or hip arthroplasty. The treatment (OMT) and control (no OMT) groups were matched on diagnosis, surgical procedure, sex, significant past medical history, and age. The participants in both groups had similar post-surgical procedures. The post-operative mean number of days to independent negotiation of stairs in the OMT group was significantly shorter (i.e., 20% reduction) compared to the control group (4.3 versus 5.4, p=0.006). Although the distance ambulated, length of hospital stay, and need for supplemental analgesics was numerically in favour of the OMT group, the between-group differences were not statistically significant at the conventional level of $\alpha=0.05$.

Evidence summary. No relevant evidence, except for knee/hip arthroplasty, was found in the Bronfort report. Overall, given the inconclusive evidence due to the paucity, clinical heterogeneity and low-medium quality of the reviewed evidence, the effectiveness/safety of rehabilitative manual therapy cannot be established. No change from the Bronfort report (inconclusive evidence).

RCTs

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Hunter 2011[216]
UK

Focus: RCT of manual therapy effects compared to standard physiotherapy in adults with stroke
Duration: 2 weeks
Follow-up: 2 weeks
Quality: medium

PARTICIPANTS:
N: 76 (50% female)
Age: 72.5 years
Inclusion: adults with stroke (infarct or haemorrhage in the anterior cerebral circulation) 8-84 days prior to trial entry; paralysed or paretic upper limb (<61/100 on Motricity Index on arm section); no clinically important upper limb pain or visible upper-limb movement deficits due to causes other than stroke</td>
<td>Intervention type: physiotherapy
Intervention: 3 doses of manual therapy (joint/soft tissue mobilisation, massage, tactile stimulation, active-assisted movements, soft tissue stretch, and/or compression) for 2 weeks
Intervention 1 (n=18): 30 min manual therapy as above
Intervention 2 (n=19): 60 min manual therapy as above
Intervention 3 (n=20): 120 min manual therapy as above
Comparison (n=19): conventional physiotherapy
Dose: see above
Providers: clinical physiotherapists</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Standard physiotherapy</th><th>Manual therapy 30 min</th><th>Manual therapy 60 min</th><th>Manual therapy 120 min</th><th>p-value</th></tr>
<tr><td>MI (mean)</td><td>12.4</td><td>10.2</td><td>17.0</td><td>15.7</td><td>NS</td></tr>
<tr><td>N (%) With MI > 1</td><td>11 (58%)</td><td>9 (50%)</td><td>12 (67%)</td><td>14 (70%)</td><td>NS</td></tr>
<tr><td>ARAT (mean)</td><td>6.5</td><td>6.8</td><td>6.6</td><td>9.8</td><td>NS</td></tr>
<tr><td>N (%) With ARAT increase of >5.7</td><td>7 (37%)</td><td>5 (29%)</td><td>8 (44%)</td><td>9 (45%)</td><td>NS</td></tr>
</table>

Specific adverse effects: not observed</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Sleszynski 1993[217]
USA

Focus: RCT of manual therapy effects compared to incentive spirometry in cholecystectomy adults
Duration: Not reported
Follow-up: 1 year
Quality: medium

PARTICIPANTS:
N: 42 (81% female)
Age: 46 years
Inclusion: cholecystectomy adults; participants with any incision other than subcostal or presence of structural deformity was excluded</td>
<td>Intervention type: osteopathy
Intervention (n=21): thoracic lymphatic pump (TLP) – manual therapy
Comparison (n=21): incentive spirometry (IS)
Dose: 3 times daily sessions until discharge
Providers: osteopaths, students</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Thoracic lymphatic pump</th><th>Incentive spirometry</th><th>p-value</th></tr>
<tr><td>N (%) with atelectasis</td><td>2/21 (5%)</td><td>2/21 (5%)</td><td>NS</td></tr>
<tr><td>FVC</td><td>0.28 SD0.18</td><td>0.39 SD0.10</td><td><0.05</td></tr>
<tr><td>FEV</td><td>0.29 SD0.19</td><td>0.40 SD0.10</td><td><0.05</td></tr>
</table>

Specific adverse effects: not observed (other than atelectasis)</td>
</tr>
</table>

<table>
<tr><th>Study and Participants</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Goldstein 2005[215]
USA

Focus: RCT of manual therapy effects compared to morphine in post-abdominal hysterectomy in women
Duration: each session of 10 minutes (OMT), 6 minutes (morphine injection)
Follow-up: 48 hours
Quality: low

PARTICIPANTS:
N: 39 (100% female)
Age: Not reported
Inclusion: adults (age > 18 years) after abdominal hysterectomy hospitalised for at least 48 hours, naïve to manipulation therapy, able to self-report pain levels; exclusions were participants with liver/kidney disease, use of antidepressants</td>
<td>Intervention type: osteopathy
Intervention: osteopathic manipulation therapy (OMT) administered on patient’s both sides in 3 sessions (sacral myofascial release, gentle thoracic and lumbar myofascial soft tissue techniques); morphine – 10 mg in 1 mL
Intervention 1 (n=10): pre-operative morphine + post-operative OMT; see above
Intervention 2 (n=10): pre-operative morphine + post-operative placebo (OMT); see above
Intervention 3 (n=10): pre-operative placebo (morphine) + post-operative OMT; see above
Comparison (n=9): pre-operative placebo (morphine) + post-operative placebo (OMT)
Dose: see above
Providers: Not reported</td>
<td><u>Results</u>

<table>
<tr><th>Change in outcome</th><th>Morphine + OMT (95% CI)</th><th>Morphine + placebo (95% CI)</th><th>Placebo + OMT (95% CI)</th><th>Placebo + placebo (95% CI)</th><th>p-value</th></tr>
<tr><td>Pain score (0 – 10)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>>0.05</td></tr>
<tr><td>Nausea score (0 – 3)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>>0.05</td></tr>
<tr><td>Vomiting score (0 – 3)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>>0.05</td></tr>
<tr><td>24 hour post-operative mean dose of morphine</td><td>0.17 (0.06, 0.28)</td><td>0.51 (0.26, 0.77)</td><td>0.36 (0.11, 0.61)</td><td>0.43 (0.17, 0.70)</td><td>Int 1 versus Int 2 (p=0.02)</td></tr>
<tr><td>48 hour post-operative mean dose of morphine</td><td>0.42 (0.16, 0.68)</td><td>1.14 (0.72, 1.55)</td><td>0.72 (0.10, 1.34)</td><td>0.98 (-0.18, 2.13)</td><td>Int 1 versus Int 2 (p=0.01)</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Non-randomised comparative studies

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr><td>Crow 2009[218]
USA

Focus: effect of osteopathic manipulation treatment (OMT) on length of hospital stay in patients with ileus after abdominal surgery
Design: retrospective chart review
Duration: not reported
Follow-up: not reported
Quality: low

PARTICIPANTS:
N: 331 (52% female)
Age: not reported
Inclusion: ileus post abdominal surgery; multiple surgeries were excluded</td><td>Intervention type: osteopathy
Intervention: OMT
Comparison: no OMT
Dose: not reported
Providers: osteopathic medical students, family practice residents

Further information available on:
ethnicity</td><td>Results

<table><tr><th>Outcome</th><th>Osteopathic manipulation treatment (95% CI)</th><th>No osteopathic manipulation treatment (95% CI)</th><th>p-value</th></tr><tr><td>Length of hospital stay (days)</td><td>11.8 (10.2, 13.4)</td><td>14.6 (12.7, 16.4)</td><td>difference: 2.7 days, p=0.029</td></tr></table>
Specific adverse effects: not reported</td></tr>
<tr><td>Yurvati 2005[220]
USA

Focus: Effect of osteopathic manipulation treatment (OMT) on cardiac haemodynamics after coronary artery bypass graft (CABG) surgery
Design: CCT
Duration: 25-30 minutes of session (OMT)
Follow-up: 5-10 minutes after OMT (OMT group) versus 2 hours post-surgery (control group)
Quality: low

PARTICIPANTS:
N: 29 (27.6% female)
Age: 56-79 years (range)
Inclusion: post-CABG surgery adults</td><td>Intervention type: osteopathy
Intervention: OMT consisting of balanced ligamentous tension, indirect myofascial release of the sternum, indirect release of the respiratory diaphragm, occipito-atlantal decompression, rib raising, Sibson’s fascial release
Comparison: no OMT
Dose: 25-30 minutes of session (OMT)
Providers: osteopathic physicians</td><td>Results

<table><tr><th>Change in outcome</th><th>OMT (95% CI)</th><th>No OMT (95% CI)</th><th>p-value</th></tr><tr><td>Mixed venous oxygen saturation (%)</td><td>3.7% (2.69, 4.7)1</td><td>–3.28% (-4.88, -1.68)</td><td>≤0.005 (in favour of OMT)</td></tr><tr><td>Cardiac index (mean)</td><td>0.51 (0.38, 0.64)</td><td>0.14 (0.06, 0.22)</td><td>≤0.02 (in favour of OMT)</td></tr></table>
Specific adverse effects: not reported</td></tr>
</table>

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Jarski 2000[219]
USA

Focus: Effect of osteopathic manipulation treatment (OMT) on pain perception, length of hospital stay, independent negotiation of stairs, and distance ambulated in adults post-knee/hip arthroplasty surgery
Design: CCT
Duration: 4 days (OMT)
Follow-up: 5 days post-surgery
Quality: medium

PARTICIPANTS:
N: 76 (60% female)
Age: 66-71 years (mean range)
Inclusion: adults post-knee/hip arthroplasty surgery, use of English, mental orientation to follow instructions and questionnaire items</td>
<td>Intervention type: osteopathy
Intervention: OMT consisting of high velocity low amplitude, muscle energy, myofascial, lymphatic pump, counterstrain, and traction techniques
Comparison: no OMT
Dose: 5-15 minute sessions of OMT for 4 days
Providers: osteopathic family practice residents</td>
<td>Results

<table>
<tr><th>Change in outcome</th><th>Osteopathic manipulation treatment</th><th>No Osteopathic manipulation treatment</th><th>p-value</th></tr>
<tr><td>Time to negotiate stairs (days)</td><td>4.3 SD1.2</td><td>5.4 SD1.6</td><td>0.006</td></tr>
<tr><td>Distance ambulated (m)</td><td>24.3 SD18.3</td><td>13.9 SD14.4</td><td>NS</td></tr>
<tr><td>Need for supplemental intramuscular analgesics N (%)</td><td>14/38 (37%)</td><td>19/38 (50%)</td><td>NS</td></tr>
<tr><td>Length of hospital stay (days)</td><td>5.9 SD1.5</td><td>6.1 SD2.2</td><td>NS</td></tr>
<tr><td>Pain perception after OMT N (%)</td><td>Decreased 15/23 (65%)

No change 8/23 (35%)

Increased 0/23 (0%)</td><td>NA</td><td>NA</td></tr>
</table>

Specific adverse effects: not reported</td>
</tr>
</table>

Systemic sclerosis

Two small randomised trials by the same research group (Maddali Bongi 2009 a and b),[221;222] both with a considerable risk of bias, examined the use of McMennell joint manipulation within the context of a comprehensive rehabilitation programme for patients with systemic sclerosis. The emphasis was on hand involvement, although one of the studies also examined parameters related to face involvement.

Both trials did not report any formal comparisons between intervention and control groups. In both trials, some mobility parameters (Hand Mobility in Scleroderma Test) were improved both after the nine week intervention and after a nine week post-intervention follow-up. Some quality of life measures (SF-36) were only improved after the intervention but not at the nine week follow-up. In one trial, disability measures were improved in the intervention group both after the intervention and at follow-up, while in the other trial the disability improvement did not persist at the follow-up measurement. However, as these results were not statistically compared with those of the comparison group (results reported as unchanged) any benefits of the intervention have to remain unclear.

Evidence summary. There is inconclusive evidence in an unclear direction for the use of McMennell joint manipulation used in a complex rehabilitation programme in systemic sclerosis.

RCTs

Study and Participants	Interventions	Outcomes
Maddali Bongi 2009a[221] Italy **Focus:** effect of a rehabilitation programme for systemic sclerosis patients **Duration:** 9 weeks **Follow-up:** 18 weeks (9 weeks post-intervention) **Quality:** low/moderate **PARTICIPANTS:** **N:** 20 (65% female) **Age:** 57.1 SD15.0 years **Inclusion:** systemic sclerosis; 10 had lung involvement, none had arthritis or myositis; all had flexion contractures, 7 had hand oedema, 7 had fingertip ulcers	**Intervention type:** physiotherapy **Intervention (n=10):** 1. *Hand involvement* treated with a combination of *connective tissue massage* and *McMennell joint manipulation* (1 hour/session, twice a week). Patients with oedematous hands were also treated with supplementary sessions of *manual lymphatic drainage* (1 hour/session, twice a week). 2. For *face involvement* a combination of *Kabat's* method, *connective tissue massage* and *kinesitherapy* was used (1 hour/session, twice a week). 3. The global rehabilitation programmes include *Hydrokinesytherapy*, performed by patients without ulcers. The patients with ulcers (n= 3) were assigned to a *land-based rehabilitation.* In both cases, patients performed *respiratory rehabilitation* exercises (1 hour/session, once a week). [detailed procedures described] **Comparison (n=10):** Patients of the observational group (controls) were followed up and recommended not to start any new physical or pharmacological therapy during the study period. **All:** educational recommendation on general measures (nutrition, skin warming and skin and mucosal protection); all patients continued pharmacological treatments without change **Dose:** see above **Providers:** not reported	• significance of results seems to refer to change from baseline, not comparison to control group; just reported that the control group did not show any significant improvement in general health condition and hands and face measures • significant improvement in the following parameters both at end of intervention and follow-up: Hand Mobility in Scleroderma Test, mouth opening (cm) • significant improvement in the following parameters only at end of intervention but not at follow-up: Physical Synthetic Index (SF-36), Mental Synthetic Index (SF-36), Health Assessment Questionnaire Disability Index, Duruoz Hand Index, fist closure (cm), FACE VAS • no significant improvement either at end of intervention or at end of follow-up: hand opening (cm) • decrease in oedema in patients with hand oedema (n=4) • overall satisfaction was high ***Specific adverse effects:*** not reported

Study and Participants	Interventions	Outcomes
Maddali Bongi 2009b[222] Italy **Focus:** effect of a rehabilitation programme for systemic sclerosis patients **Duration:** 9 weeks **Follow-up:** 18 weeks (9 weeks post-intervention) **Quality:** low/moderate **PARTICIPANTS:** **N:** 40 (75% female) **Age:** 57.8 SD11.8years **Inclusion:** systemic sclerosis; 16 had lung involvement; none had arthritis or myositis; all had flexion contractures; 18 had fingertip ulcers	**Intervention type:** physiotherapy **Intervention (n=10):** connective tissue massage and McMennell joint manipulation plus daily home exercises (hand and arm) **Comparison (n=10):** daily home exercise programme only **All:** educational recommendation on general measures (nutrition, skin warming and skin and mucosal protection); all patients continued pharmacological treatments without change **Dose:** manual therapy: two 1 h sessions per week; home exercises: 20 min daily **Providers:** not reported	• significance of results seems to refer to change from baseline, not comparison to control group; in the exercise only group, only fist closure was improved after the end of the intervention, but not after the end of follow-up • significant improvement in the following parameters both at end of intervention and follow-up: Hand Mobility in Scleroderma Test, Cochin hand functional disability scale, fist closure, Health Assessment Questionnaire Disability Index • significant improvement in the following parameters only at end of intervention but not at follow-up: Mental Synthetic Index (SF-36), Physical Synthetic Index (SF-36), • no significant improvement either at end of intervention or at end of follow-up: hand opening ***Specific adverse effects:*** not reported

Conditions / interventions that were 'conclusive' in the Bronfort report

Musculoskeletal conditions

Back pain

Dagenais 2010[223] conducted a systematic review of spinal manipulation therapy or mobilisation for acute low back pain. Fourteen studies involving 2027 participants were included. Half the studies were rated as being of higher methodological quality, and half were rated as being of lower methodological quality. Techniques delivered in the intervention groups included high velocity low amplitude thrust, rotational or instrument-delivered manipulation, or mobilisation. The number of treatment sessions ranged from 1 to 20 (most studies 5 to 10), delivered over 1 to 12 weeks. Treatments were mainly delivered by chiropractors or physiotherapists, with a small number delivered by medical doctors or osteopaths. Control interventions included physical modalities, medication, education, exercise, lumbar supports, sham or placebo treatment, and bed rest. Follow-up periods were between less than a month to two years. Results from most studies suggest that 5 to 10 sessions of SMT administered over 2 to 4 weeks achieve equivalent or superior improvement in pain and function when compared with other commonly used interventions, such as physical modalities, medication, education, or exercise, for short, intermediate, and long-term follow-up (one third of studies found more pain reduction with spinal manipulation at one or more time point than the control groups, two thirds showed no difference, none found spinal manipulation to be inferior to other treatments). Five studies reported on adverse events, all of which were minor and temporary. The authors suggest that clinicians should discuss the role of spinal manipulative therapy as a treatment option for patients with acute low back pain who do not find adequate symptomatic relief with self-care and education alone.

A systematic review by Kent 2010[224] compared targeted manual therapy and / or exercise with non-targeted interventions in patients with non-specific low back pain. Four studies were included, all of which were high quality. Two of the studies included both manual treatment (manipulation / mobilisation) and exercise in the targeted treatment group, one included only manual therapy (mostly mobilisation), and one included only exercise (McKenzie directional preference exercises). In the manual therapy trials, no significant differences to the non-targeted treatment groups were found. The review authors suggest that the studies may not have been adequately powered and that more research is needed.

In a Cochrane systematic review, Rubinstein 2011[225] investigated the effects of spinal manipulative therapy in chronic low back pain. Twenty-six RCTs including 6070 patients were included, nine of these had a low risk of bias. Seven of the studies compared spinal manipulative therapy with inert or sham therapy, in 21 studies the intervention was compared against another active intervention (including acupuncture, education, back school, exercise, massage, pain clinic, myofascial therapy, pharmaceutic therapy, short-wave diathermy, standard therapy, standard physiotherapy, ultrasound), and in five studies, spinal manipulative therapy plus another intervention was compared against that intervention alone. Spinal manipulation was delivered by a variety of health professionals including chiropractors, physiotherapists, osteopaths, orthomanual therapists, a bone-setter, and a naprapath. Types of treatment included high velocity low amplitude thrust, Maitland mobilisation, flexion-distraction mobilisation, rotational thrust and various unspecified techniques. The average maximum number of allowed treatments was eight, and the average duration of treatment was seven weeks. Overall, there was high-quality evidence that spinal manipulative therapy has a statistically significant

short-term effect on pain relief and functional status in comparison with other interventions as well as varying quality of the evidence that spinal manipulative therapy has a statistically signifi cant short-term effect on pain relief and functional status when it is added to another intervention. However, the size of the effects was small and not apparently clinically relevant (pain, mean difference -4.16, 95% CI: -6.97, -1.36; function, SMD -0.22, 95% CI: -0.36, -0.07, for manipulation in comparison with other interventions). No effects of manipulation technique or profession of the therapist were seen. None of the studies examining adverse effects reported serious complications. The authors suggested that the decision to refer to spinal manipulative therapy should be based on costs, preferences of the patient and providers, and relative safety of the treatment options.

Walker 2011[226] conducted a Cochrane systematic review of combined chiropractic interventions for low back pain. Twelve studies involving 2887 patients with low back pain were included, three of these had low risk of bias. The included studies had a range of intervention components apart from chiropractic spinal manipulative therapy including cold, heat, massage, exercise, electrical muscle stimulation, education, ultrasound, flexion-distraction, and dry needling. For combined chiropractic therapy versus other therapies in acute and subacute low back pain, there was a significant benefit for the chiropractic group in terms of short term pain relief (three low quality studies, SMD -0.25, 95% CI: -0.46, -0.04, p=0.02). Short term effects on disability were reported by four low quality studies and overall, there was also a significant effect in favour of combined chiropractic treatment (SMD -0.36, 95% CI: -0.70, -0.02). Longer term effects both for pain and disability were only reported by two studies and were significant in only one of these. For combined chiropractic therapy versus other therapies in chronic low back pain, two studies with a low and one study with a high risk of bias were included. Overall, there was no significant effect of combined chiropractic treatment on short or longer term pain relief, disability, or general health status. Inconsistent results for pain and disability outcomes were seen in populations with back pain of mixed duration in response to combined chiropractic treatment compared to other therapies. No trials were found comparing combined chiropractic treatment to no treatment. Only two of the trials reported on adverse events, these were minor and transient. The review authors concluded that combined chiropractic interventions slightly improved pain and disability in the short term and pain in the medium term for acute and subacute low-back pain, but current evidence neither supports nor refutes that these interventions provide a clinically meaningful difference for pain or disability in people with low-back pain when compared to other interventions. Any demonstrated differences in effects were small and not clinically relevant compared to other treatments and any benefits did not appear to be long-lasting. Due to the lack of studies, no conclusions could be drawn on comparison to no treatment. There is a need for more high-quality trials in this area.

Evidence summary. There is moderate positive evidence for spinal manipulation / mobilisation in acute low back pain. There is moderate positive evidence for spinal manipulation / mobilisation in chronic low back pain (of unclear clinical relevance) (degraded from Bronfort report). There is moderate positive evidence for combined chiropractic interventions in low back pain (of unclear clinical relevance).

Neck pain

Leaver 2010[227] conducted a systematic review of conservative interventions versus placebo, sham, minimal or no intervention for reducing pain and disability in non-specific neck pain. Of the eight included papers relevant to manual therapy, four obtained quality scores of 8 out of 10, while the rest

scored 5 to 7. There were four sham-controlled comparisons (three trials) of a single high-velocity manipulation (thoracic in one study and cervical in two studies). Three additional trials investigated other manual therapy techniques (bone setting, spinal mobilisation techniques, naprapathic therapy) with minimal or no intervention. Pooled results for the three manipulation studies showed a significant analgesic effect of the manipulation (WMD -22, 95% CI: -21, -11). The trials did not assess medium or long term outcomes or disability. The trials investigating other types of manual therapy reported significant improvements in pain and disability compared to control, but these significant differences were not maintained in the medium or long term (reported for one trial for pain and for two for disability). One additional trial investigated the effects of multimodal therapy including chiropractic manipulation / mobilisation, massage and exercises compared to control (advice only). Pain relief was significantly better in the multimodal group (mean difference -21, 95% CI: -34, -7), longer term pain or disability outcomes were not available. The review authors concluded that the results support the use of therapies combining manual therapy and exercise as well as the short term analgesic effect of single modalities of neck or thoracic manipulation or neck mobilisation.

Gross 2010[228] conducted a Cochrane systematic review of manipulation or mobilisation for neck pain. Twenty-seven trials were included, of which nine had a low risk of bias. Sixteen trial investigated manipulation alone of the cervical region (four with a low risk of bias). There was moderate quality evidence (two trials) that cervical manipulation produces similar changes in pain, function and patient satisfaction when compared to mobilisation for subacute or chronic neck pain at short or intermediate follow-up. There was low quality evidence (three trials) that cervical manipulation alone versus control may provide immediate and short term pain relief following one to four treatment sessions in participants with acute or chronic neck pain. There were six trials investigating thoracic manipulation (one with a low risk of bias). The higher quality trial favoured a single session of thoracic manipulation compared to placebo for immediate pain relief in chronic neck pain. The lower quality trials reported mixed results for the effects of thoracic manipulation compared or added to a range of treatments (such as electrothermal therapy, physiotherapy). Eight trials (five with a low risk of bias) investigated the use of cervical mobilisation alone. There was no difference between mobilisation and manipulation and mixed results for a range of mobilisation interventions compared to other treatments (some positive results for Maitland mobilisation techniques and neural dynamic techniques). Eight of the 27 trials reported adverse events, with three reporting that no adverse events occurred and five reporting that adverse events were benign and transient. The authors concluded that the evidence suggests some immediate or short term pain relief with a course of cervical manipulation or mobilisation alone, and of thoracic manipulation with or without adjunctive treatment. Some mobilisation techniques may be more effective than others. Optimal technique and dose need to be determined.

Another review by the same group of authors (D'Sylva 2010)[229] examined the effectiveness of manual therapy (manipulation, mobilisation, soft tissue treatment) with or without physical medicine modalities for neck pain. Nineteen trials were included, seven of which had a low risk of bias. In five trials a combined manipulation and mobilisation intervention was used. In three trials, there was no significant effect on pain, function / disability, or global perceived effect when compared to placebo (detuned electrotherapy) in subacute and chronic neck pain in the short term. In one trial, there was a small positive effect of the intervention when compared to no treatment in the short and long term in chronic neck pain with headache (pain, function / disability, global perceived effect). Mixed results for pain, function and disability outcomes were obtained for comparisons against physiotherapy care, GP care, or exercise. Ten trials combined manipulation, mobilisation and soft tissue techniques in their intervention groups (four had a low risk of bias). Seven of the trials (in acute, subacute or chronic neck

pain patients) found no significant difference in pain outcomes when comparing the intervention group to a range of other active interventions (collar, medication, advice, intramuscular anaesthetic, stretching, soft tissue therapy and ultrasound). No significant differences between intervention groups were seen in function or disability. However, one trial in acute neck pain with a low risk of bias (n=221, comparison against short wave diathermy) found significant improvements with respect to pain, quality of life and patient satisfaction in the short and partially in the intermediate term. In six studies (two with a low risk of bias), manual therapy was combined with physical medicine modalities. In comparison to other active treatments (generally also treatment combinations), there was generally no significant effect on pain, function and disability, or global perceived effect. Eight of the trials reported on adverse events, with two reporting that no adverse events occurred and the rest reporting benign and transient adverse events. In conclusion, the authors found some limited evidence for the use of a combination of manipulation and mobilisation with or without soft tissue techniques both in acute and chronic neck pain.

A third review from the same group (Miller 2010)[230] assessed the effects of manual therapy combined with exercise in neck pain. Seventeen trials were included, of which five had a low risk of bias. Overall, there was a significant effect of manipulation and / or mobilisation combined with exercise on pain when compared to control (SMD -0.48, 95%CI: -0.66, -0.30, p<0.00001). When considering different comparison interventions, the results remained significant when compared to sham / no treatment (intermediate and long term follow-up), when compared to traditional care (at least two of collar, advice, medication), manipulation / mobilisation only, exercise only (at short but not long term follow-up), or advice. These results applied to acute, subacute and chronic neck pain. Effects on function were less consistent (significant benefit of the intervention when compared to sham / no treatment, advice, manipulation / mobilisation only). No significant differences were seen on quality of life outcomes (five trials), and mixed results for global perceived effect (manipulation / mobilisation plus exercise significantly better compared to sham / no treatment or traditional care but not when compared to exercise alone). Patient satisfaction was significantly greater when compared to manipulation / mobilisation alone but not when compared to exercise alone. Three of the trials reported adverse events, which were benign and transient. The authors concluded that there is evidence to support the use of manipulation / mobilisation combined with exercise in (sub)acute and chronic neck pain but that there is still a lack of high quality evidence.

Evidence summary. There was moderate positive evidence to support the use of manipulation and / or mobilisation combined with exercise for neck pain of any duration. There was inconclusive favourable evidence for cervical or thoracic manipulation alone or combined manipulation and mobilisation with or without soft tissue techniques.

Whiplash-associated disorder

Shaw 2010[231] conducted a systematic review of chiropractic management of adults with whiplash-associated disorders. Based on five low quality comparative studies the authors suggest that for acute whiplash-associated disorders, a multimodal treatment approach including active and passive mobilisation and exercises is recommended. Manual therapy components of the interventions included manipulative treatment, Maitland mobilisation, activator-assisted manipulation, and McKenzie mobilisation. Two low quality comparative studies involving manual therapy as part of multimodal treatments were identified for sub-acute whiplash. The authors concluded that there is evidence to support the use of multimodal therapy for improving pain (posture instruction, mobilisation, massage,

cervical range of motion exercises). Manual therapy included cervical massage or mobilisation and manual therapy as part of a physiotherapy package. For chronic whiplash-associated disorders, the authors identified two low quality comparative studies involving manual therapy. The studies provided evidence of the effectiveness of exercise, however, the benefits of manual therapy were unclear. Manual therapy components included chiropractic care and high velocity low amplitude manipulation.

Teasell and colleagues (2010) conducted a series of systematic reviews of treatment for whiplash-associated disorders.[232-234] In their review of interventions for acute whiplash the authors included two trials involving some form of manual mobilisation as part of multimodal treatments, however, the effectiveness of that intervention component was not commented on in detail. The authors concluded that activation-based treatment is recommended in the management of acute whiplash-associated disorder (exercise and active mobilisation).[234] The second review was concerned with interventions for subacute whiplash-associated disorder.[233] Four studies (two RCTs of moderate quality and two case series) were included that assessed the effects of cervical and / or thoracic manipulation. There was limited evidence for the short term effectiveness of the manipulation intervention, however, further high quality evidence is needed to confirm the findings. The third review was concerned with the effects of non-invasive interventions for chronic whiplash-associated disorder.[232] Two studies were included that assessed the effects of manual therapy. One uncontrolled study examined the effects of chiropractic cervical manipulation. The study reported short term improvements in symptoms but the review authors concluded that there was insufficient evidence to support the effectiveness of the intervention. A further moderate quality RCT comparing an intervention group with a combination of Gestalt therapy, Rosen bodywork and cranio-sacral therapy with a non-intervention control group found no significant differences in pain, function, sick leave or quality of life after three months. However, the study had a high attrition rate.

Evidence summary. There is moderate positive evidence for the management of acute whiplash-associated disorder with a combination of mobilisation and exercise. There is inconclusive evidence in a favourable direction for cervical and / or thoracic manipulation in subacute whiplash-associated disorder. There is inconclusive evidence in an unclear direction for chiropractic cervical manipulation and cranio-sacral therapy in chronic whiplash-associated disorder.

Adhesive capsulitis

An update of our searches identified a recently published systematic review (Health Technology Assessment) on the management of frozen shoulder (Maund 2012).[235] The review included three relevant trials involving manual therapy (Vermeulen 2006, Wies 2003, Yang 2007).[150;151;236] One of these was judged to be of satisfactory quality (Yang 2007),[151] Vermeulen 2006 appeared to be of moderate quality and Wies 2003[236] had a considerable risk of bias. Vermeulen 2006[150] compared high grade with low grade mobilisation of the glenohumeral joint in 100 patients (twice weekly for 12 weeks), Wies 2003[236] compared nine weeks of osteopathy (the Niel-Asher technique) with physiotherapy (manual therapy and exercise) or control (breathing exercises, massage and range of motion exercises) in 30 patients, and Yang 2007[151] compared a group receiving end-range plus mid-range mobilisation with a group receiving mobilisation with movement plus mid-range mobilisation (twice weekly for three weeks, n=30). Vermeulen 2006[150] found no significant difference between the comparison groups in pain (not reported by the other studies, none of the studies found any significant differences between the groups receiving different types of manual therapy with respect to function / disability. With respect to range of motion, Vermeulen 2006[150] found significantly more improvement

in range of motion with high grade mobilisation, there was no significant difference in improvements in range of motion between the osteopathy and the physiotherapy groups in the study by Wies 2003[236], and the study by Yang 2007[151] found no significant difference between the improvements in external rotation between the study groups but internal rotation was significantly more improved in the mobilisation with movement group.

Evidence summary. There is moderate positive evidence for high grade mobilisation, inconclusive favourable evidence for mobilisation with movement, osteopathy (Niel-Asher technique), and manual therapy with exercise (additions with respect to the Bronfort report).

Hip or knee osteoarthritis

Brantingham 2012[97] conducted a systematic review (review update) of manipulative therapy for lower extremity conditions. They included two high, two moderate and two low quality trials relevant to hip osteoarthritis and two high, six moderate and one low quality trials relevant to knee osteoarthritis. The authors concluded that there was moderate evidence for manipulative therapy of the hip combined with multimodal or exercise therapy for short-term treatment of hip osteoarthritis but limited evidence with respect to long term effects. There was moderate evidence for manipulative therapy of the knee and/or full kinetic chain combined with multimodal or exercise therapy for short-term treatment of hip osteoarthritis but limited evidence with respect to long term effects.

French 2011[237] conducted a systematic review investigating the effectiveness of manual therapy alone in hip or knee osteoarthritis. The authors did not include any studies over and above those reported in the Bronfort report. There was moderate evidence that manual therapy was more effective than exercise in patients with hip osteoarthritis in the short and long term. Overall, there was inconclusive evidence regarding the effectiveness of manual therapy in hip or knee osteoarthritis.

A systematic review by Jansen 2011[238] compared strength training or exercise alone with exercise therapy with passive manual mobilisation in patients with knee osteoarthritis. Two relevant RCTs involving manual therapy and exercise versus usual care were included (van Baar 1998, Deyle 2000).[239;240] The quality ratings of the two trials were 7 and 5 of 9. In a meta-analysis, both pain and function were significantly improved in the groups receiving both exercise and manual mobilisations compared to control (effect size 0.69, 95% CI: 0.41, 0.97 for pain and 0.39, 95% CI: 0.01, 0.77). The review authors concluded that exercise therapy plus manual mobilisation showed a moderate effect size on pain compared to the small effect sizes for strength training or exercise therapy alone and that to achieve better pain relief in patients with knee osteoarthritis physiotherapists or manual therapists might consider adding manual mobilisation to optimise supervised active exercise programmes.

Evidence summary. There is moderate positive evidence for manual mobilisation combined with exercise for knee osteoarthritis. There is moderate positive evidence for manipulation / mobilisation for hip osteoarthritis.

Patello-femoral pain syndrome

One systematic review concerned with the treatment of patellofemoral pain using manual therapy (published after the date of our main search) was identified. Brantingham 2012[97] conducted a

systematic review (review update) of manipulative therapy for lower extremity conditions. They identified two high, five moderate and two low quality trials concerning manual therapy for patellofemoral pain syndrome and concluded that there was moderate evidence for manual therapy (mobilisation / manipulation) of the knee and/or full kinetic chain and of the ankle and/or foot, combined with multimodal or exercise therapy and limited evidence regarding long term effects.

Evidence summary. There was moderate positive evidence for manipulation / mobilisation combined with exercise therapy in patellofemoral pain syndrome (no change from the Bronfort report).

Headache and other conditions

Migraine

Two new systematic reviews were identified on the treatment of migraine using manual therapy (Chaibi 2011, Posadzki 2011).[241;242] Neither of these included any relevant primary studies in addition to those included in the Bronfort report (Nelson 1998, Parker 1978 and Tuchin 2000 included by both).[243-245] Chaibi 2011 concluded that the current RCT evidence suggests that chiropractic spinal manipulative therapy might be as effective as propranolol and topiramate in the prophylactic management of migraine but that because of the methodological shortcomings of the included studies further high quality RCTs are needed to confirm these findings. Posadzki 2011 concluded that there was currently no evidence to support the use of spinal manipulations for the treatment of migraine headaches (based on no significant difference between manipulation groups and other active interventions; however, improvements over time were seen in all intervention groups).

Evidence summary. While we recognise that there are considerable limitations in the evidence, and in the light of the fact that there were no new primary studies, we confirm Bronfort's conclusion that there is moderate positive evidence for the use of spinal manipulative therapy in migraine (based both on the evidence presented in the present section and the evidence presented in the section on miscellaneous headaches).

Table 3. Evidence summary

Condition	Intervention	Bronfort evidence			New / additional evidence			New evidence?
		Inconclusive	Moderate	High	Inconclusive	Moderate	High	
Musculoskeletal								
Spinal								
Low back pain	Combined chiropractic treatment					positive		yes
• (acute)	Spinal manipulation / mobilisation		positive			positive		yes (?)
• (chronic)				positive		positive		yes (?)
Sciatica / radiating leg pain	Spinal manipulation / mobilisation	favourable			favourable			yes
Neck pain (acute / subacute / chronic)	Cervical spinal manipulation / mobilisation alone	favourable			favourable			yes
	Manipulation and mobilisation with / without soft tissue treatment				favourable			yes
	Thoracic spinal manipulation / mobilisation alone		positive		favourable			yes
	Manipulation / mobilisation with exercise		positive			positive		yes
Whiplash-associated disorder • (acute)	Mobilisation with exercise		positive			positive		no
• (subacute)	Cervical / thoracic manipulation				favourable			yes
• (chronic)	Chiropractic cervical manipulation				unclear			yes
	Cranio-sacral therapy				unclear			yes
Mid back pain	Spinal manipulation	favourable			favourable			no
Coccydynia	Spinal manipulation	favourable			favourable			no
Temporomandibular disorders	Mobilisation / massage	favourable			favourable			no
	Mandibular manipulation				unclear			yes
	Intra-oral myofascial therapy				favourable			yes
	Osteopathic manual therapy (cervical and temporomandibular joint regions)				favourable			yes
Myofascial pain syndrome	Ischaemic compression				favourable			yes
• (active upper trapezius trigger points, neck pain)	Trigger point release				non-favourable			yes
	Integrated neuromuscular inhibition technique				favourable			yes
Upper extremity disorders								
Carpal tunnel syndrome	Mobilisation	favourable			favourable			no
	Trigger point therapy	favourable			favourable			yes
	Diversified chiropractic care				unclear			yes
	Neurodynamic technique				unclear			yes

Condition	Intervention	Bronfort evidence			New / additional evidence			New evidence?
		Inconclusive	Moderate	High	Inconclusive	Moderate	High	
	Soft tissue mobilisation (with or without Graston instrument)				unclear			yes
Lateral epicondylitis	Manipulation	non-favourable			non-favourable			no
	Manual tender point therapy	favourable			favourable			no
	Mobilisation with exercise	favourable			favourable			
Shoulder disorders • (shoulder girdle pain / dysfunction)	Manipulation / mobilisation (mobilisation with movement)		positive			positive		no
• (rotator cuff disorder)	Manipulation / mobilisation (with exercise)	favourable				positive		yes
• (adhesive capsulitis)	High grade mobilisation		positive			positive		no
	Mobilisation with movement				favourable			yes
	Osteopathy (Niel-Asher technique)				favourable			yes
	Manual therapy with exercise				favourable			yes
• (minor neurogenic shoulder pain)	Cervical lateral glide mobilisation and / or high velocity low amplitude manipulation with soft tissue release and exercise				favourable			yes
• (soft tissue shoulder disorders)	Myofascial treatments (ischaemic compression, deep friction massage, therapeutic stretch)					positive		yes
Lower extremity disorders								
Ankle sprains	Manipulation / mobilisation	favourable			favourable			no
	Muscle energy technique				favourable			yes
Ankle fracture rehabilitation	Mobilisation		negative			negative		no
	Kaltenborn-based manual therapy				favourable			yes
Morton's neuroma / metatarsalgia	Manipulation / mobilisation	favourable			favourable			no
Hallux limitus	Manipulation / mobilisation	favourable			favourable			no
Plantar fasciitis	Manipulation / mobilisation with exercise		positive			positive		no
	Trigger point therapy				favourable			yes
Hallux abducto valgus	Manipulation / mobilisation	favourable			favourable			yes
Hip osteoarthritis	Manipulation / mobilisation		positive			positive		yes
Knee osteoarthritis	Mobilisation with exercise		positive			positive		yes
Patellofemoral pain syndrome	Manipulation / mobilisation with exercise		positive			positive		yes
Headache and other								
Cervicogenic headache	Spinal manipulation		positive			positive		no

Condition	Intervention	Bronfort evidence			New / additional evidence			New evidence?
		Inconclusive	Moderate	High	Inconclusive	Moderate	High	
	Self-mobilising apophyseal glides		positive			positive		no
	Friction massage and trigger points	non-favourable			non-favourable			no
	Mobilisation	unclear				positive		yes
Migraine headache	Spinal manipulation		positive			positive		no
Tension-type headache	Spinal manipulation	unclear			unclear			yes
	Osteopathic care				favourable			yes
	Spinal mobilisation				favourable			yes
Miscellaneous headache	Mobilisation	favourable				positive		yes
Cervicogenic dizziness	Self-mobilising apophyseal glides		positive			positive		no
	Manipulation / mobilisation				favourable			yes
Balance in elderly people	Diversified chiropractic care				unclear			yes
Fibromyalgia	Spinal manipulation	unclear			unclear			no
	Cranio-sacral therapy	favourable			favourable			yes
	Massage-myofascial release therapy	favourable			favourable			yes
Non-musculoskeletal								
Asthma	Spinal manipulation		negative		unclear			yes
	Osteopathic manual therapy	favourable			favourable			no
	Cranio-sacral therapy				favourable			yes
ADHD	Osteopathic treatment				unclear			yes
Cancer care	Chiropractic care				unclear			yes
	Manipulation in osteosarcoma					negative		yes
Cerebral palsy	Osteopathic manual therapy (cranio-sacral, cranial, myofascial release)				unclear			yes
Chronic fatigue syndrome / myalgic encephalomyelitis	Osteopathic manual therapy				favourable			yes
Chronic pelvic pain • (interstitial cystitis / painful bladder syndrome / chronic prostatitis)	Myofascial therapy				favourable			yes
• (chronic pelvic pain in women)	Distension of painful pelvic structures				favourable			yes
• (chronic prostatitis / chronic pelvic pain)	Osteopathic manual therapy				favourable			yes
Cystic fibrosis	Mobilisation				unclear			yes

Condition	Intervention	Bronfort evidence			New / additional evidence			New evidence?
		Inconclusive	Moderate	High	Inconclusive	Moderate	High	
Paediatric dysfunctional voiding	Osteopathic manual therapy				favourable			yes
Paediatric nocturnal enuresis	Spinal manipulation	favourable			favourable			no
	Chinese pinching massage				favourable			yes
Infant colic	Spinal manipulation		negative			negative		no
	Cranial osteopathic manual therapy	favourable			favourable			no
Dysmenorrhoea	Spinal manipulation		negative			negative		no
Premenstrual syndrome	Spinal manipulation	unclear			unclear			no
Menopausal symptoms	Fox's low force osteopathic technique plus cranial techniques				favourable			yes
Gastrointestinal disorders • (reflux disease, duodenal ulcer)	Spinal manipulation				unclear			yes
• (irritable bowel syndrome)	Osteopathic manual therapy				favourable			yes
Hypertension • (stage 1 hypertension)	Spinal manipulation added to diet		negative			negative		no
• (stage 1 hypertension)	Upper cervical (NUCCA) spinal manipulation	favourable			favourable			no
	Instrument assisted spinal manipulation	unclear			unclear			no
	Osteopathic manual therapy				unclear			yes
	Gonstead full spine chiropractic care				unclear			yes
Intermittent claudication	Osteopathic manual therapy				favourable			yes
Insomnia	Spinal manipulation				unclear			yes
Otitis media	Osteopathic manual therapy	unclear			unclear			no
Parkinson's disease	Osteopathic manual therapy				favourable			yes
Pneumonia in elderly adults	Osteopathic manual therapy	favourable			favourable			no
COPD in elderly adults	Osteopathic manual therapy				unclear			yes
Back pain during pregnancy	Spinal manipulation				favourable			yes
Care during labour / delivery	Spinal manipulation				unclear			yes
Care of preterm infants	Physiotherapeutic / osteopathic manual therapy				unclear			yes
Surgery rehabilitation	Osteopathic manual therapy				favourable			yes
Stroke rehabilitation	Mobilisation				unclear			yes
Systemic sclerosis	McMennell joint manipulation				unclear			yes

Adverse events

Seven systematic reviews (Carnes 2009, Carnes 2010, Carlesso 2010, Gouveia 2009, Stevinson 2002, Stuber 2012, Haldeman 1999, Miley 2008)[46;49;52;53;246-249] and seven primary studies (Boyle 2008, Hayes 2006, Alcantara 2009, Choi 2011, Miller 2008, Rajendran 2009, Sweeney 2010)[250-256] were identified for this section. The systematic review by Carnes and colleagues was published as a technical report (Carnes 2009)[246] and journal article (Carnes 2010).[46] Of the seven primary studies, four were retrospective/prospective cohort studies (Boyle 2008, Hayes 2006, Miller 2008, Rajendran 2009),[250;251;254;255] one case series (Choi 2011),[253] and two cross-sectional surveys (Alcantara 2009, Sweeney 2010).[252;256]

In their publication, Carlesso and colleagues (Carlesso 2010),[53] systematically reviewed the literature on adverse events associated with the use of cervical manipulation and mobilisation in adults with neck pain (medium quality). The authors searched five bibliographic databases, three trial registries, and grey literature sources (e.g., conference proceedings, International Federation of Manual Therapists) from 1998 to 2009. The review included 14 randomised studies and three observational cohort studies. The studies were assessed for quality using the Cochrane tool (randomised trials) and Modified Critical Appraisal Skills Program Form (CASP; cohort studies), and the McHarm scale for adverse events. For manipulation versus control, two meta-analyses showed increased rate of transient neurological symptoms (RR=1.96, 95% CI: 1.09, 3.54) and similar rate for increased neck pain (RR=1.25, 95% CI: 0.84, 1.87). The authors were unable to draw definitive conclusions regarding the occurrence of adverse events after manipulation due to the paucity, bias, and low quality of reported evidence.

Carnes and colleagues (Carnes 2009, Carnes 2010)[46; 246] conducted a high quality comparative systematic review of harms reported (up to March 2008) and published in prospective studies of manual therapy. This review compared the risk of adverse events (defined as major, moderate, and minor) between manual therapy and other alternatives from 8 cohort studies (22898 participants) and 31 RCTs (5060 participants). None of the studies documented the occurrence of death, cerebrovascular accidents, or stroke. The meta-analyses of randomised trials suggested an increased risk of mild (short-term and mild intensity) to moderate adverse events (medium to long term; moderate intensity) in manual therapy versus general practitioner care (pooled RR=1.91, 95% CI: 1.39, 2.64). The risk of mild to moderate adverse events in manual therapy groups was similar to that in exercise (pooled RR=1.04, 95% CI: 0.83, 1.31) or placebo groups (pooled RR=1.84, 95% CI: 0.93, 3.62). The risk of mild to moderate adverse events was significantly lower in manual therapy versus drug therapy (pooled RR=0.05, 95% CI: 0.0, 0.20). None of the RCTs documented any major adverse event. The incidence of major adverse events after manual therapy as reported in the cohort studies was 0.007%. In the cohort studies, the pooled incidence of mild to moderate adverse events after manual therapy was 41.00% (95% CI: 17.00, 68.00). Most adverse events occurred within 24 hours of treatment.[246] The annual risk of stroke associated with cervical manipulation was estimated to be around 1 per 50,000 to 100,000 patients.[246]

In their systematic review of medium quality, Gouveia and colleagues (Gouveia 2009)[49] summarised the evidence on safety of chiropractic interventions (spinal manipulation) from a randomised trial, two case-control studies, 6 cohort studies, 12 surveys, and 100 case reports. The authors searched two bibliographic databases (Pubmed and Cochrane Library) from 1966 to 2007. No formal quality assessment of included studies was reported. One included RCT showed a statistically non-significant

risk of any adverse events for manipulation versus mobilisation (OR=1.44, 95% CI: 0.85, 2.43). One case-control study indicated a statistically significant association between manipulation and vertebral artery dissections (VAD) within 30 days (OR=6.62, 95% CI: 1.4, 30.0) or pain before stroke (OR=3.76, 95% CI: 1.3, 11.0). The frequency of adverse events ranged from 33% to 61% most of which were benign and transitory. Life-threatening events such as stroke and death were estimated to be 5 per 100,000 manipulations and 2.68 per 10,000,000 per manipulations, respectively.

To explore the risk factors of vertebrobasilar artery dissection, Haldeman and colleagues (Haldeman 1999)[248] conducted a systematic review (low quality) of such case reports published in English language between 1966 and 1993. The authors searched 3 relevant databases; identified, and included 367 case reports, of which 115 (31%) had occurred after the administration of cervical manipulation. The remaining 160 (43%) and 95 (26%) cases were due to spontaneous onset and trauma, respectively. Seventy reports (61%) of the primary case reports occurring after cervical manipulation failed to provide any description of manipulation procedure used. Of the 45 reports providing this description, 26 cases were associated with rotation (with or without extension/flexion) and 5 cases with twisting movements. The remaining 14 cases were reported after traction, passive mobilisation, thrust with traction, violent jerking, stretch-twist, and flexion-extension procedures. The paucity of information due to underreporting and inconsistent patterns of risk factors prevented the authors from ascertaining what type of manipulation or procedure is most likely to cause vertebrobasilar artery dissection.

Miley and colleagues (Miley 2008)[249] conducted a systematic review of evidence to explore a causality of association between cervical manipulative therapy and vertebral artery dissection (VAD) with subsequent stroke. Three relevant electronic databases were searched from 1950 to 2007. The review included one systematic review, eight cohort studies, three case-control studies, four case reports, and one survey. To evaluate the evidence, the authors applied the Bradford Hill's seven criteria for causation. Five (dose response, large effect, consistency, biologic plausibility, and temporal sequence) of the seven criteria for causation were met and supported weak to moderate strength of evidence suggesting a causal association between cervical manipulative therapy and VAD with associated stroke.

In a systematic review (low quality) by Stevinson and colleagues (Stevinson 2002),[52] evidence on adverse events associated with spinal manipulation was summarised from systematic reviews, cohort studies, case-control studies, case series, case reports, and surveys. The authors searched three relevant electronic databases from inception to 2001, contacted experts, and scanned reference lists of potentially relevant reports. The review found that minor transient adverse events occurred in about half of the patients receiving spinal manipulation, the most common event being local discomfort, headache, tiredness, and dizziness. The incidence of serious adverse events based on case series and case reports was estimated to range from one event per 1,000,000-2,000,000 participants to one event per 400,000 participants. The most common serious adverse events were vertebrobasilar accidents, disc herniation, and cauda equine syndrome.

Stuber and colleagues (Stuber 2012)[247] systematically reviewed the evidence on adverse events after spinal manipulation in women during pregnancy and postpartum periods (medium quality). The authors searched three relevant electronic databases (from inception to 2011) to identify English- and French-language peer reviewed publications. Systematic reviews, randomised trials, cohort studies, case-control studies, case series, case reports, and surveys were eligible for inclusion in the review. Conference proceedings, cross-sectional, descriptive studies, and narrative reviews were excluded. The study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) tools.

The authors included two systematic reviews, one prospective cohort study, and four case reports. The majority of study participants had neck, headache, and/or low back pain. Of the two included systematic reviews, one reported the absence of adverse events and the other reported a case report with an adverse event. In the cohort study of 78 pregnant women receiving spinal manipulation, three (3.8%) experienced increased pain. According to the four case reports, women 23-38 years of age were treated with spinal manipulation and subsequently experienced memory loss, vertigo, swelling/neck pain, and lower extremity numbness/neck pain. There is paucity of data on adverse events after spinal manipulation in women during pregnancy or postpartum periods. This could be explained by the rarity of such events.

In one ecological cohort study (low quality), Boyle and colleagues (Boyle 2008)[250] attempted to determine if at an ecological level, the annual rates of chiropractor utilisation were associated with annual incidence rates of hospitalisations with vertebrobasilar artery (VBA) stroke in two Canadian Provinces (Ontario and Saskatchewan) between 1993 and 2004. All incident cases for the period of 1993-2004 were ascertained from hospital discharge data. Yearly population estimates were used as denominators to calculate incidence rates. The rates of chiropractic utilisation (annual number of encounters per chiropractor and annual number of services provided by chiropractor) were calculated separately for Ontario (data from Ontario Ministry of Health and Long-Term Care) and Saskatchewan (data from Chiropractic Association of Saskatchewan). The crude cumulative incidence rates of hospitalisation due to VBA stroke during 1993-2002 for Ontario and Saskatchewan were 0.750 and 0.855 per 100,000 person-years, respectively. The incidence in both Provinces was higher for men versus women (ranges; 0.964-1.545 versus 0.542-0.559) and for individuals aged 45 years or older versus individuals younger than 45 years (ranges; 1.846-2.184 versus 0.145-0.098). In 2000, there was a 360% (up to 1.8 per 100,000 population) and 38% (up to 1.0 per 100,000 population) increase in annual incidence of VBA stroke hospitalisations in Saskatchewan and Ontario, respectively. During the study period, there was no change in chiropractic utilisation rates for Saskatchewan. However, for Ontario, during the same period, a steady decline in the utilisation rates was observed. The authors concluded that at ecological level, there was no association between the chiropractic utilisation rates and annual incidence of VBA stroke.

In one cohort study (low quality), Hayes and colleagues (Hayes 2006)[251] retrospectively reviewed medical records of 346 paediatric patients (19 years or younger) who had paid at least two visits to osteopathic manipulative medicine offices. The patients were retrospectively followed-up for the incidence of treatment-associated aggravations (post-treatment worsening of symptoms or complaints) and treatment-associated complications (cerebrovascular accidents, dislocation, fracture, pneumothorax, sprains/strains, or death). The outcomes were determined subjectively (patient- or parent-based reports) and objectively (through physical examinations). The most frequent diagnoses of the study population were otitis media (10.6%), developmental delay (6.7%), well check (6.0%), plagiocephaly (5.6%), scoliosis (5.0%), and asthma (4.8%). Other less prevalent conditions were attention deficit hyperactivity disorder (ADHD), migraine, allergies, and reflux. The treatment consisted of cranial manipulation, myofascial release/soft tissue technique, or both. During the follow-up, no treatment-associated complications were documented. Of the 346 patients, 31 (9.0%) experienced at least one manipulation-associated aggravation. The average number of office visits in this subgroup was greater than 13 with a median of 8. The most frequent manipulation-associated aggravations were worsening symptoms (2.0%), behaviour problems (1.4%), irritability (1.4%), pain (1.2%), and soreness (1.2%). The frequency of remaining events (e.g., headache, dizziness, tiredness, flu-like symptoms) was under 1.0%. The authors concluded that in paediatric patients the incidence of

iatrogenic reactions after osteopathic manipulation is low and this treatment appears to be safe if administered by physicians specialised in osteopathic manipulation.

Miller and colleagues (Miller 2008)[254] conducted a retrospective uncontrolled cohort study (low quality) of 697 pediatric patients younger than 3 years (colic, irritability, birth trauma), visiting a chiropractic clinic. The authors documented parent-reported adverse events that occurred in the children after they had received paediatric spinal manipulative therapy (PSMT). No parent reported serious adverse event. Parents of seven of 697 (1.0%) children reported an adverse event (increased crying for six children and not feeding well/mild distress for one child). The reported events were mild-and transient in nature, not requiring medical care.

In a cohort study (low quality) by Rajendran and colleagues (Rajendran 2009),[255] the authors prospectively followed 60 adult patients with spinal pain and/or reduced mobility treated with osteopathic manual techniques (e.g., high velocity low amplitude manipulation, muscle energy, massage, counterstrain, cranial manipulation) to document the occurrence of adverse events following the treatment. At the last post-treatment follow-up (7 days), there were a total of 535 reported adverse events (based on responses of 47 patients). Of all 535 reports, the most commonly reported events were local pain (24.3%), local stiffness (18.3%), and worsening of presenting complain (11.8%). The authors could not analyse the adverse event data according to type of treatment because the patients received mixture of different manual techniques.

In a population-based case-series study, Choi and colleagues (Choi 2011),[253] using administrative health records, reviewed and described demographic characteristics, health care utilisation, and co-morbidities of 93 VBA stroke cases hospitalised between April 1993 and March 2002. All 93 patients had consulted a chiropractor within the year before their stroke. The mean age of the study sample was 57.6 years and 49.5% were females. About 96% of the cases had consultations with a primary care physician and 75.3% had one or more co-morbidities. The most frequent co-morbidities one year within the stroke were neck pain and headaches (66.7%, 95% CI: 57.0, 76.3), disease of circulatory system (63.4%, 95% CI: 54.8, 74.2), and disease of nervous system (47.3%, 95% CI: 38.7, 58.1). The prevalence of cardiovascular and cerebrovascular disease was similar between the cases who had visited chiropractor a month before their stroke versus those who had visited chiropractor more than one month before their stroke (p=0.13).

Sweeney and colleagues (Sweeney 2010),[256] conducted a survey to ascertain the use of manual therapy (i.e., manipulation and mobilisation) by the Irish chartered physiotherapists and describe adverse events associated with the use of these techniques. This was a postal survey, which included a 44-item self-administered questionnaire with 4 sections on demographic data, use of High Velocity Thrust Techniques (HVTT), use of non-HVTT techniques, and the occurrence of adverse events. The reminders were sent to non-responders 4 weeks after the initial survey. Of the 259 surveyed physiotherapists, 127 (49%) responded with complete information. All 127 (100%) responders used non-HVTT and 34 (27%) used HVTT. Ninety-nine (78%) of the non-HVTT group practitioners reported to have used cervical traction. Eighteen (53%) of the responders administering HVTT and 44 (40%) of those administering non-HVTT techniques reported to have performed the assessment of vertebrobasilar insufficiency (VBI). Of the 127 responders, 33 (26%) reported an adverse event in the previous 2 years. According to the type of technique administered, of the 34 responders using HVTT technique, 5 (15%) reported an adverse event (mostly of mild nature) and of the 127 responders using non-HVTT technique, 26 (20%) reported an adverse event (mostly mild but three serious adverse events such as drop attack, fainting, transient ischemic attack). Of the 99 responders who used cervical

traction, 2 (2%) reported an adverse event (speaking gibberish, awake but non-responsive/talk with difficulty).

In a study conducted by Alcantara and colleagues (Alcantara 2009),[252] the authors surveyed 21 chiropractors and 239 parents of paediatric patients (aged 18 years or younger) to evaluate the safety of paediatric chiropractic. The survey sent to chiropractors included information on patient demographic data (e.g., age, gender, number of visits), presenting complaints, chiropractic technique/spinal regions used for patient care, treatment-associated aggravations (defined as worsening of symptoms or complaints following treatment), and treatment-associated complications (defined as cerebrovascular accidents, dislocation, fracture, pneumothorax, sprains/strains, or death as a result of treatment). The parent survey included information on parents'/guardians' gender, age, level of education as well as treatment-associated aggravations, and treatment-associated complications. The chiropractors' survey provided by 21 chiropractors included data on 577 patients with the following clinical presentation: wellness care (46%), musculoskeletal complaints (26%), digestion/elimination problems (7%), ear/nose/throat problems (6%), neurological problems (6%), immune dysfunction (5%), and other (4%). The chiropractic techniques used were regional or full spine manipulation using diversified technique, Gonstead technique, Thompson technique, activator methods, cranial techniques, and others. The chiropractors' survey revealed three reports of treatment-associated aggravations (based on 5,438 visits) such as 'muscle stiffness,' 'spine soreness through the seventh visit,' and 'stiff/sore'. No treatment-associated complications were reported. The parent survey provided by 239 parents/guardians, included data on 239 patients with the following clinical presentations: wellness care (47%), musculoskeletal complaints (22.6%), ear/nose/throat problems (4.2%), neurological problems (3%), colic (2.5%), immune dysfunction (1.2%), digestion/elimination problems (3.7%), birth trauma (2.9%), and other (10.9%). The parent survey revealed two reports of treatment-associated aggravations (soreness of the knee and stiffness of the cervical spine). There was no report of treatment-associated complications.

Evidence summary. This review is an appraisal and summary of evidence on safety of spinal/cranial manual therapy (chiropractic manipulation, osteopathic manipulation, mobilisation, and other techniques) in adults and children from seven systematic reviews,[46;49;52;53;246-249] four retrospective/prospective cohort studies,[250;251;254;255] one case-series,[253] and two cross-sectional surveys.[252;256] This section summarises evidence on harms additional to that presented in the Bronfort report.[40] In their report, Bronfort and colleagues categorised adverse events into two groups: minor/non-serious (mild-to-moderate intensity of transient nature) and serious/major adverse events.

In general, the findings of this review are in agreement with those of the previous research[40] in showing that, with manual therapy, mild-to-moderate adverse events of transient nature (e.g., worsening symptoms, increased pain, soreness, headache, dizziness, tiredness, nausea, vomiting) are relatively frequent. For example, the reviewed evidence from high,[46;246] medium,[49] and low[52] quality systematic reviews has indicated that about half of the individuals receiving manual therapy had experienced mild-to-moderate adverse event which had resolved within 24-74 hours. The reviewed evidence, in agreement with the Bronfort report, has also indicated that serious (or major) adverse events after manual therapy are very rare (e.g., cerebrovascular events, disc herniation, vertebral artery dissection, cauda equine syndrome, stroke, dislocation, fracture, transient ischemic attack). Evidence on safety of manual therapies in children or paediatric populations is very scarce; the findings from two low quality cohort studies and one survey are consistent with those for adults indicating that transient mild to moderate intensity adverse events in manual treatment practice occur relatively commonly compared to more serious or major adverse events which are very rare.

There is relative paucity of comparative safety data even for mild-to-moderate adverse events. In a series of recent meta-analyses of adverse events reported in randomised trials,[46;246] the use of manipulation was associated with a reduced risk compared to drug therapy, similar risk compared to placebo or exercise, and a higher risk of adverse events compared with GP care.
There has been much uncertainty and variability around the incidence rate estimates of serious adverse events due to the lack of proper denominators, inconsistent definition of the outcomes, use of data collection tools of different validity, inaccurate number of events (due to underreporting and/or losses to follow-up), and deficient study design (e.g., case series, case reports, ecological cohort study, questionnaire surveys).[49;52;246;249;250]

Although previous epidemiological studies showed an association between chiropractic manipulation and an increased risk of vertebrobasilar artery (VBA) stroke, more recent research has suggested that this association is non-causal.[253] Specifically, the alternative explanation for the observed associations is that patients with early symptoms of VBA stroke (neck pain, headache) are more likely to visit chiropractors than those without such symptoms.

Since chiropractors and other practitioners use a combination of different manual techniques, it is difficult to ascertain which type of technique is associated with an increased risk of serious adverse events. Some low quality survey-based evidence suggested that cervical non-high velocity thrust techniques were associated with more serious adverse events compared to high velocity thrust techniques.[256] In the systematically reviewed case-report studies, the use of cervical manipulation with rotational and twisting movements has been implicated in association with serious adverse events.[246;248]

The evidence on adverse events in manual therapy warrants a cautious interpretation due to relative paucity of evidence and poor methodological quality of the included primary studies. Most reports of serious adverse events have been based on low quality retrospective cohort studies, case-control studies, case reports, case-series, and cross-sectional surveys. Given these study designs, it is difficult, if impossible, to establish causality between the use of manual therapy and the occurrence of adverse event. The interpretation of results of such studies is complicated by the potential of selection/measurement bias, unknown temporality, inadequate follow-up length, invalid data collection tools, attrition bias, underreporting, or subjective reports of outcomes. Moreover, some unaccounted risk factors (e.g., arterial diameter, unusual headache, migraine, neck pain, recent trauma, history of cardiovascular disease) may increase the risk of adverse events independently of manual therapy and thus lead to spurious association between the treatment and the adverse event or obscure this association through confounding and/or effect modification.

Systematic reviews

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Carlesso 2010[53] **Focus:** To explore, assess, and synthesise the risk of adverse events associated with cervical manual therapies (manipulation, mobilisation) in adults with neck pain **Quality of systematic review:** medium	**INCLUSION CRITERIA** **Study design:** randomised trials, non-randomised trials, cohort studies, and cross sectional surveys **Participants:** adults with neck pain/disorders with radicular findings or cevicogenic headache receiving manual therapies **Interventions**: manual interventions including cervical manipulation (high velocity low amplitude force applied to the cervical vertebrae) and mobilisation (low velocity manual force applied with varying amplitude to the cervical vertebrae or soft tissue techniques) **Outcomes:** any adverse events following manual treatment **METHODOLOGY** 5 relevant databases and 3 trial registries searched from 1998 to 2009 without language restriction; hand search of reference lists for grey literature; details on study selection; quality assessment of studies presented; excluded studies and reasons for exclusions are listed; evidence was graded for strength (high, moderate, low, very low) **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 14 randomised trials (Bronfort 2001, Chen 2007, Dziedzic 2005, Evans 2003, Haas 2003, Haas 2004, Hoving 2002, Hurwitz 2004, Jull 2002, Kanlayanaphotporn 2009, Mayor 2008, McReynolds 2005, Strunk 2008, Zhi 2008) and three cohort studies (Cagnie 2004, Rubinstein 2007, Thiel 2007) **Study quality:** the Cochrane tool (RCTs), a modified Critical Appraisal Skills Program (CASP) form (cohort studies), and the McHarm scale (adverse events) **Study characteristics:** Chronic neck pain (5 studies), acute/subacute neck pain (1 study), subacute and chronic neck pain (4 studies), mixed duration neck pain (5 studies), duration not specified (2 studies); cervicogenic headache (3 studies), mechanical neck pain (6 studies), non-specific neck pain (6 studies); RCTs had moderate to high risk for harms quality **Excluded studies eligible for current review:** not reported	**RESULTS** <u>Manipulation versus control</u> Transient neurological symptoms RR=1.96, 95% CI: 1.09, 3.54 Neck pain RR=1.25, 95% CI: 0.84, 1.87 **CONCLUSIONS** The authors were unable to draw definitive conclusions regarding the occurrence of adverse events after manipulation due to the paucity, bias, and low quality of reported evidence

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Carnes 2009[246] Carnes 2010[46] **Focus:** To explore and provide prevalence, incidence, and risk of adverse events associated with manual therapies; provide definitions and characterise the nature of adverse events **Quality of systematic review:** high	**INCLUSION CRITERIA** **Study design:** systematic reviews, randomised/non-randomised trials, cohort studies, case-control studies, and case series **Participants:** children and adults receiving manual therapies **Interventions**: manual interventions that involve physical contact excluding any mechanical devices including manipulation (high velocity and small/large amplitude), mobilisation (low grade velocity and small/large amplitude, neuromuscular/cranio-sacral techniques), and massage **Outcomes:** adverse events **METHODOLOGY** 12 relevant databases searched from inception to 2008; hand search of reference lists; details on study selection; quality assessment of studies presented; excluded studies and reasons for exclusions are listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 17 reviews (systematic, non-systematic), 31 randomised trials, 9 cohort studies (prospective), and 34 other study designs (surveys, retrospective, cross-sectional, and case series) **Study quality:** a modified Critical Appraisal Skills Programme (CASP) for non-randomised studies; Koes's criteria (1995) for quality appraising of randomised trials; specific adverse event quality criteria was also used **Study characteristics:** included studies reporting adverse events ranged in quality and design and represented surveys, case notes, observational studies (cross-sectional, retrospective, and prospective cohort). The quality score of randomised trials ranged from 58-70. About half of the studies were conducted by chiropractors; 13 studies were done by neurologists and medics, 8 studies by physiotherapists, and 3 studies by osteopaths; studies were conducted in Europe (n=18),UK (n=6), USA/Canada (n=15), and Australia/New Zealand (n=4). Most studies focused on spinal manipulation. **Excluded studies eligible for current review:** not reported	**RESULTS** No deaths, cerebrovascular accidents or stroke were reported in any randomised study or prospective cohort study <u>RCTs</u> • Mild to moderate adverse events in manual therapy versus general practitioner care (pooled RR=1.91, 95% CI: 1.39, 2.64) • Manual therapy versus exercise (pooled RR=1.04, 95% CI: 0.83, 1.31) • Manual therapy versus placebo (pooled RR=1.84, 95% CI: 0.93, 3.62) • Manual therapy versus drug therapy (pooled RR=0.05, 95% CI: 0.0, 0.20) <u>Cohort studies</u> • The incidence of major adverse events: 0.007%. • The pooled incidence of mild to moderate adverse events 41.00% (95% CI: 17.00, 68.00). • The annual risk of stroke associated with cervical manipulation was estimated to be around 1 per 50,000 to 100,000 patients **CONCLUSIONS** The risk of major events (e.g., death, vascular event) in individuals receiving manual therapy is very low, lower than from taking medication; about half of the subjects receiving manual therapy experience mild to moderate adverse events 24-72 hours after intervention; the risk of events with manual therapy is lower than that with drug therapy but higher than usual care

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Gouveia 2009[49] **Focus:** To explore, assess, and synthesise the risk of adverse events associated with chiropractic techniques (manipulation) **Quality of systematic review:** medium	**INCLUSION CRITERIA** **Study design:** randomised trials, cohort studies, case-control studies, case reports, and surveys **Participants:** patients who received chiropractic spinal manipulation **Interventions**: chiropractic spinal manipulation **Outcomes:** any adverse events following chiropractic spinal manipulation **METHODOLOGY** 2 relevant databases searched from 1966 to 2007 without language restriction; hand search of reference lists details on study selection; quality assessment not presented; excluded studies and reasons for exclusions not listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 1 randomised trial (Hurwitz 2004), 6 cohort studies (Rivett 1996, Senstad 1996, Leboeuf-Yde 1997, Senstad 1997, Barrett 2000, Cagnie 2004), 12 surveys (Gutmann 1983, Dvorak 1985, Michaeli 1993, Carey 1993, Haynes 1994, Lee 1995, Coulter 1996, Klougart 1996, Lynch 1998, Stevinson 2001, Duperyon 2003, Reuter 2006) **Study quality:** not presented **Study characteristics:** randomised study conducted in USA; cohort studies of spinal manipulative therapy conducted in New Zealand, Norway, Sweden, UK, Belgium; surveys conducted in Germany, Sweden, South Africa, Australia, USA, Denmark, Ireland, UK, and France **Excluded studies eligible for current review:** not reported	**RESULTS** <u>Frequency of adverse events (benign and transitory)</u> 33% to 61% • Frequency of stroke: 5 per 100,000 manipulations • Frequency of serious adverse events: 1.46 per 10,000,000 per manipulations • Frequency of death:2.68 per 10,000,000 per manipulations <u>RCT (manipulation versus mobilisation)</u> Any adverse events OR=1.44, 95% CI: 0.85, 2.43 <u>Case-control studies</u> Vertebral artery dissections within 30 days OR=6.62, 95% CI: 1.4, 30.0 Pain before stroke OR=3.76, 95% CI: 1.3, 11.0 **CONCLUSIONS** Chiropractic techniques are associated with common occurrence of benign and transitory adverse events; serious adverse events such as stroke are rare as reported in prospective observational studies; the authors were unable to draw definitive conclusions regarding the occurrence of adverse events after manipulation due to the paucity, bias, and low quality of reported evidence

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Haldeman 1999[248] **Focus:** To explore and review types of manipulation techniques associated with vertebrobasilar artery dissection **Quality of systematic review:** low	**INCLUSION CRITERIA** **Study design:** case reports **Participants:** patients with vertebrobasilar artery dissection **Interventions**: spinal manipulation **Outcomes:** any adverse events following chiropractic spinal manipulation **METHODOLOGY** 3 relevant databases (MEDLINE, Chirolars, and Chiropractic Research Abstracts Collection) searched from 1966 to 1993; search was restricted to English publications; hand search of reference lists details on study selection; quality assessment not presented; reasons for exclusions were listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 367 case reports **Study quality:** not presented **Study characteristics:** 160 case reports (spontaneously occurring), 115 case reports (after manipulation), and 95 case reports (trivial and major trauma) **Excluded studies eligible for current review:** not reported	**RESULTS** • Of the 367 cases, 115 (31%) had occurred after the administration of cervical manipulation, 160 (43%) had occurred spontaneously, and 26% after trauma • Only 45 (40%) of the 115 reports of cases associated with manipulation, provided some information on type of procedures used during cervical manipulation, most of which was associated with rotation (26 cases) and twisting movements (5 cases). The remaining 14 cases were associated with traction, passive mobilisation, thrust with traction, violent jerking, stretch-twist, and flexion-extension procedures **CONCLUSIONS** The paucity of information due to underreporting and inconsistent occurrence of specific types of manipulation techniques prevented the authors from ascertaining what type of manipulation or procedure is most likely to cause vertebrobasilar artery dissection

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Miley 2008[249] **Focus:** To systematically review and explore relevant evidence if cervical manipulation causes vertebral artery dissection (VAD) and associated stroke **Quality of systematic review:** low	**INCLUSION CRITERIA** **Study design:** randomised trials, cohort studies, case-control studies, case reports, and surveys **Participants:** patients who received cervical manipulation, patients with VAD/stroke **Interventions**: cervical manipulation **Outcomes:** VAD/stroke **METHODOLOGY** 3 relevant databases (MEDLINE, Embase, CINAHL) searched from 1950 to 2007; evidence was assessed using the Bradford Hill's 7 criteria for causation (dose response, large effect, consistency, biologic plausibility, reversibility, specificity, and temporal sequence); strength of evidence graded (weak, moderate, strong); study quality assessment not presented; excluded studies and reasons for exclusions not listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 1 systematic review (Ernst 2007), 8 cohort studies (Reuter 2006, Dziewas 2003, Haldeman 2002, Hufnagel 1999, Haneline 2003, Saeed 2000, Bousser 2001, Showalter 1997), 3 case-control study (Dittrich 2007, Smith 2003, Rothwell 2001), 4 case reports (Nadgir 2003, Miller 1974, Rothwell 2002, Sherman 1981), 1 survey (Lee 1995) **Study quality:** not presented **Study characteristics:** not reported **Excluded studies eligible for current review:** not reported	**RESULTS** • Five of the seven criteria for causation (dose response, large effect, consistency, biologic plausibility, and temporal sequence) were met and supported weak to moderate strength of evidence suggesting a causal association between cervical manipulative therapy and VAD with associated stroke • In a large case-control study, in younger patients (< 45 years), visits to chiropractors were associated with a higher risk of VAD/stroke (OR=5.03, 95% CI: 1.32, 43.87). The association was not significant in patients 45 years or older • VAD/stroke incidence estimate attributable to cervical manipulation: 1.3 cases per 100,000 persons **CONCLUSIONS** The authors conclude that the weak to moderate strength evidence suggests causal association between the use of cervical manipulative therapy and VAD/stroke

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Stevinson 2002[52] **Focus:** To systematically review evidence on adverse events associated with spinal manipulation **Quality of systematic review:** low	**INCLUSION CRITERIA** **Study design:** systematic reviews, cohort studies, case-control studies, case reports, and surveys **Participants:** patients who received spinal manipulation, patients with adverse events spinal after manipulation **Interventions**: spinal manipulation **Outcomes:** Any adverse event **METHODOLOGY** 3 relevant databases (MEDLINE, Embase, Cochrane library) searched up to 2001; no language restrictions were applied; experts were contacted; reference lists of potentially relevant reports were scanned; study quality assessment not presented; excluded studies and reasons for exclusions not listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 3 systematic reviews (Ernst 2001, Assendelft 1996, Di Fabio 1999), 4 cohort studies (Saeed 2000,Senstad 1997, Leboeff-Yde 1997, Barrett 2000), 1 case-control study (Rothwell 2001), 5 case series (Ole 1999, Rydell 1999, Hufnagel 1999, Beran 2000, Jeret 2000), 17 case reports, 3 surveys (Lee 1995, Lynch 1998, Stevinson 2001) **Study quality:** not presented **Study characteristics:** not reported **Excluded studies eligible for current review:** not reported	**RESULTS** • Minor transient adverse events occurred in about half of the patients receiving spinal manipulation; the most common events were local discomfort, headache, tiredness, and dizziness • The incidence of serious adverse events based on case series and case reports ranges from 1 event per 1,000,000-2,000,000 participants to 1 event per 400,000 participants. The most common serious adverse events were vertebrobasilar accidents, disc herniation, and cauda equine syndrome • In a large case-control study, in younger patients (< 45 years), visits to chiropractors were associated with a higher risk of VAD/stroke (OR=5.03, 95% CI: 1.32, 43.87). The association was not significant in patients 45 years or older **CONCLUSIONS** Although mild-moderate transient adverse events are common after spinal manipulation, serious adverse events are very rare

Study	Inclusion criteria and methodology	Included studies	Results and Conclusions
Stuber 2012[247] **Focus:** To systematically review evidence on adverse events associated with spinal manipulation in women during pregnancy or postpartum periods **Quality of systematic review:** medium	**INCLUSION CRITERIA** **Study design:** Systematic reviews, randomised trials, cohort studies, case-control studies, case series, case reports, and surveys **Participants:** women during pregnancy or postpartum periods after spinal manipulation with or without adverse event **Interventions**: spinal manipulation (high velocity low amplitude) **Outcomes:** Any adverse event **METHODOLOGY** 3 relevant databases (MEDLINE, CINAHL, Index to Chiropractic Literature) searched up to 2011; no language restrictions were applied; reference lists of potentially relevant reports were scanned; English- and French-language peer reviewed publications were eligible; study quality assessed using the Scottish Intercollegiate Guidelines Network (SIGN) tools; excluded studies not listed; reasons for exclusions listed (conference proceedings, cross-sectional, descriptive studies, and narrative reviews) **Data analysis:** text and tables **Subgroups / sensitivity analyses:** not reported	**N included studies:** 2 systematic reviews (Stuber 2008, Khorsan 2009), 1 cohort study (Murphy 2009), 4 case reports (Ng 2001, Parkin 1978, Schmitz 2005, Heiner 2009) **Study quality:** the overall SIGN rating for systematic reviews: "++" (good quality); the overall SIGN rating for the cohort study: "+" (acceptable) **Study characteristics:** The majority of study participants had neck, headache, and/or low back pain. In case reports, women's age ranged from 23 to 38 years. Publication year range: 1978-2009 **Excluded studies eligible for current review:** not reported	**RESULTS** **Systematic reviews** (Stuber 2008, Khorsan 2009) • Absence of adverse events (Stuber 2008) • One case report with adverse event (Khorsan 2009) **Cohort study** (Murphy 2009) • Three women (3/78; 3.8%) experienced increased pain **Case reports** • Memory loss, poor coordination of the right hand, difficulty with articulation, and unsteady gait (Ng 2001) • Vertigo, total occlusion of the left vertebral artery (Parkin 1978) • Swelling/neck pain, type II odontoid fracture with ventral displacement producing spinal cord compression, paravertebral haematoma, a tumour in the C2 vertebral body (Schmitz 2005) • Lower extremity numbness/neck pain, right sided epidural haematoma (Heiner 2009) **CONCLUSIONS** There is paucity of data on adverse events after spinal manipulation in women during pregnancy or postpartum periods. This could be explained by the rarity of such events

Observational studies

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr><td>Cohort studies</td><td></td><td></td></tr>
<tr><td>Boyle 2008[250]
Canada

Focus: to determine if at an ecological level, the annual rates of chiropractor utilisation were associated with annual incidence rates of hospitalisations with vertebrobasilar artery (VBA) stroke in two Canadian Provinces
Duration: NA
Follow-up: 1993-2004
Quality: low

PARTICIPANTS:
N: NA (ecological study)
Age: not reported
Inclusion: hospitalised/discharged with VBA stroke</td><td>Intervention: chiropractic utilisation rate
Comparison: different chiropractic utilisation rates
Dose: NA
Providers: chiropractors</td><td>Results

<table><tr><th>Change in outcome</th><th>Ontario 1993-2002</th><th>Saskatchewan 1993-2002</th></tr><tr><td>N of hospitalisations with VBA stroke</td><td>818</td><td>82</td></tr><tr><td>Crude cumulative incidence per 100,000 person-years</td><td>0.750</td><td>0.855</td></tr><tr><td>Males</td><td>0.964</td><td>1.545</td></tr><tr><td>Females</td><td>0.542</td><td>0.559</td></tr><tr><td>Age <=45 years</td><td>0.145</td><td>0.098</td></tr><tr><td>Age >45 years</td><td>1.846</td><td>2.184</td></tr></table>
<u>Saskatchewan</u>
In 2000, there was 360% increase in annual incidence of VBA stroke hospitalisations (up to 1.8 per 100,000 population); during the study period, chiropractic utilisation rates were stable

<u>Ontario</u>
In 2000, there was 38% increase in annual incidence of VBA stroke hospitalisations (up to 1.0 per 100,000 population); during the study period, chiropractic utilisation rates steadily declined

At ecological level, there was no correlation between the chiropractic utilisation rates and annual incidence of VBA stroke

Specific adverse effects: VBA stroke</td></tr>
</table>

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Hayes 2006[251]
USA

Focus: Effect of osteopathic manipulation treatment (OMT) on in paediatric population (17 years or younger)
Duration: at least two office visits
Follow-up: 1 year
Quality: low

PARTICIPANTS:
N: 346 (50% female)
Age: 7.37 years (SD=5.51)
Inclusion: paediatric patients 19 years or younger with at least two visits to osteopathic manipulative medicine offices</td>
<td>Intervention: OMT consisting of cranial manipulation, myofascial release/soft tissue technique, or both.
Comparison: none
Dose: at least 2 visits to osteopathic physicians
Providers: osteopathic physicians</td>
<td>Results
<table>
<tr><th>OMT associated aggravation</th><th>N of patients</th><th>Incidence % (95% CI)</th></tr>
<tr><td>Worsening symptoms</td><td>7</td><td>2.0 (0.8, 4.1)</td></tr>
<tr><td>Behaviour problems</td><td>5</td><td>1.4 (0.5, 3.3)</td></tr>
<tr><td>Irritability</td><td>5</td><td>1.4 (0.5, 3.3)</td></tr>
<tr><td>Pain</td><td>4</td><td>1.2 (0.3, 2.9)</td></tr>
<tr><td>Soreness</td><td>4</td><td>1.2 (0.3, 2.9)</td></tr>
<tr><td>Headache</td><td>2</td><td>0.6 (0.1, 2.1)</td></tr>
<tr><td>Dizziness</td><td>1</td><td>0.3 (0.0, 1.6)</td></tr>
<tr><td>Flu-like symptoms</td><td>1</td><td>0.3 (0.0, 1.6)</td></tr>
<tr><td>Treatment reaction</td><td>1</td><td>0.3 (0.0, 1.6)</td></tr>
<tr><td>Tiredness</td><td>1</td><td>0.3 (0.0, 1.6)</td></tr>
</table>
Specific adverse effects: no documented treatment-associated complications (cerebrovascular accidents, dislocation, fracture, pneumothorax, sprains/strains, or death)

31 patients had treatment-associated aggravations (9.0%, 95% CI: 6.2, 12.5)

The authors’ conclusion: in paediatric patients, the incidence of iatrogenic reactions after osteopathic manipulation is low and this treatment appears to be safe if administered by physicians specialised in osteopathic manipulation</td>
</tr>
</table>

Study	Interventions	Outcomes
Miller 2008[254] UK **Focus:** To follow-up and document parental reports of adverse events in children younger than 3 years after receiving chiropractic manual treatment **Duration:** 2 years **Follow-up:** Not reported **Quality:** low **PARTICIPANTS:** **N:** 697 (41% female) **Age:** 5-8 weeks (range) **Inclusion:** paediatric patients younger than 3 years with colic and/or irritability presenting to a chiropractic teaching clinic within the study period	**Intervention:** paediatric spinal manipulative therapy (PSMT) applied to full spine, decompression, pelvis, upper/lower extremity, massage, other **Comparison:** no comparison **Dose:** Not reported **Providers:** osteopathic specialists	**Outcomes:** any adverse events reported by a patient's parent **Results** No parent reported serious adverse event; parents of 7 of 697 (1.0%) children reported an adverse event; the events (increased crying for six children and not feeding well/mild distress for one child) were mild-and transient in nature requiring no medical care ***Specific adverse effects:*** crying, not feeding well, mild distress

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr>
<td>Rajendran 2009[255]
UK

Focus: To explore the feasibility of conducting a follow-up study and collecting the most often reported adverse events by patients after receiving osteopathic manual treatment (OMT)
Duration: Not reported
Follow-up: 7 days post-treatment
Quality: low

PARTICIPANTS:
N: 60 (57% female)
Age: mean: 43.5 (SD: 13.0) years; 19-71 years (range)
Inclusion: Adults (> 18 years) with a new complain (pain in lower back, head/neck, upper limb, pelvis/hip buttock, lower limb, upper/mid back, stomach/abdomen, lack of mobility) with no prior manual treatment within the past 6 months</td>
<td>Intervention: OMT consisting of high velocity low amplitude thrust manipulation, direct techniques (articulatory, muscle energy, direct soft tissue), indirect techniques (functional, balanced ligament tension, counterstrain), other techniques (cranial visceral manipulation, Chapman’s reflexes, lymph-pump technique)
Comparison: no comparison
Dose: Not reported (treatment delivery according to normal clinic procedures)
Providers: 4th year osteopathic students</td>
<td>Outcomes: any adverse events (i.e., additional effects of treatment) reported by a patient using a 15-item check-list

Results
<table>
<tr><th>Number of reported adverse events [cumulative]</th><th>7 days of follow-up</th></tr>
<tr><td>Local pain</td><td>130</td></tr>
<tr><td>Local stiffness</td><td>98</td></tr>
<tr><td>Worsening of complain</td><td>63</td></tr>
<tr><td>Radiating pain</td><td>40</td></tr>
<tr><td>Unexpected tiredness</td><td>39</td></tr>
<tr><td>Pain/discomfort</td><td>38</td></tr>
<tr><td>Stiffness/reduced mobility</td><td>32</td></tr>
<tr><td>Headaches</td><td>24</td></tr>
<tr><td>Fainting/dizziness/vertigo</td><td>20</td></tr>
<tr><td>Numbness/tingling (legs/feet)</td><td>17</td></tr>
<tr><td>Muscle weakness</td><td>11</td></tr>
<tr><td>Vision disturbance</td><td>8</td></tr>
<tr><td>Tinnitus</td><td>7</td></tr>
<tr><td>Numbness/tingling (arms/hands)</td><td>5</td></tr>
<tr><td>Nausea/vomiting</td><td>3</td></tr>
<tr><td>Total</td><td>535</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr><td>Case studies</td><td></td><td></td></tr>
<tr><td>Choi 2011[253]
Canada

Focus: To describe demographic characteristics, health care utilisation, and co-morbidities of VBA stroke cases

PARTICIPANTS:
N: 93 (49.5% female)
Age: mean: 57.6 (SD: 16.1) years
Inclusion: patients hospitalised (between April 1993 and March 2002) for VBA stroke, who had consulted a chiropractor within the year before their stroke</td><td>Intervention: chiropractic care within the year before stroke</td><td>Outcomes: VBA stroke

Results
About 96% of the VBA stroke cases had consultations with a primary care physician and 75.3% had one or more co-morbidities

<table>
<tr><th>Co-morbidities</th><th>VBA cases (n=93)</th></tr>
<tr><td>Neck pain and headaches</td><td>62 (66.7%)</td></tr>
<tr><td>Circulatory system diseases</td><td>59 (63.4%)</td></tr>
<tr><td>Nervous system diseases</td><td>44 (47.3%)</td></tr>
<tr><td>Musculoskeletal system and connective tissue diseases</td><td>41 (44.1%)</td></tr>
<tr><td>Respiratory system diseases</td><td>36 (38.7%)</td></tr>
<tr><td>Hypertension</td><td>34 (36.6%)</td></tr>
<tr><td>Accidents, violence, poisoning</td><td>33 (35.5%)</td></tr>
<tr><td>Heart disease</td><td>28 (30.1%)</td></tr>
<tr><td>Digestive system disease</td><td>28 (30.1%)</td></tr>
<tr><td>Upper respiratory tract infections</td><td>28 (30.1%)</td></tr>
<tr><td>Endocrine, nutritional metabolic diseases</td><td>26 (28.0%)</td></tr>
<tr><td>Skin diseases</td><td>25 (26.9%)</td></tr>
<tr><td>Genitourinary system diseases</td><td>23 (24.7%)</td></tr>
<tr><td>Mental disorders</td><td>18 (19.4%)</td></tr>
<tr><td>Diabetes</td><td>15 (160.1%)</td></tr>
<tr><td>Cerebrovascular disease</td><td>14 (15.1%)</td></tr>
<tr><td>Neoplasms</td><td>12 (12.9%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Interventions</th><th>Outcomes</th></tr>
<tr><td>Surveys</td><td></td><td></td></tr>
<tr><td>Sweeney 2010[256]
Ireland

Focus: to document the use of manual therapy (i.e., manipulation and mobilisation) by the chartered physiotherapists in Ireland and describe adverse events associated with the use of these techniques

PARTICIPANTS:

N: 127 physiotherapists responders
Age: mean: 33.3 (SD: 7.05) years
Mean number of years of experience: 13.81 years (SD 7.23)
Education: 40 (32%) had no post-graduate qualification in manual therapy, 23 (18%) had Master’s degree in manual therapy, 14 (11%) had a higher Diploma in Manipulative Therapy, 13 (10%) had a general Master’s degree, and 37 (29%) had attended a variety of short courses (e.g., Cyriax, McKenzie, Kaltenborn, Mulligan, myofascial techniques, muscle energy, etc…)
Inclusion: practicing current members of the chartered physiotherapists in Ireland</td><td>Survey: 44-item self-administered postal survey containing 4 sections (demographic data, use of HVTT/non-HVTT techniques, the occurrence of adverse events); reminders sent to non-responders 4 weeks after the initial survey</td><td>Results

Response rate: 127/259 (49%);
Intervention: All 127 (100%) responders used non-High Velocity Thrust Techniques (non-HVTT) and 34 (27%) used High Velocity Thrust Techniques (HVTT)

<table>
<tr><th>Technique</th><th>N of responders</th><th>Adverse event</th></tr>
<tr><td rowspan="4">HVTT</td><td>1 (3%)</td><td>Headache</td></tr>
<tr><td>2 (6%)</td><td>No details</td></tr>
<tr><td>1 (3%)</td><td>Dizziness/soreness of cervical muscle</td></tr>
<tr><td>1 (3%)</td><td>Dizziness</td></tr>
<tr><td rowspan="6">Non-HVTT</td><td>10 (30%)</td><td>Transient dizziness, nausea, symptoms</td></tr>
<tr><td>6 (18%)</td><td>No details</td></tr>
<tr><td>1 (3%)</td><td>Drop attack</td></tr>
<tr><td>1 (3%)</td><td>Fainting</td></tr>
<tr><td>1 (3%)</td><td>Transient ischemic attack</td></tr>
<tr><td>7 (20%)</td><td>Paresthesia, whiplash, dizziness, blurred vision, nausea, irritability, upper limb/neck pain increase, disorientation, sensory loss</td></tr>
<tr><td rowspan="2">Cervical traction</td><td>1 (3%)</td><td>Speaking gibberish</td></tr>
<tr><td>1 (3%)</td><td>Awake but non-responsive/talk with difficulty</td></tr>
</table>

Vertebrobasilar Insufficiency (VBI) assessment: 18 (53%) of the responders administering HVTT and 44 (40%) of those administering non-HVTT techniques
Adverse events: 33/127 (26%) reported an adverse event. For HVTT technique, 5/34 (15%) reported an adverse event (mostly of mild nature); for non-HVTT technique, 26/127 (20%) reported an adverse event (mostly mild but three serious adverse events such as drop attack, fainting, transient ischemic attack); for cervical traction, 2/99 (2%) reported an adverse event</td></tr>
</table>

Study	Interventions	Outcomes
Alcantara 2009[252] USA **Focus:** to document the use and evaluate the safety of paediatric chiropractic through surveying chiropractors and parents of paediatric patients **PARTICIPANTS:** **Chiropractors** **N:** 21 responders **Age:** not reported **Mean number of years of experience:** not reported **Education:** not reported **Inclusion:** Chiropractor in good standing with the Board of Chiropractor Examiners, agree to terms of participation in the survey, maintaining patient confidentiality **Parents of paediatric patients** **N:** 239 responders **Age:** see Results in Table **Mean number of years of experience:** NA **Education:** see Results in Table **Inclusion:** parents of paediatric patients (aged 18 years or younger) who received chiropractic care (1-12 visits)	**Chiropractor survey:** The survey sent to chiropractors included information on patient demographic data (e.g., age, gender, number of visits), presenting complaints, chiropractic technique/spinal regions used for patient care, treatment-associated aggravations (defined as worsening of symptoms or complaints following treatment), and treatment-associated complications (defined as cerebrovascular accidents, dislocation, fracture, pneumothorax, sprains/strains, or death as a result of treatment) **Parent survey:** The parent survey included information on parents'/guardians' gender, age, level of education as well as treatment-associated aggravations, and treatment-associated complications	**Results** **Chiropractor survey** Response rate: 21 chiropractor responders provided data on 577 paediatric patients Demographics of patients: mean age 7.45 years; 273 females and 304 males, mean number of office visits: 9.4 Presentation of patients: wellness care (46%), musculoskeletal complaints (26%), digestion/elimination problems (7%), ear/nose/throat problems (6%), neurological problems (6%), immune dysfunction (5%), and other (4%). Intervention: The chiropractic techniques used were regional or full spine manipulation using diversified technique, Gonstead technique, Thompson technique, activator methods, cranial techniques, and others Adverse events: The chiropractors' survey revealed three reports of treatment-associated aggravations (based on 5,438 visits) such as 'muscle stiffness,' 'spine soreness through the seventh visit,' and 'stiff/sore'. No treatment-associated complications were reported **Parent survey** Response rate: 239 parents of paediatric patients provided data on 239 paediatric patients Demographics of parents: mean age 35.6 years, 222 females and 16 males; PhD (n=7), Master's degree (n=29), Baccalaureate (n=73), college certification (n=35), some college (n=61), high school graduates (n=26), some high school (n=3), unknown (n=5) Presentation of patients: wellness care (47%), musculoskeletal complaints (22.6%), ear/nose/throat problems (4.2%), neurological problems (3%), colic (2.5%), immune dysfunction (1.2%), digestion/elimination problems (3.7%), birth trauma (2.9%), and other (10.9%) Adverse events: The parent survey revealed two reports of treatment-associated aggravations (soreness of the knee and stiffness of the cervical spine). There was no report of treatment-associated complications

Chapter 4 – Comparative cost-effectiveness and cost-utility evaluations of manual therapy interventions

Objectives

To review systematically the cost-effectiveness and cost-utility of manual therapy interventions relative to no treatment, placebo, or other active treatments.

Results

Search results

The titles/abstracts of the 1,014 publications included in the catalogue were screened using the stricter criteria specifying economic evaluation or analysis (e.g., costs, cost-effectiveness, cost-utility, economic analysis), of which 120 passed and were judged to be potentially relevant for full text review. The full text screening of the 120 publications excluded 78 publications, most of which did not report results for cost-effectiveness or cost-utility analysis. The remaining 42 publications, representing 28 unique studies (11 systematic review/health technology assessment reports,[257-267] 16 RCTs,[118;136;268-295] and one controlled cohort study[296]), were included in the review. The entire screening process including the study flow and reasons for exclusion is provided in Figure 12 in Appendix V (Section A). The list of excluded studies and reasons for exclusions are provided in Table 4 of Appendix V (Section A).

Systematic reviews assessing economic evaluations of different treatments including manual therapy

This review identified 11 systematic review (SRs)/health technology assessment (HTA) reports (11 publications) that critically assessed and reported economic evaluations of various treatments including manual therapy.[257-267] Basic characteristics of these reports are presented in Table 5 of Appendix V (Section B). Briefly, the included SRs assessed and critically appraised randomised and non-randomised controlled studies reporting economic evaluations of chiropractic care,[257] spinal manipulation/manual therapy,[261;265] complementary therapies,[258] complementary and alternative medicine (CAM),[259;260;262;263;267] general practitioner (GP) care,[264;265] conservative (non-operative) treatments,[266] relative to other treatments (e.g., acupuncture, soft tissue massage, homeopathy, hypnosis, biofeedback, clinical rehabilitation, education, back school, nutritional supplements, plant-based medications, exercise, mind-body approaches neuroreflexotherapy). The condition of interest for the majority of included reviews was back pain or low back pain (BP/LBP).[257;259;261;262;264-267] The reported search strategies covered at least two major electronic databases (e.g., MEDLINE, Embase). All systematic reviews except for one[261] included studies that reported different types of economic evaluations such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-consequence analysis (CCA), cost-minimisation analysis (CMA), cost-benefit analysis (CBA). One systematic review included only those studies that reported CUA.[261] The majority of systematic reviews identified

at least one study already included in this review.[268;280;282;289;291;293;294] No additional study eligible for inclusion in this review was identified (see Appendix V (Section B); Table 5).

Given the heterogeneity in terms of included studies, country of conduct, and types of treatments, the conclusions regarding the cost-effectiveness of manual therapies across the systematic reviews were inconsistent. In general, the evidence on the cost-effectiveness of chiropractic spinal manipulation for the treatment of back or neck pain was either inconclusive due to inconsistent results/paucity of data [257;259-261;266;267] or indicated higher costs with some benefit in favour of spinal manipulation. [258;262-265]

Studies evaluating cost-effectiveness and cost-utility of manual therapy

Study characteristics

A total of 17 unique studies (31 publications) were eligible for inclusion in the review.[118;136;268-296]

Five studies (all RCTs) were reported only as study protocols (in five publications), which provided information only on the study objectives, planned sample size, design features, and planned analysis.[118;273-276] The basic study characteristics for these ongoing trials (protocols) are presented in Appendix V (Section C) Table 6. Briefly, the studies are conducted in Australia (n=2),[118;274] the Netherlands (n=1),[273] and the USA (n=2).[275;276] The study participants enrolled in the American[275;276] and Dutch trials [273] are diagnosed with non-specific LBP and participants in the two remaining Australian trials present either with rotator cuff pathology[274] or lateral epicondylagia.[118] The planned sample size of the trials ranges from 132[118] to 480[275] participants. The duration of follow-up across the studies ranges from 22 weeks[274] to 52 weeks.[118;273;275;276] Test interventions to be evaluated in these trials are physiotherapy (combination of manual therapy, exercise, or massage),[273;274] physiotherapy plus corticosteroid injection,[118] manual therapy plus exercise,[275] or monodisciplinary chiropractic care (spinal manipulation, mobilisation, soft tissue massage, flexion, distraction, hot/cold packs).[276] The control interventions include usual physiotherapy,[273] placebo,[118;274] corticosteroid injection,[118] exercise,[275] or multidisciplinary integrative care (spinal manipulation, mobilisation, soft tissue massage, flexion, distraction, medication, self-care education, traditional Chinese medicine, trigger point therapy, and Swedish massage).[276] For all five trials, the estimation of direct health care/non-health care costs (e.g., health care, doctor visits, study treatment, hospitalisation, prescription medication, out of pocket expenses, travel expenses) and indirect costs (e.g., loss of productivity, inactivity days without paid jobs, absence from work) will be based on societal perspective. The planned economic evaluation performed for these trials will include cost-effectiveness (units: incremental cost per improved pain or disability) and/or cost-utility analysis (units: incremental cost per quality adjusted life years gained).

The remaining 12 unique studies (completed ones reporting any results), of which 11 were RCTs and 1 non-RCT (prospective cohort study),[296] were reported in 26 publications.[136;268-272;277-296] The following 10 studies by Bosmans 2011,[284-286] Williams 2004,[271;272] the UK BEAM trial team 2004,[268-270] Niemisto 2005,[289;290] Rivero-Arias 2006[294;295] Bergman 2010,[136;277-279] Whitehurst 2007,[291;292] Korthals-de Bos 2003,[282;283] Lewis 2007,[280;281] and Lin 2008[287;288] were reported in multiple publications.

The basic study, participant, treatment, methodology, and outcome characteristics for the 12 included trials are presented in

Table 7 in Appendix V (Section C). All economic evaluations except for one non-randomised controlled study[296] were based on randomised control trials (RCTs). Briefly, the included studies were conducted in the UK,[268;272;280;291;293;294] the Netherlands,[277;282;284] Finland,[289] the USA,[296] and Australia.[287] The study publication year ranged from 2003[282] to 2011.[284] The study sample size of the RCTs ranged from 94 [287] to 1,334 participants.[268] The single non-randomised study included 2,780 participants.[296] The duration of follow-up across studies ranged from 6 months[272;277;280;287] to 24 months.[289]

The included studies evaluated participants recruited from general primary care practices, chiropractors' or physiotherapists' offices. The participants enrolled in the studies presented with spinal pain (low back, upper back, and/or neck),[272] low back pain,[268;289;291;293;294;296] neck pain,[280;282;284] shoulder pain,[277] and ankle fractures.[287] Most of the studies excluded participants with specific causes of spinal pain such as previous spinal or shoulder surgery/pathology, rheumatoid arthritis, malignancies, ankylosing spondylitis, severe osteoporosis, pregnancy, osteoarthritis, neurologic disorders, haemophilia, spinal infection, psychiatric disease, or herniated disc. Some studies excluded participants who received treatments similar to those under study 2-6 months before the trial entry[268;291;293;294;296] or those who had contraindications to study treatments.[277;280;293;296] The mean age of the included study participants ranged from 37[289] to 51 years.[280]

In the reviewed studies, interventions whose main components included manual therapy techniques (e.g., manipulation, mobilisation) were compared with usual GP care,[268;272;277;282;296] GP advice,[289] physiotherapist advice,[294] a pain management programme (back pain education, strengthening, stretching, aerobic exercise, cognitive behavioural approach),[291;293] exercise,[284] physiotherapy (active, postural, relaxation, walking exercises),[282;287] or advice and exercise.[280] Most interventions lasted for 6 to 12 weeks. Further detail on the interventions evaluated in the included studies is provided in Table **8** (Appendix V, Section C).

Most economical analyses of cost-effectiveness were based on pain intensity (visual analog scale) and disability measures (ODI, RMDQ, NDI scores). The utility for QALY was based on the quality of life scale (EuroQoL EQ-5D or AQoL). The perspective of economical evaluations in the included studies was societal,[277;280;282;284;289;294] or public payer/primary care.[268;272;280;287;291;293;294;296] Given the short follow-up in most studies (12 months), no discounting was considered.

Quality of economic evaluations of included studies

The quality assessment for the economical portion of the 12 included studies is presented in Table 9 (Appendix V, Section C). In general, all studies provided some information for the majority of the 12 items included in the checklist. All economical evaluations except for one study (Haas et al. 2005[296]) were conducted alongside RCTs. In all studies the research question was clearly formulated, with good descriptions of the test intervention, control group intervention, and comparative effectiveness results. The majority of the studies identified and reported all of the important costs (i.e., direct medical, direct non-medical, indirect) and consequences (i.e., efficacy outcome measures). Since for more than half of the studies costs were not individually itemised, it was not clear how the total costs were calculated,

namely what types of costs were included in calculations of the total costs. All studies reported the valuation methods of costs and consequences, which were judged as adequate. Since the follow-up of the majority of studies was 12 months or shorter, there was no need to perform discounting. Therefore, the quality assessment item number 7 on discounting was rated as 'Yes' for all studies. The incremental cost-effectiveness and/or cost-utility analysis results (i.e., ratios, cost-effectiveness plane) were reported in all except for one study (Lin et a. 2008).[287] Amongst 11 studies that reported ICERs, only one failed to account for uncertainty in the cost-effectiveness ratio estimate.[296] The methods for exploring uncertainty included sensitivity analysis, cost-effectiveness plane, bootstrapping techniques for confidence intervals, and cost-effectiveness acceptability curves. Most studies provided detailed discussion sections by highlighting most important issues such as main study findings, interpretation of the findings in light of uncertainty, study strengths and limitations, consistency of the study findings across other similar studies, and knowledge gaps/future directions.

Cost-effectiveness and cost-utility of included studies

Results for cost-effectiveness/cost-utility analyses of included studies are presented by condition in the text below as well as in Table 10 (Appendix V, Section C).

Spinal Pain (low back, upper back, and/or neck)

Although in a randomised 6-month trial by Williams and colleagues,[271;272] addition of osteopathic manipulation (osteopathic manipulation plus advice on keeping active, exercise regularly, and avoiding excessive rest) to usual GP care was numerically more effective (incremental gain in QALY: 0.025) and also more costly (£303 versus £215) compared to GP care alone, none of the differences (i.e., increments) in cost or QALY (p=0.16) between the two groups was statistically significantly different. The addition of osteopathic manipulation to GP care was associated with an ICER estimate of £3,560 per QALY gained. Since this estimate is lower than the threshold of £30,000 suggested by the National Institute of Clinical Excellence (NICE), this treatment (i.e., osteopathic manipulation plus usual GP care) may be considered a potentially cost-effective option for patients with spinal pain.

Low Back Pain

Of the three PT interventions compared in the RCT by Critchley and colleagues,[293] the pain management (back pain education, strengthening, stretching, aerobic exercise, cognitive behavioural approach) was shown to be a more cost-effective option (i.e., dominant treatment) compared with individual PT (joint manipulation, mobilisation, massage, back care advice) or spinal stabilisation PT (muscle training, exercise) 18 months post-baseline. Individual PT was more effective but marginally more costly than spinal stabilisation, with a mean ICER of £1,055 per QALY gained. The probability that individual PT is cost-effective versus spinal stabilisation was below 40% across the entire range of acceptability curve willingness to pay values.

In one 12-month non-randomised study, Haas et al.[296] evaluated cost-effectiveness of chiropractic care (spinal manipulation, exercise, physical modalities, self-care education) relative to GP care (prescription drugs, exercise, self-care advice) separately in patients with chronic and acute LBP. The

patients receiving chiropractic care experienced significantly greater reductions in mean pain (VAS score) and disability (Oswestry Disability Questionnaire) scores compared to those in the GP care group 12 months after the baseline. The beneficial effect of chiropractic care was more pronounced in patients with chronic LBP (pain: 7.3 point reduction, disability: 5.4 point reduction) compared to patients with acute LBP (pain: 3.6 point reduction, disability: 2.7 point reduction). Total adjusted incremental health care costs (direct) were only marginally (i.e., statistically non-significantly) higher for chiropractic care versus GP care in both chronic ($1.00[£0.65], p>0.90) and acute ($43.00[£28], p>0.20) patients. The ICER for pain and disability in chronic patients was $0.10[£0.06] per score improvement. The corresponding ICERs for pain and disability in acute patients were $12.00[£7.80] and $16.1[£10.50] per score improvement, respectively. Thus, the findings of this study indicated that a short-term chiropractic care was more cost-effective than GP care, especially in patients with chronic LBP.

In a randomised trial of two years of follow-up, Niemisto and colleagues,[289;290] evaluated the cost-effectiveness of combination of manipulation treatment, stabilisation exercise, and physician consultation compared to physician consultation alone in patients with LBP of at least 3 months of duration. This study demonstrated significantly reduced pain intensity for the combined manipulation treatment compared to physician consultation alone (VAS score: 30.7 versus 33.1, p=0.01). The ICERfor the combined manipulation treatment versus physician consultation alone for pain improvement was acceptable 75% of the time ($512.00[£318.00] per one score improvement on VAS). The acceptability curve indicated the maximum willingness-to-pay threshold of $2,100.00[£1,300.00] for the same degree of improvement in pain. The benefit of the combined manipulation treatment compared to physician consultation alone in reducing disability at 24 months after the baseline was not statistically significant (Oswestry Disability Index score: 12.0 versus 14.0, p=0.20). The corresponding ICERfor disability was acceptable only 65% of the time given the willingness-to-pay threshold of $4,200.00[£2,600.00].

The randomised trial by Rivero-Arias et al.[294;295] compared and reported the 12 month cost-utility (based on EuroQol EQ-5D) of PT (joint manipulation, mobilisation, massage, stretching, exercise) plus advice (to remain active) compared to advice alone in 286 participants with LBP of 6 weeks or longer duration. At 12 months of follow-up, there was a numerically higher total cost incurred (£264.00 versus £204.00) and QALYs gained (0.74 versus 0.69) for the participants receiving PT plus advice versus advice alone group, but neither the incremental mean total cost (£60.00, 95% CI: -5, 126) nor the mean QALY (0.02, 95% CI: -0.02, 0.07) between the two treatment groups were statistically significant. The study reported mean ICER of £3,010.00 per QALY gained. Although this estimate fell within the acceptability threshold of willingness to pay (£5,000.00 per QALY gained), the estimated probability of PT plus advice being more cost-effective than advice alone was only 60%.

The UK Back Pain Exercise and Manipulation (BEAM) randomised trial [268-270] assessed cost-utility of adding manipulation (a multidisciplinary group developed a package of techniques representative of those used by the UK chiropractic, osteopathic, and physiotherapy professions), exercise, or manipulation followed by exercise to GP care (Best care in general practice) in patients with non-specific LBP of at least one month duration. A total of 1,334 trial participants, selected from 14 general practice office centers across the UK were randomised to receive one of the four interventions and were followed-up for 12 months. Over 12 months, all three groups of exercise (£486.00), manipulation (£541.00), and manipulation plus exercise (£471.00) incurred higher mean total costs compared to GP care (£346.00). The mean number of QALYs gained was also improved for the three groups (0.635, 0.659, and 0.651, respectively) compared to GP care (0.618). Relative to GP care, the

addition of manipulation alone to GP care demonstrated a greater mean incremental number of QALYs gained (0.041; 95% CI: 0.016, 0.066) than the addition of exercise (0.017; 95% CI: -0.017, 0.051) or manipulation plus exercise (0.033; 95% CI: -0.001, 0.067) to GP care. The incremental cost-utility ratios (versus GP care) for adding manipulation alone, exercise alone, or manipulation plus exercise to GP care were £4,800, £8,300, and £3,800, respectively. The combination of manipulation and exercise was shown to be a dominant intervention relative to exercise alone because of lower costs (£471.00 versus £486.00) and better outcomes in the number of QALYs gained for the former intervention (0.651 versus 0.635). The findings of this study also indicated that manipulation alone for additional £70.00 could gain extra 0.008 QALYs compared to manipulation plus exercise, yielding an ICER of £8,700. According to the study results, the most cost-effective treatment option for patients with low back pain amongst the four treatments was the addition of manipulation alone to GP care if the willingness-to-pay was at least £10,000 per QALY gained.

The randomised trial conducted by Whitehurst and colleagues,[291;292] compared the cost-utility and cost-effectiveness of manual physiotherapy (articulatory mobilisation, manipulation, or soft tissue techniques, spinal stabilisation, back exercise, ergonomic advice, back education) and a brief pain management (BPM) program in patients with acute non-specific LBP (< 12 weeks of duration). At 12 months post-baseline, the mean cost per patient for the manual physiotherapy was only numerically (i.e., statistically non-significantly) greater compared to BPM (mean difference: 52.19, 95% CI: -19.22, 123.62). Although the gains in disability (RMDQ mean score change: 0.33, 95% CI: -0.82, 1.49) and utility (mean QALYs gained: 0.022, 95% CI: -0.02, 0.07) were in favour of manual physiotherapy versus BPM, these differences between the two interventions were not statistically significantly different. The ICER for manual physiotherapy relative to BPM was £2,362 per QALY gained. According to the cost-utility acceptability curve analysis, there was 83% chance that manual physiotherapy was more cost-effective compared to BPM, given the conservative threshold of £10,000.00 per QALY gained. This study demonstrated an ICER of £156.00 per one RMDQ score improvement for manual physiotherapy versus BPM. The study results suggested that manual physiotherapy was more cost-effective than BPM in treating patients for acute non-specific LBP.

Neck Pain

Bosmans et al.[284-286] randomised 146 patients with non-specific neck pain of 4-12 weeks of duration to receive manual therapy (manipulation consisting of passive movement of a joint beyond its active and passive limit of motion with a localised thrust of small amplitude; mobilisation using skilled low grade passive movement with large amplitude to restore movement and relieve pain) or behavioural graded activity (BGA) program (gradually increasing levels of exercise) for 6 weeks. The authors evaluated the cost-effectiveness and cost-utility of BGP relative to manual therapy during 12 months of follow-up. Compared to manual therapy, treatment with BGA was associated with a statistically significant reduction in pain intensity (mean VAS score: 0.88, 95% CI: 0.02, 1.70) and disability (mean Neck Disability Index score: 2.40, 95% CI: 0.22, 4.50). The differences in perceived recovery (mean score difference: 0.02) and QALY gained (mean score difference: -0.02) between the two treatment groups were not significantly different ($p>0.05$). The total costs were higher for BGA program versus manual therapy, but this difference was not significant (mean difference €260.00[£183.60], 95% CI: -107[-75], 825[582]). BGA was shown to be more cost-effective than manual therapy in reducing pain intensity (€296.00[£209] per improved pain score) and disability (€110.00[£77.70] per improved disability score). There was no difference between the two treatments in terms of relative cost-utility.

Similarly, BGA was not more cost-effective versus manual therapy in improving perceived recovery in patients with subacute neck pain (€13,083.00[£9,178.00] per improved score for recovery).

In their randomised trial, Korthals-de Bos et al.[282;283] compared cost-effectiveness and cost-utility for manual therapy (combination of techniques described by Cyriax, Kaltenborn, Maitland, and Mennel using muscular and articular mobilisation, coordination or stabilisation, and joint mobilisation with low-velocity passive movements), physiotherapy (active postural and relaxation exercises), and GP care (advice, educational booklet, and anti-inflammatory agents if necessary) administered to 183 patients with non-specific neck pain of at least two weeks of duration. During 12 months of follow-up after the randomisation, manual therapy was significantly less costly compared with physiotherapy (mean difference: -€850.00[£535.50], 95% CI: -2,258.00[-1,422.54], -239.00[-151.00]) or GP care (mean difference: -€932.00[-£587.20], 95% CI: -1,932.00[-1,217.00], -283.00[-178.30]). Moreover, manual therapy was significantly more effective in reducing pain intensity than physiotherapy (mean difference: 1.20, 95% CI: 0.10, 2.10), but not disability (mean difference: 0.90, 95% CI: -1.90, 3.60). Although the mean perceived recovery score in the manual therapy group (71.7) was numerically higher compared to physiotherapy (62.7) and GP care (56.3), these differences were not statistically significant ($p>0.05$). Likewise, no significant difference was observed between manual therapy and GP care for the reductions in pain intensity (mean difference: 0.10, 95% CI: -0.80, 1.10) or disability (mean difference: -1.40, 95% CI: -4.10, 1.30). The mean utility score was highest for manual therapy (0.82), but it was not significantly different from those for physiotherapy (0.79) or GP care (0.77). The manual therapy demonstrated dominance (both less costly and more effective) over physiotherapy for pain intensity (98% bootstrap ratios in the area of dominance on cost-effectiveness plane), perceived recovery (85% bootstrap ratios in the area of dominance on cost-effectiveness plane), and utility (87% bootstrap ratios were in the area of dominance on cost-utility plane). Similarly, manual therapy was dominant over GP care for perceived recovery (96% bootstrap ratios in the area of dominance on cost-effectiveness plane) and utility (97% bootstrap ratios in the area of dominance on cost-utility plane). According to the acceptability curve, at the ceiling cost-effectiveness ratio of zero, there was a 98% chance that manual therapy was more cost-effective than physiotherapy for pain intensity. Physiotherapy and GP care did not differ in either costs or in improving neck related pain or disability.

Lewis and colleagues[280;281] conducted an economic evaluation (cost-utility and cost-effectiveness) alongside a randomised trial in which advice and exercise (A&E) plus manual therapy (passive/active assisted hands-on movements, joint and soft tissue mobilisations or manipulations graded as appropriate to the patient's signs and symptoms) or shortwave diathermy (PSWD) were compared to A&E alone in patients with non-specific neck pain. At 6 months of follow-up, A&E alone group incurred slightly higher total cost (£372.72) compared to manual therapy (£303.31) or PSWD (£338.40). The cost differences across the three interventions were not statistically significant ($p>0.05$). Similarly, there was no significant between-group difference in the 6-month post-baseline mean disability (Northwick Park Neck Pain Questionnaire: 11.5 versus 10.2 versus 10.3, respectively) or mean QALYs gained (0.362 versus 0.342 versus 0.360, respectively). The cost-effectiveness planes displayed high uncertainty. For disability, the A&E had higher probability of being cost-effective (up to 60%) than SMT or PSWD (40% or less) at all the willingness-to-pay thresholds >£50.00. The SMT had a higher probability of being cost-effective (up to 55%) than A&E or PSWD (45% or less) but only at willingness-to-pay thresholds <£50.00. For QALYs, the SMT had higher probability of being cost-effective (up to 55%) than A&E or PSWD (30% or below). At willingness-to-pay threshold of £30,000 per QALY gained, the probabilities for SMT, A&E, and PSWD were 44%, 30%, and 26%, respectively. Given the study results from societal perspective, the choice of more optimal treatment (between SMT or A&E) is likely to depend on the type of outcome measure.

Shoulder Pain

In their randomised trial, Bergman et al.[136;277-279] evaluated cost-effectiveness of spinal manual therapy (high velocity low amplitude manipulation and passive low velocity mobilisation within the range of joint motion) in addition to usual GP care (advice, analgesics, and anti-inflammatory agents, if necessary) compared with usual GP care alone in 150 patients with non-specific shoulder pain of any duration. At 6 months of follow-up, the manual therapy group incurred slightly but non-significantly higher total costs compared to the GP care alone group (mean difference: €121.00[£76.23], 95% CI: -340.00[-214.00], 581.00[366.00]). The improvements in perceived recovery (mean difference: 5.0%, 95% CI: -10.1, 20.2), shoulder pain (mean difference: 0.7, 95% CI: -1.0, 2.5), and general health (mean difference: 0.03, 95% CI: -0.04, 0.09) were numerically in favour of the manual therapy, but the differences between the two groups were not statistically significant. The mean shoulder disability score was the only outcome favouring the manual therapy over GP care with statistically significant difference (mean difference: 12.7, 95% CI: 1.3, 24.1). The incremental cost-effectiveness ratios for the manual therapy versus GP care for perceived recovery, shoulder pain, shoulder disability, and general health were €2,876.00[£1,811.88], €175.00[£110.25], €5.00[£3.15], and €2,952.00[£1860.00], respectively. At the ceiling ratio of €10,000.00[£6,300.00], the manual therapy had a 65% probability of being more cost-effective than GP care alone.

Ankle Fracture rehabilitation

Lin et al.[287;288] conducted an economic evaluation alongside a randomised trial in which manual therapy (large amplitude oscillatory anterior-posterior glides of the talus) added to physiotherapy was compared to physiotherapy alone in patients with ankle fractures. At 6 months of follow-up, there were no differences between the manual treatment and physiotherapy groups in either quality of life (mean AQoL score difference: 1.3, p=0.04) or lower extremity function (mean lower extremity functional scale difference: -1.0, p=0.70). Similarly, total health care costs were not significantly different between the two groups (AU$ 187.66[£80.00], p=0.31). Given the absence of difference in the effectiveness and costs, the authors did not undertake the cost-effectiveness analysis and concluded that the addition of manual therapy to physiotherapy was not a cost-effective option compared to physiotherapy alone in adults with ankle fracture.

Summary

This systematic review summarised and appraised the cost-effectiveness and cost-utility of manual therapy treatments (chiropractic manipulation, osteopathic manipulation, physiotherapy manual techniques) relative to other interventions evaluated in 12 studies. Chapter 5 provides a detailed discussion of the findings in this section, however, it is difficult to draw definitive conclusions regarding the comparative cost-effectiveness of manual therapy techniques in patients presenting with spinal pain due to the paucity and clinical heterogeneity of the identified evidence.

Chapter 5 – Discussion

Outline of what we achieved

A catalogue including 1014 records was compiled. The catalogue included around 300 systematic reviews and 500 RCTs, including any new ones published and identified by our searches since the publication of the Bronfort report, as well as evidence from around 100 non-randomised comparative studies, and 20 studies including qualitative elements. New relevant systematic reviews or RCTs published since the completion of the Bronfort report were summarised systematically, as were any relevant systematic reviews and RCTs omitted from the Bronfort report. A comprehensive evaluation of adverse events was undertaken (7 systematic reviews, 7 primary studies). A systematic review of 28 cost-effectiveness studies was conducted. A dissemination event explored the attitudes and implications of patients and professionals to the reported findings.

Summary

Clinical effectiveness

The current report catalogued and summarised recent systematic reviews, RCTs and comparative effectiveness studies that were not all included in the Bronfort report (e.g. non-English literature) and compared results and updated conclusions. A large number of studies was included (over 1000 in the evidence catalogue, over 100 in the more detailed summaries). The majority of studies were concerned with musculoskeletal conditions, and the majority of these were about spinal disorders. The most common study design was the RCT. There were relatively few non-randomised comparative and qualitative studies meeting the current inclusion criteria.

The majority of conditions previously reported to have "inconclusive" or "moderate" evidence ratings by Bronfort remained the same. Evidence ratings changed in a positive direction from inconclusive to moderate evidence ratings in only three cases (manipulation / mobilisation (with exercise) for rotator cuff disorder, mobilisation for cervicogenic and miscellaneous headache). It was also noted that some evidence ratings by Bronfort changed in the current report in a negative direction from moderate to inconclusive evidence or high to moderate evidence ratings. In addition, evidence was identified on a large number of non-musculoskeletal conditions that had not previously been considered by Bronfort; all this evidence was rates as inconclusive.

Overall, it was difficult to make conclusions or generalisations about all the conditions due limitations in quality of evidence, short follow-up periods reported (<12 months), and high uncertainty in the effectiveness measures. Most reviewed evidence was of low to moderate quality and inconsistent due to substantial methodological and clinical diversity, thereby rendering some between-treatment comparisons inconclusive. The differences in the therapy providers' experience, training, and approaches may have additionally contributed to the inconsistent results.

Cost-effectiveness and cost utility

Twelve primary studies compared cost-effectiveness and/or cost-utility of manual therapy interventions to other treatment alternatives in reducing non-specific musculoskeletal pain (spinal, shoulder, ankle). All economic evaluations except for one were conducted alongside randomised controlled trials. The economic perspective in the reviewed studies was either societal, primary care organization/public payer, or both.

Generally, in studies of low back and shoulder pain, both the incurred total costs and improvements in pain, disability, and QALYs gained tended to be greater for manual therapy (i.e., osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, chiropractic manipulation) interventions compared to alternative treatments (i.e., usual GP care, pain management, spinal stabilisation, GP advice, or exercise). Based on the reported estimates of incremental cost-effectiveness/utility ratios and associated uncertainty, manual therapy (chiropractic spinal manipulation, osteopathic spinal manipulation, or combination of manipulation and mobilisation) in addition or alone may be a more cost-effective option compared to usual GP care (alone or with exercise), spinal stabilisation, GP advice, advice to remain active, or brief pain management for improving low back or shoulder pain and disability in a short-term (12 months or less). Specifically, the observed extra costs needed for one unit improvement in low back or shoulder pain/disability score or one QALY's gain were lower than the willingness-to-pay thresholds reported across the studies. Based on the findings from the UK BEAM study, the addition of chiropractic and osteopathic manipulations to exercise and GP care was dominant (less costly and more effective) over the combination of exercise and GP care.

In contrast to low back or shoulder pain studies, neck pain studies showed manual therapy interventions (chiropractic manipulation plus joint mobilisation with low-velocity passive movements) to have incurred predominantly lower total costs compared to alternative treatments such as behavioral graded physical activity program, physiotherapy, GP care, or advice plus exercise. Overall, the evidence on cost-effectiveness of manual therapy for reducing neck pain, disability, and QALYs gained in comparison to other treatments was not consistent across the studies. For example, in one study, manual therapy (small amplitude thrust manipulation plus large-amplitude mobilisation) was less cost-effective than behavioral graded physical activity, while in another study, manual therapy (various chiropractic manipulation techniques plus low-velocity articular mobilisation) dominated either physiotherapy or GP care. The results of economic evaluation from one neck pain study comparing cost-effectiveness of manual therapy (hands-on passive or active movements, mobilisation, soft tissue/joint spinal manipulation) with advice and exercise were inconclusive due to high uncertainty.

It is difficult to draw firm conclusions regarding the cost-effectiveness of manual therapies relative to other treatments given the paucity of evidence, clinical heterogeneity, short period of follow-up and high uncertainty in the estimates of incremental cost-effectiveness ratios of the reviewed studies. Deficiencies in study methodology and reporting quality of certain aspects further complicates the interpretation of the study findings. For example, according to the Drummond checklist (items number 4, 5) it was not clear how costs were considered and calculated for some studies. Moreover, post-baseline between-group differences in the effectiveness measures were either statistically non-significant, or if significant, their size was clinically negligible. Small sample size studies reporting wide confidence intervals may render statistically non-significant differences inconclusive. The length

of follow-up for most studies was one year or shorter, thereby making it unclear or difficult to estimate what would be the long-term economic and clinical consequences for the study populations of interest. Additionally, the non-specific or contextual effects (e.g., intervention fidelity, placebo effect, practitioner's experience, skill set) due to the complexity of interventions and lack of patient blinding may have biased the study results.[297] Since none of the studies employed a sham/control arm, it is difficult to tease out the specific effects of treatment from patients' differential expectation (or practitioner's experience/skill set) across the study treatment arms. The patients' improvement was characterised by subjective outcome measures such as pain, disability, and quality of life. The measurements of subjective (i.e., patient-centered) outcomes are especially prone to bias in the absence of blinding. Moreover, manual therapy interventions employed across these studies were not homogeneous, but rather combinations of various manual techniques (e.g., chiropractic care, high velocity low amplitude manipulation, joint mobilisation, soft tissue techniques, physiotherapy manual techniques) with other interventions (e.g., physical therapy, exercise, GP care) leading to different effectiveness profiles, thereby limiting the comparability of results across studies. Finally, some studies indicated a great uncertainty in the distribution of incremental pairs of cost and effectiveness along the cost-effectiveness planes.[280;287;293;296]

The applicability of findings from this review may be limited to only countries with similar health care system and considerations of utility (e.g., calculations based on the same quality of life score). Therefore, global application of these findings would not be appropriate. The degree of applicability is additionally limited by the differences in components of manual therapy interventions in the reviewed studies.

The findings of the cost effectiveness review cannot be directly compared to those of other systematic reviews,[257-267] given the differences in the scope, research question, and study inclusion/exclusion criteria (types of economic evaluations, design, and interventions). More details on these systematic reviews are provided in the Results section and Appendix IV, Section B (Table 5). In the past two decades, there have been several large-scale government-funded investigations conducted to elucidate the effects of chiropractic care. Two examples of these research efforts are the reports of Ontario Ministry of Health (Canada)[298] and the New Zealand commission.[299] The findings of both reports supported the safety and effectiveness of chiropractic care in improving musculoskeletal symptoms in patients with back pain.

Limitations and strengths

The clinical effectiveness review was limited by the extent of information provided in the included primary studies and clinical/methodological diversity of the included evidence. Since the current report referred to the quality ratings by Bronfort, a similar grading system as Bronfort needed to be used; this prevented the use of different methodological approaches to grade the overall evidence or changes in evidence. Most studies had small sample size and methodological limitations. For the majority of RCTs it was not clear if the methods for randomization were adequate and the treatment allocation was appropriately concealed. In many cases, either the studies were no blinded or the blinding status of outcome assessors could not be determined. It should be noted that in most situations where physical treatments are applied, blinding is very difficult or impossible to achieve. The lack of description of adequacy of randomisation methods, treatment allocation concealment, and blinding in the studies complicates valid interpretation of the review results. Furthermore, there was a

substantial clinical and methodological diversity across the included studies that may have contributed to the observed inconsistencies in the results. For example, there has been a large variation in types of manual therapy and their modes of application across studies, which was compounded by differences in control treatments thereby limiting comparability between the study results. Moreover, the therapy provider's experience, training, and approaches used varied across the trials and this variation may have additionally impacted on the trial results. The above-mentioned clinical diversity limited the extent of statistical pooling of trial results. Poorly and scarcely reported harms data limited our ability to make meaningful comparisons of rates of adverse events between the treatments.

We attempted to take into account a user perspective by considering qualitative studies, however, we only identified a very limited number of studies reflecting patient views of manual therapy.

One of the main strengths of the clinical effectiveness review is its broad scope in terms of reviewed interventions, populations/conditions, and outcome measures. This review identified, appraised, and summarised a large amount of relevant literature. The review authors employed systematic, comprehensive, and independent strategies to minimise the risk of bias in searching, identifying, selecting, extracting, and appraising the evidence. The broad search strategy, not restricted by the language or year of publication, was applied to multiple electronic and other bibliographic sources.

The cost-effectiveness and cost utility review also has its own strengths; specifically, the reviewers used systematic, comprehensive, and independent strategies to minimise the risk of bias in searching, identifying, retrieving, screening, abstracting, and appraising the primary studies. The search strategy was applied to multiple electronic sources and was not restricted by the language or year of publication. Moreover, this review included only controlled trials, of which, all except for one were randomised trials with adequate methods of randomization and treatment allocation concealment. One advantage of this review over others is that it includes only those studies that evaluated costs and effectiveness simultaneously through cost-effectiveness and/or cost-utility analyses by providing incremental ratios and the associated uncertainty measures. Most of the included studies presented their economical evaluations from societal perspective, which is considered the most optimal approach.[300]

All relevant costs (i.e., direct, indirect) applicable to any given economic perspective, whether societal or public payer, were adequately considered in the majority of the reports. Similarly, most studies reported to have conducted sensitivity analysis (intention-to-treat versus completers), bootstrapping, and cost-effectiveness acceptability curves to address missing data/losses to follow-up and uncertainty around the incremental cost-effectiveness ratios, respectively. Given the problems of interpretation for negative incremental cost-effectiveness ratios (i.e., ratios falling in the dominance South East and North West quadrants of the cost-effectiveness plane), the use of cost-effectiveness acceptability curves has been the preferred method over the generation of 95% confidence intervals.[301]

One of the main limitations of the cost effectiveness and cost utility review stems from the reviewed evidence itself. Namely, this review found the paucity of evidence of cost-effectiveness/cost-utility evaluations for manual therapy interventions. The insufficient amount of evidence may be explained by lack of funding, difficulties in obtaining cost data, lack of expertise in economic outcomes, and/or perceived societal discomfort with assigning monetary units to human health.[261] Next limitation is that this review extracted only those outcomes used in the economical evaluations of included studies. The reviewed evidence for the study reports was inconsistent due to substantial methodological and/or

clinical diversity, small sample size, and short follow-up. The differences in the therapy provider's experience, training, and approaches may have additionally contributed to heterogeneous results.

Dissemination event

The dissemination event held at the University of Warwick in June 2012 involved 23 people (14 male, 9 female) of which 21 were professionals (mainly chiropractors) and two were patients and provided an opportunity to explore what users and professionals thought about the findings and the implications. A detailed summary of the main issues raised is provided in Appendix VI.

A series of questions were explored with the attendees. Some important issues were raised following the presentation of the findings.

The attendees were in agreement that the findings provided a platform or baseline for future research. They were encouraged by the findings and felt this presented many opportunities for further collaborative research. They recognised that there had been a plethora of evidence published, but concluding anything from it was very difficult due to the limited high quality research. They wanted to see more high quality research being funded, widespread dissemination to clinicians and students being educated on how to undertake high quality research.

Further research considerations included specific conditions as well as exploring patients' experiences in terms of satisfaction, acceptability and attitudes towards treatment outcomes. There was discussion about the need for an RCT – possibly chiropractic versus usual GP care. The attendees recognised the value of evaluating the cost effectiveness of interventions. They also would like to see more evaluation and synthesis of the available trial evidence.

There was some surprise about the limited number of high quality non-RCTs and the lack of any new evidence change. They had expected to hear more research would have been published. The attendees discussed how they would like to see the results disseminated through published papers, publications in the context of the Bronfort findings to address the question collaboratively "what works", and publications of the positive findings for patients.

The attendees finally provided a useful perspective on what they would like to happen to the materials. They would like to be kept up-to-date with College of Chiropractors' findings and thought that these should be made available to chiropractors on a subscription basis. They stated that the three undergraduate colleges need to work together and discuss the mechanism to maintain the catalogue. There was a suggestion that greater communication could take place through forums or a Wiki.

Research needs / recommendations

The current research has highlighted the need for long-term large pragmatic head-to-head trials reporting clinically relevant and validated efficacy outcomes along with full economic evaluations. Ideally, future studies should use and report unit cost calculation and costs need to be broken down by each service to allow the judgment as to whether all relevant costs applicable to a given perspective were considered and how the total costs were calculated. If ethically justifiable, future trials need to include sham or no treatment arm to allow the assessment and separation of non-specific effects (e.g.,

patient's expectation) from treatment effects. Furthermore, future research needs to explore which characteristics of manual therapies (e.g., mode of administration, length of treatments, number of sessions, and choice of spinal region/points) are important in terms of their impact on clinically relevant and patient-centered outcomes. Also, strong efforts are needed to improve quality of reporting of primary studies of manual therapies.

The following key research needs and recommendations were highlighted from the report findings:

- There is a need to maintain and update the catalogue

  As this is a rapidly changing field of research, there is a need to regularly update the catalogue developed by the team at the University of Warwick with new evidence. With time permitting, the catalogue could be supplemented with conference proceedings and unpublished literature.

- The current research provides a strong argument in support of further trials in this area (e.g. funding from NIHR Health Technology Assessment Programme) through research collaboration

  The work undertaken has highlighted many gaps in the literature and areas that need further high-quality research (e.g. non-musculoskeletal conditions). It has also brought together many leading professionals and active patient representatives during the dissemination event. There is a need to maintain the collaborative network formed at the dissemination event and to support the generation of research teams who might lead applications for future funding. Sources of funding might include the NIHR Health Technology Assessment Programme (NIHR HTA) and Service Delivery and Organisation programme (SDO).

- Provision of more training and education in research for the chiropractic community is needed – this includes training in secondary research

  The weaknesses highlighted in terms of the quality of published evidence raise questions about the level of research, methodological training and education being delivered in the chiropractic community. It would be useful to provide more training in research methods, study design and also secondary research. Students and professionals working in this area might benefit from courses in understanding research and critical appraisal, to enable them to learn to identify, interpret, appraise and apply research relating to health care. These capabilities are essential for advanced professional expertise in health care. The key aims of these future courses might be to:
  - Demonstrate a critical understanding of the conceptual foundations of research relating to health care
  - Encourage the understanding of principles and practice of evidence based health care and their application in specific areas of clinical practice
  - Learn to appraise evidence produced by different types of research design and its role in the development of health care services and clinical practice
  - Apply the principles and techniques of critical appraisal to evaluate the limitations of research evidence, including complex interventions and studies at the forefront of methodological development
  - Show a critical understanding of the implications of research for clinical practice and service development

- Studies need to be developed that involve qualitative research methods to explore patient attitudes, satisfaction and acceptability towards manual therapy treatments, this could also take the form of mixed methods studies exploring both effectiveness and patient views
  The review has identified limited qualitative research exploring patient attitudes, satisfaction and acceptability towards manual therapy treatments. This raises the question have studies of patients' satisfaction and attitudes been undertaken but not published, possibly because of non-significant results or the lack of standardised measures, concerns about validity and reliability responsiveness of the instruments developed? Furthermore, there has been limited consideration of the reasons for withdrawal and drop-out in many studies. Through a series of qualitative studies (e.g. focus groups, semi-structured interviews), researchers might undertake a needs assessment to evaluate the most common factors causing therapeutic non-compliance and drop-out. We encourage research teams to explore the relationship between needs, satisfaction and quality of life, and focus on the important gaps that have been highlighted in the current knowledge base (see inconclusive evidence ratings).

- Greater consistency is needed across research groups in this area in terms of definition of participants, interventions, comparators and outcomes

  Studies should provide demographic information about all participants, including the methods of recruitment and setting. The chronicity of any condition should be taken into account. Trials are needed comparing (spinal) manipulation versus mobilisation. Trials are needed looking at the effect of different components of complex manual therapy interventions. There needs to be a clearer definition of manual therapy components and interventions. The integration of active (e.g. exercise) and passive components in interventions should be studied in depth, and outcomes should also consider recurrence of any disorders. Future studies need to explore which characteristics (e.g., length, mode of administration, component of manual therapy intervention) are important in their impact on patient-centred outcomes. The paucity and clinical heterogeneity of the identified evidence make it difficult to pool evidence across studies and draw conclusions. For this reason, it is paramount that researchers have consistency in methods of reporting and measures being used. For example, it is strongly encouraged that researchers in this area become more familiar with patient-oriented outcomes measures, such as health-related quality of life. This approach is often considered to be the 'gold standard' in the evaluation of healthcare services and outcome assessment. Although there are a large variety of generic and disease specific instruments to examine quality of life, using a combination of generic and disease-specific health-related quality of life questionnaires can often provide complementary information; agreement on or development of suitable measures by the chiropractic community is of considerable importance. Future trials should also clearly report adverse events systematically.

- More research is needed on non-musculoskeletal conditions

  The limited inconclusive evidence identified in the area of non-musculoskeletal conditions highlights the growing need for further high-quality research. Through maintaining a collaborative network of professionals, patients, academics and other stakeholders with an interest in this topic, agreement needs to made on which conditions should be explored further in the first instance.

- High quality, long-term, large, randomised trials reporting effectiveness and cost-effectiveness of manual therapy are needed for more definitive conclusions

  In developing trials in this area, it is essential that researchers use (if appropriate) adequate randomisation procedures, blinding of outcome assessment, adequate placebo measures, standardised outcome assessment (including patient-oriented outcomes), and detail losses to follow-up – referring to the CONSORT criteria. It is also essential that future trials use adequate sample sizes, explore long-term follow-up, report adverse events systematically.

More high quality evidence from well-conducted prospective controlled studies will help policy makers, health care providers, and patients in providing valid recommendations in terms of optimal treatment choices for a given patient population.

Conclusions

The current report provides a platform for further research into the clinical and cost-effectiveness of manual therapy for the management of a variety of musculoskeletal and non-musculoskeletal conditions. There is need to maintain and update the catalogue. Limited research had been published on many non-musculoskeletal conditions. Raising awareness about the importance of undertaking high quality research is needed among the chiropractic community. The magnitude of benefit and harm of all manual therapy interventions across the many conditions reported cannot be reliably concluded due to the poor methodological quality and clinical diversity of included studies.

Overall, manual therapy techniques such as osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilisation techniques, and chiropractic manipulation in addition to other treatments or alone appeared to be more cost-effective than usual GP care (alone or with exercise), spinal stabilisation, GP advice, advice to remain active, or brief pain management for improving low back/shoulder pain/disability and QALYs gained during one year. Moreover, chiropractic manipulation dominated (i.e., less costly and more effective than alternative treatment) either physiotherapy or GP care in improving neck pain and QALYs gained. The evidence regarding cost-effectiveness of manual therapy (hands-on passive or active movements, mobilisation, soft tissue/joint spinal manipulation) compared to advice plus exercise in reducing neck pain was limited in amount and inconclusive due to high uncertainty. Further research and good quality evidence from well-conducted studies is needed to draw more definitive conclusions and valid recommendations for policy making.

It is important to consider whether the evidence which is available provides a reliable representation of the likely success of manual therapy as provided in the UK. Given the considerable gaps in the evidence and the patchy reporting on techniques and interventions used (and often a lack of description of techniques used), and the fact that many reported studies failed to consider the generalisability of the findings to the range of settings in which manual therapy is practised in the UK, this is unlikely. There is a need to consider the whole package of care, rather than just single manipulation or mobilisation interventions. A mixed methods approach should be considered for expanding the evidence base and addressing the complexities of this important discipline in health care.

Acknowledgements

The team would like to thank the following people for their valuable contributions to the study: Professor Martin Underwood, Ms Sandra Schlager, Ms Amy Grove, Mrs Jas Bains, Ms Bola Ola, Mrs Hannah Fraser, Dr Beth Hall, Professor Christina Cunliffe, and Dr Gay Swait.

Appendix I – Search strategies

Database	**Number retrieved (before duplicate removal)**
MEDLINE (Ovid)	6232
Mantis	788
Index to Chiropractic Literature	593
CINAHL	3263
the specialised databases Cochrane Airways Group trial register, Cochrane Complementary Medicine Field register, and Cochrane Rehabilitation Field register (via CENTRAL)	1130 (n.b. all picked up in CENTRAL search)
Embase	7546
Science Citation Index and Social Science Citation Index	2585
AMED	2749
CDSR	36
NHS DARE	96
NHS HTA	17
NHS EED	20
CENTRAL (full search)	1405
ASSIA	308

Medline via Ovid searched on 25/08/2011

1	Musculoskeletal Manipulations/	647
2	Manipulation, Orthopedic/	3196
3	Manipulation, Chiropractic/	599
4	Manipulation, Spinal/	947
5	Manipulation, Osteopathic/	275
6	Chiropractic/	2910
7	((orthopaedic or orthopedic or chiropract$ or chirother$ or osteopath$ or spine or spinal or vertebra$ or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint$) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	3748
8	((manual or manipulat$ or mobilis$ or mobiliz$) adj (therap$ or intervention$ or treat$ or rehab$)).tw.	2087
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	10834
10	Osteopathic Medicine/	2395
11	osteopath$.tw.	3382
12	chiropractic$.tw.	2684
13	chirother$.tw.	16
14	10 or 11 or 12 or 13	6949
15	9 or 14	14942

16	"friction massage$".tw.	22
17	naprapath$.tw.	13
18	Rolfing.tw.	17
19	"myofascial release".tw.	53
20	"Bowen technique".tw.	5
21	"apophyseal glide$".tw.	7
22	"bone setting".tw.	47
23	bonesetting.tw.	14
24	"body work$".tw.	103
25	"high-velocity low-amplitude".tw.	94
26	HVLA.tw.	21
27	((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	17
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	386
29	15 or 28	15151
30	meta.ab.	37484
31	synthesis.ab.	356691
32	literature.ab.	333797
33	randomized.hw.	385278
34	published.ab.	229952
35	meta-analysis.pt.	30214
36	extraction.ab.	106463
37	trials.hw.	241415
38	controlled.hw.	476605
39	search.ab.	111279
40	medline.ab.	37563
41	selection.ab.	186391
42	sources.ab.	136598
43	trials.ab.	231023
44	review.ab.	521671
45	review.pt.	1668378
46	articles.ab.	43106
47	reviewed.ab.	273309
48	english.ab.	34846
49	language.ab.	55323
50	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3593074
51	comment.pt.	449950
52	letter.pt.	723862
53	editorial.pt.	282269
54	Animals/	4854330
55	Humans/	12014638
56	54 and 55	1282233
57	54 not 56	3572097
58	51 or 52 or 53 or 57	4613893

59	50 not 58	3118764
60	29 and 59	3786
61	meta-analysis.mp,pt.	47915
62	review.pt.	1668378
63	search$.tw.	167947
64	61 or 62 or 63	1800589
65	29 and 64	1754
66	60 or 65	3869
67	randomized controlled trial.pt.	314563
68	controlled clinical trial.pt.	83211
69	randomized.ab.	220397
70	placebo.ab.	127540
71	drug therapy.fs.	1488387
72	randomly.ab.	159149
73	trial.ab.	227916
74	groups.ab.	1056224
75	67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	2752777
76	exp animals/ not humans.sh.	3654092
77	75 not 76	2335094
78	29 and 77	2268
79	exp Cohort Studies/	1124315
80	cohort$.tw.	181429
81	controlled clinical trial.pt.	83211
82	Epidemiologic Methods/	27602
83	limit 82 to yr="1971-1988"	9410
84	79 or 80 or 81 or 83	1268588
85	29 and 84	1737
86	66 or 78 or 85	5540
87	interview$.mp.	191377
88	experience$.mp.	552122
89	qualitative.tw.	86147
90	qualitative research/	11344
91	87 or 88 or 89 or 90	772947
92	29 and 91	1194
93	86 or 92	6056
94	Economics/	26136
95	exp "costs and cost analysis"/	159102
96	economics, dental/	1829
97	exp "economics, hospital"/	17368
98	economics, medical/	8493
99	economics, nursing/	3851
100	economics, pharmaceutical/	2258
101	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	343421
102	(expenditure$ not energy).ti,ab.	14521
103	value for money.ti,ab.	654

104	budget$.ti,ab.	14687
105	94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104	457195
106	((energy or oxygen) adj cost).ti,ab.	2340
107	(metabolic adj cost).ti,ab.	607
108	((energy or oxygen) adj expenditure).ti,ab.	13432
109	106 or 107 or 108	15754
110	105 not 109	453621
111	letter.pt.	723862
112	editorial.pt.	282269
113	historical article.pt.	278980
114	111 or 112 or 113	1272089
115	110 not 114	428994
116	Animals/	4854330
117	Humans/	12014638
118	116 not (116 and 117)	3572097
119	115 not 118	404419
120	29 and 119	562
121	93 or 120	**6232**

Embase via Ovid searched on 25/08/2011

1	manipulative medicine/	7272
2	bodywork/	45
3	chiropractic/	2951
4	craniosacral therapy/	53
5	orthopedic manipulation/	1881
6	osteopathic medicine/	2414
7	((orthopaedic or orthopedic or chiropract$ or chirother$ or osteopath$ or spine or spinal or vertebra$ or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint$) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	4560
8	((manual or manipulat$ or mobilis$ or mobiliz$) adj (therap$ or intervention$ or treat$ or rehab$)).tw.	2891
9	osteopath$.tw.	4117
10	chiropractic$.tw.	3238
11	chirother$.tw.	40
12	"friction massage$".tw.	41
13	naprapath$.tw.	18
14	Rolfing.tw.	27
15	"myofascial release".tw.	84
16	"Bowen technique".tw.	6
17	"apophyseal glide$".tw.	9
18	"bone setting".tw.	60
19	bonesetting.tw.	14
20	"body work$".tw.	141
21	"high-velocity low-amplitude".tw.	121

22	HVLA.tw.	32
23	((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	39
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	19709
25	meta-analys$.mp.	74979
26	search$.tw.	203498
27	review.pt.	1696600
28	25 or 26 or 27	1878448
29	24 and 28	2776
30	random:.tw.	641600
31	placebo:.mp.	253896
32	double-blind:.tw.	116791
33	30 or 31 or 32	808498
34	24 and 33	2033
35	exp cohort analysis/	98966
36	exp longitudinal study/	44517
37	exp prospective study/	168438
38	exp follow up/	537174
39	cohort$.tw.	227949
40	35 or 36 or 37 or 38 or 39	887958
41	24 and 40	1364
42	interview$.tw.	194152
43	qualitative.tw.	101743
44	exp health care organization/	870597
45	42 or 43 or 44	1110257
46	24 and 45	2741
47	health-economics/	30325
48	exp economic-evaluation/	169204
49	exp health-care-cost/	163072
50	exp pharmacoeconomics/	137702
51	47 or 48 or 49 or 50	388203
52	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	436803
53	(expenditure$ not energy).ti,ab.	17340
54	(value adj2 money).ti,ab.	934
55	budget$.ti,ab.	18435
56	52 or 53 or 54 or 55	455470
57	51 or 56	685131
58	letter.pt.	735696
59	editorial.pt.	376448
60	note.pt.	442547
61	58 or 59 or 60	1554691
62	57 not 61	613975
63	(metabolic adj cost).ti,ab.	657

64	((energy or oxygen) adj cost).ti,ab.	2542
65	((energy or oxygen) adj expenditure).ti,ab.	15191
66	63 or 64 or 65	17722
67	62 not 66	609976
68	exp animal/	1623481
69	exp animal-experiment/	1457412
70	nonhuman/	3690694
71	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.	4063433
72	68 or 69 or 70 or 71	5880755
73	exp human/	12433930
74	exp human-experiment/	292054
75	73 or 74	12435312
76	72 not (72 and 75)	4640149
77	67 not 76	566499
78	24 and 77	1020
79	29 or 34 or 41 or 46 or 78	**7546**

AMED via Ovid searched on 30/08/2011
N.b. no search filters are available for AMED. Therefore, due to high numbers retrieved from the subject search, I have translated the Medline filters used.

1	manipulation/	624
2	musculoskeletal manipulations/	86
3	exp manipulation chiropractic/	851
4	exp manipulation osteopathic/	213
5	spinal manipulation/	706
6	peripheral manipulation/	74
7	chiropractic/	5953
8	osteopathy/	1312
9	mobilisation/	283
10	peripheral mobilisation/	125
11	spinal mobilisation/	124
12	((orthopaedic or orthopedic or chiropract$ or chirother$ or osteopath$ or spine or spinal or vertebra$ or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint$) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	2659
13	((manual or manipulat$ or mobilis$ or mobiliz$) adj (therap$ or intervention$ or treat$ or rehab$)).tw.	1397
14	osteopath$.tw.	1804
15	chiropractic$.tw.	7038
16	chirother$.tw.	32
17	"friction massage$".tw.	28
18	naprapath$.tw.	8
19	Rolfing.tw.	25

20	"myofascial release".tw.	51
21	"Bowen technique".tw.	7
22	"apophyseal glide$".tw.	6
23	"bone setting".tw.	6
24	bonesetting.tw.	3
25	"body work$".tw.	38
26	"high-velocity low-amplitude".tw.	95
27	HVLA.tw.	23
28	((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	20
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	11202
30	meta-analysis.mp,pt.	631
31	review.mp,pt.	14913
32	search$.tw.	3188
33	30 or 31 or 32	16591
34	29 and 33	975
35	randomized controlled trial.pt.	1997
36	controlled clinical trial.pt.	70
37	randomized.ab.	5335
38	placebo.ab.	1981
39	clinical trials/ or randomized controlled trials/ or double blind method/ or random allocation/	3365
40	randomly.ab.	3839
41	trial.ab.	5572
42	groups.ab.	16288
43	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	25693
44	exp animals/ not humans.sh.	5883
45	43 not 44	24839
46	29 and 45	1003
47	cohort studies/	259
48	follow up studies/	896
49	longitudinal studies/	110
50	prospective studies/	370
51	cohort$.tw.	3023
52	47 or 48 or 49 or 50 or 51	4143
53	29 and 52	132
54	interview$.mp.	7711
55	experience$.mp.	14946
56	qualitative.tw.	3977
57	54 or 55 or 56	21625
58	29 and 57	741
59	Economics/	2048
60	exp "costs and cost analysis"/	1023
61	(economic$ or cost or costs or costly or costing or price or prices or pricing or	5729

	pharmacoeconomic$).ti,ab.	
62	(expenditure$ not energy).ti,ab.	225
63	value for money.ti,ab.	18
64	budget$.ti,ab.	166
65	59 or 60 or 61 or 62 or 63 or 64	7429
66	((energy or oxygen) adj cost).ti,ab.	285
67	(metabolic adj cost).ti,ab.	66
68	((energy or oxygen) adj expenditure).ti,ab.	441
69	66 or 67 or 68	724
70	65 not 69	7063
71	letter.pt.	4564
72	editorial.pt.	5336
73	71 or 72	9899
74	70 not 73	6897
75	exp Animals/	65654
76	Humans/	59771
77	75 not (75 and 76)	5883
78	74 not 77	6869
79	29 and 78	536
80	34 or 46 or 53 or 58 or 79	**2749**

Cochrane Airways Group trial register, Cochrane Complementary Medicine Field register and Cochrane Rehabilitation Field register via the Cochrane Library (CENTRAL) searched on 30/08/2011

#1 MeSH descriptor Musculoskeletal Manipulations, this term only
#2 MeSH descriptor Manipulation, Orthopedic, this term only
#3 MeSH descriptor Manipulation, Chiropractic, this term only
#4 MeSH descriptor Manipulation, Spinal, this term only
#5 MeSH descriptor Manipulation, Osteopathic, this term only
#6 MeSH descriptor Chiropractic, this term only
#7 ((orthopaedic or orthopedic or chiropract* or chirother* or osteopath* or spine or spinal or vertebra* or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint*) NEAR/3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)):ti,kw,ab
#8 ((manual or manipulat* or mobilis* or mobiliz*) NEXT (therap* or intervention* or treat* or rehab*)):ti,kw,ab
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Osteopathic Medicine, this term only
#11 osteopath*:ti,kw,ab
#12 chiropractic*:ti,kw,ab
#13 chirother*:ti,kw,ab
#14 (#10 OR #11 OR #12 OR #13)
#15 (#9 OR #14)
#16 ("friction massage" OR "friction massages" OR naprapath* OR Rolfing OR "myofascial release" OR "Bowen technique" OR "apophyseal glide" OR "apophyseal glides" OR "bone setting"

OR bonesetting OR "body work" OR "body works" OR "high-velocity low-amplitude" OR HVLA):ti,kw,ab
#17 ((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) NEAR/3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)):ti,kw,ab
#18 (#16 OR #17)
#19 (#15 OR #18) 1608
#20 (SR-AIRWAYS) in Clinical Trials
26755
#21 (SR-COMPMED) in Clinical Trials
39144
#22 (SR-REHAB) in Clinical Trials 5377
#23 (#19 AND #20) **22**
#24 (#19 AND #21) **810**
#25 (#19 AND #22) **298**

Cochrane Database of Systematic Reviews (CDSR) and CENTRAL via the Cochrane Library searched on 30/08/2011

#1 MeSH descriptor Musculoskeletal Manipulations, this term only
#2 MeSH descriptor Manipulation, Orthopedic, this term only
#3 MeSH descriptor Manipulation, Chiropractic, this term only
#4 MeSH descriptor Manipulation, Spinal, this term only
#5 MeSH descriptor Manipulation, Osteopathic, this term only
#6 MeSH descriptor Chiropractic, this term only
#7 ((orthopaedic or orthopedic or chiropract* or chirother* or osteopath* or spine or spinal or vertebra* or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint*) NEAR/3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)):ti,kw,ab
#8 ((manual or manipulat* or mobilis* or mobiliz*) NEXT (therap* or intervention* or treat* or rehab*)):ti,kw,ab
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Osteopathic Medicine, this term only
#11 osteopath*:ti,kw,ab
#12 chiropractic*:ti,kw,ab
#13 chirother*:ti,kw,ab
#14 (#10 OR #11 OR #12 OR #13)
#15 (#9 OR #14)
#16 ("friction massage" OR "friction massages" OR naprapath* OR Rolfing OR "myofascial release" OR "Bowen technique" OR "apophyseal glide" OR "apophyseal glides" OR "bone setting" OR bonesetting OR "body work" OR "body works" OR "high-velocity low-amplitude" OR HVLA):ti,kw,ab
#17 ((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) NEAR/3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)):ti,kw,ab
#18 (#16 OR #17)
#19 (#15 OR #18)
CDSR **36** (33 reviews, 3 protocols)

DARE	96	
CENTRAL	**1405**	
Methodology database	34	
HTA	17	
NHS EED	20	
Cochrane Groups	0	
TOTAL		**1608**

CINAHL via EBSCO searched on 02/09/2011

n.b. search reads from bottom to top

#	Query	Results
S108	S62 or S75 or S79 or S84 or S107	**3263**
S107	S46 and S106	877
S106	S102 NOT S105	91959
S105	S103 NOT (S103 AND S104)	19393
S104	MH Human	643247
S103	MH Animals	20680
S102	S97 NOT S101	92156
S101	S98 or S99 or S100	284664
S100	PT commentary	123175
S99	PT letter	107805
S98	PT editorial	125645
S97	S95 or S96	100024
S96	TI (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)	68711
S95	S91 or S94	46377
S94	S92 or S93	11637
S93	MH Health Resource Utilization	7062
S92	MH Health Resource Allocation	4823
S91	S85 NOT S90	38689
S90	S86 or S87 or S88 or S89	354375
S89	MH Business+	53776
S88	MH Financing, Organized+	71712
S87	MH Financial Support+	226604
S86	MH Financial Management+	28046
S85	MH Economics+	359283
S84	S46 and S83	279
S83	S80 or S81 or S82	69741
S82	TX qualitative stud*	40219
S81	MH Audiorecording	21422
S80	TI interview OR AB interview	23731
S79	S46 and S78	984
S78	S76 or S77	135735
S77	TI cohort* OR AB cohort*	35468
S76	(MH "Prospective Studies+")	120544

S75	S46 and S74	1557
S74	S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73	589111
S73	TX allocat* random*	248
S72	MH Quantitative Studies	6760
S71	MH Placebos	6004
S70	TX placebo*	21404
S69	TX random* allocat*	2543
S68	MH Random Assignment	26198
S67	TX randomi* control* trial*	30470
S66	TX ((singl* N1 blind*) or (singl* N1 mask*)) or TX ((doubl* N1 blind*) or (doubl* N1 mask*)) or TX ((tripl* N1 blind*) or (tripl* N1 mask*)) or TX ((trebl* N1 blind*) or (trebl* N1 mask*))	491906
S65	TX clinic* N1 trial*	102677
S64	PT Clinical trial	48879
S63	MH Clinical Trials+	97579
S62	S46 and S61	700
S61	S52 NOT S60	33079
S60	S56 OR S59	301587
S59	S57 NOT (S57 AND S58)	19393
S58	MH Human	643247
S57	MH Animals	20680
S56	S53 or S54 or S55	284664
S55	PT Editorial	125645
S54	PT Letter	107805
S53	PT Commentary	123175
S52	S47 or S48 or S49 or S50 or S51	38152
S51	TX systematic review OR TX systematic overview	28467
S50	MH Literature Review+	11509
S49	TX metaanalys*	329
S48	TX meta analys*	15229
S47	MH Meta Analysis	10675
S46	S22 or S28 or S45	33846
S45	S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S44	1297
S44	S40 or S41 or S42 or S43	39
S43	TX (Maitland N3 traction*) or TX (Kaltenborn N3 traction*) or TX (Evejenth N3 traction*) or TX (Evjenth N3 traction*) or TX (Mulligan N3 traction*) or TX (McKenzie N3 traction*) or TX (Cyriax N3 traction*) or TX (Mills N3 traction*) or TX (Mennell N3 traction*) or TX (Stoddard N3 traction*)	5
S42	TX (Maitland N3 mobili?*) or TX (Kaltenborn N3 mobili?*) or TX (Evejenth N3 mobili?*) or TX (Evjenth N3 mobili?*) or TX (Mulligan N3 mobili?*) or TX (McKenzie N3 mobili?*) or TX (Cyriax N3 mobili?*) or TX (Mills N3 mobili?*) or TX (Mennell N3 mobili?*) or TX (Stoddard N3 mobili?*)	27
S41	TX (Maitland N3 adjustment*) or TX (Kaltenborn N3 adjustment*) or TX (Evejenth N3 adjustment*) or TX (Evjenth N3 adjustment*) or TX (Mulligan N3 adjustment*) or TX (McKenzie N3 adjustment*) or TX (Cyriax N3 adjustment*) or TX (Mills N3 adjustment*) or TX (Mennell N3 adjustment*) or TX (Stoddard N3 adjustment*)	0

S40	TX (Maitland N3 manipulat*) or TX (Kaltenborn N3 manipulat*) or TX (Evejenth N3 manipulat*) or TX (Evjenth N3 manipulat*) or TX (Mulligan N3 manipulat*) or TX (McKenzie N3 manipulat*) or TX (Cyriax N3 manipulat*) or TX (Mills N3 manipulat*) or TX (Mennell N3 manipulat*) or TX (Stoddard N3 manipulat*)	11
S39	TX HVLA	41
S38	TX high-velocity low-amplitude	140
S37	TX body work*	685
S36	TX bonesetting	4
S35	TX bone setting	54
S34	TX apophyseal glide*	9
S33	TX Bowen technique	37
S32	TX myofascial release	215
S31	TX Rolfing	72
S30	TX Naprapath*	7
S29	TX friction massage*	45
S28	S23 or S24 or S25 or S26 or S27	27527
S27	TX chirother*	2
S26	TX chiropractic*	24748
S25	TX osteopath*	3416
S24	MH Osteopathy	1205
S23	MH Osteopathic Medicine	77
S22	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S16 or S21	18486
S21	S17 or S18 or S19 or S20	6188
S20	TX (manual N1 rehab*) or TX (manipulat* N1 rehab*) or TX (mobile?* N1 rehab*)	40
S19	TX (manual N1 treat*) or TX (manipulat* N1 treat*) or TX (mobile?* N1 treat*)	557
S18	TX (manual N1 intervention*) or TX (manipulat* N1 intervention*) or TX (mobile?* N1 intervention*)	179
S17	TX (manual N1 therap*) or TX (manipulat* N1 therap*) or TX (mobile?* N1 therap*)	5741
S16	S12 or S13 or S14 or S15	6268
S15	TX (orthop#edic N3 traction*) or TX (chiropract* N3 traction*) or TX (chirother* N3 traction*) or TX (osteopath* N3 traction*) or TX (spine N3 traction*) or TX (spinal N3 traction*) or TX (vertebra* N3 traction*) or TX (craniocervical N3 traction*) or TX (craniosacral N3 traction*) or TX (cervical N3 traction*) or TX (lumbar N3 traction*) or TX (occiput N3 traction*) or TX (invertebral N3 traction*) or TX (thoracic N3 traction*) or TX (sacral N3 traction*) or TX (sacroilial N3 traction*) or TX (joint* N3 traction*)	242
S14	TX (orthop#edic N3 mobili?*) or TX (chiropract* N3 mobili?*) or TX (chirother* N3 mobili?*) or TX (osteopath* N3 mobili?*) or TX (spine N3 mobili?*) or TX (spinal N3 mobili?*) or TX (vertebra* N3 mobili?*) or TX (craniocervical N3 mobili?*) or TX (craniosacral N3 mobili?*) or TX (cervical N3 mobili?*) or TX (lumbar N3 mobili?*) or TX (occiput N3 mobili?*) or TX (invertebral N3 mobili?*) or TX (thoracic N3 mobili?*) or TX (sacral N3 mobili?*) or TX (sacroilial N3 mobili?*) or TX (joint* N3 mobili?*)	1367

S13	TX (orthop#edic N3 adjustment*) or TX (chiropract* N3 adjustment*) or TX (chirother* N3 adjustment*) or TX (osteopath* N3 adjustment*) or TX (spine N3 adjustment*) or TX (spinal N3 adjustment*) or TX (vertebra* N3 adjustment*) or TX (craniocervical N3 adjustment*) or TX (craniosacral N3 adjustment*) or TX (cervical N3 adjustment*) or TX (lumbar N3 adjustment*) or TX (occiput N3 adjustment*) or TX (invertebral N3 adjustment*) or TX (thoracic N3 adjustment*) or TX (sacral N3 adjustment*) or TX (sacroilial N3 adjustment*) or TX (joint* N3 adjustment*)	430
S12	TX (orthop#edic N3 manipulat*) or TX (chiropract* N3 manipulat*) or TX (chirother* N3 manipulat*) or TX (osteopath* N3 manipulat*) or TX (spine N3 manipulat*) or TX (spinal N3 manipulat*) or TX (vertebra* N3 manipulat*) or TX (craniocervical N3 manipulat*) or TX (craniosacral N3 manipulat*) or TX (cervical N3 manipulat*) or TX (lumbar N3 manipulat*) or TX (occiput N3 manipulat*) or TX (invertebral N3 manipulat*) or TX (thoracic N3 manipulat*) or TX (sacral N3 manipulat*) or TX (sacroilial N3 manipulat*) or TX (joint* N3 manipulat*)	4826
S11	MH Trager Method	20
S10	MH Rolfing	58
S9	MH Hellerwork	5
S8	MH Structural-Functional-Movement Integration	33
S7	MH Craniosacral Therapy	220
S6	MH Chiropractic	8641
S5	MH Manipulation, Osteopathic	235
S4	MH Myofascial Release	159
S3	MH Manipulation, Chiropractic	2718
S2	MH Manipulation, Orthopedic	1283
S1	MH Manual Therapy	1906

CINAHL Totals
Subject search = 33846
Subject search plus SIGN SR filter = 700
Subject search plus SIGN RCT filter = 1557
Subject search plus Cohort filter = 984
Subject search plus Qualitative filter = 279
Subject search plus Economic filter = 877
Subject search AND (all filters combined with OR) = 3263

SCI and SSCI via Web of Science searched on 06/09/2011

# 41	**2,585**	#40 AND #25 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 40	**3,199,001**	#39 OR #29 OR #28 OR #27 OR #26 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 39	**1,005,197**	#34 NOT #38 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*

# 38	**29,406**	#37 OR #36 OR #35 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 37	**20,390**	TS=((energy or oxygen) NEAR/1 expenditure) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 36	**1,520**	TS=(metabolic NEAR/1 cost) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 35	**8,646**	TS=((energy or oxygen) NEAR/1 cost) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 34	**1,016,684**	#33 OR #32 OR #31 OR #30 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 33	**57,314**	TS=budget* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 32	**929**	TS="value for money" *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 31	**26,364**	TS=(expenditure* not energy) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 30	**957,320**	TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 29	**940,671**	TS=(interview* or experience* or qualitative) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 28	**208,875**	TS=cohort* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 27	**1,023,892**	TS=(random* or placebo* or double-blind*) or TS=(double SAME blind*) or TI=trial* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 26	**356,113**	TS=("meta analysis" or meta-analys* or "systematic review" or "systematic reviews" or search*) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 25	**8,668**	#24 OR #23 OR #17 OR #4 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 24	**3,599**	TS=((orthopaedic or orthopedic or chiropract* or chirother* or osteopath* or spine or spinal or vertebra* or craniocervical or craniosacral or "cranio sacral" or cervical

		or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint*) NEAR/1 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 23	**2,098**	#22 OR #21 OR #20 OR #19 OR #18 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 22	**1,300**	TS=("manual therapy" or "manual therapies" or "manual therapeutics" or "manual therapist" or "manual therapists" or "manual intervention" or "manual interventions" or "manual treatment" or "manual treatments" or "manual rehabilitation") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 21	**603**	TS=("manipulative therapy" or "manipulative therapies" or "manipulative therapeutics" or "manipulative therapist" or "manipulative therapists" or "manipulative intervention" or "manipulative interventions" or "manipulative treatment" or "manipulative treatments" or "manipulative rehabilitation") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 20	**186**	TS=("manipulation therapy" or "manipulation therapies" or "manipulation therapeutics" or "manipulation therapist" or "manipulation therapists" or "manipulation intervention" or "manipulation interventions" or "manipulation treatment" or "manipulation treatments" or "manipulation rehabilitation") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 19	**13**	TS=("mobilisation therapy" or "mobilisation therapies" or "mobilisation therapeutics" or "mobilisation therapist" or "mobilisation therapists" or "mobilisation intervention" or "mobilisation interventions" or "mobilisation treatment" or "mobilisation treatments" or "mobilisation rehabilitation") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 18	**113**	TS=("mobilization therapy" or "mobilization therapies" or "mobilization therapeutics" or "mobilization therapist" or "mobilization therapists" or "mobilization intervention" or "mobilization interventions" or "mobilization treatment" or "mobilization treatments" or "mobilization rehabilitation") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 17	**407**	#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 16	**94**	TS=((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) NEAR/3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 15	**24**	TS=HVLA

		Databases=SCI-EXPANDED, SSCI Timespan=All Years *Lemmatization=On*
# 14	**80**	TS="high-velocity low-amplitude" *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 13	**118**	TS=("body work" OR "body works" OR "body working") *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 12	**5**	TS=bonesetting *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 11	**20**	TS="bone setting" *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 10	**8**	TS=(apophyseal NEAR/1 glide*) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 9	**2**	TS="Bowen technique" *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 8	**41**	TS="myofascial release" *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 7	**15**	TS=Rolfing *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 6	**6**	TS=naprapath* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 5	**22**	TS=(friction NEAR/1 massage*) *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 4	**4,684**	#3 OR #2 OR #1 *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 3	**39**	TS=chirother* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 2	**2,856**	TS=chiropractic* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*
# 1	**1,948**	TS=osteopath* *Databases=SCI-EXPANDED, SSCI Timespan=All Years* *Lemmatization=On*

MANTIS searched via ChiroAccess (https://www.chiroaccess.com) on 14/09/2011

(meta analysis[all] OR meta-analys*[all] OR systematic review[all] OR systematic reviews[all]) AND (chiropractic[discipline] OR osteopathic medicine[discipline] OR physical therapy[discipline]) Restrict Search Years to: 2009 to 2011	25
(random*[all] OR placebo*[all] OR double-blind*[all] OR double blind*[all] or trial*[ti]) AND (chiropractic[discipline] OR osteopathic medicine[discipline] OR physical therapy[discipline]) Restrict Search Years to: 2009 to 2011	124
(cohort*[all] OR prospective[all]) AND (chiropractic[discipline] OR osteopathic medicine[discipline] OR physical therapy[discipline]) Restrict Search Years to: 1996 to 2011	322
(qualitative[all] OR interview*[all]) AND (chiropractic[discipline] OR osteopathic medicine[discipline] OR physical therapy[discipline]) Restrict Search Years to: 1996 to 2011	378
TOTAL (n.b. it is not possible in MANTIS to combine sets, so I removed duplicates in Reference Manager)	849
After duplicates removed	**788**

Index to Chiropractic Literature searched on 15/09/2011 (http://www.chiroindex.org)

S1	Subject:"Review Literature as Topic", Year: from 2009 to 2011	22
S2	Subject:"Meta-Analysis as Topic", Year: from 2009 to 2011	2
S3	, Year: from 2009 to 2011, Publication Type:Review	80
S4	All Fields:"meta analysis", Year: from 2009 to 2011	11
S5	All Fields:"meta analyse", Year: from 2009 to 2011	1
S6	All Fields:"meta analyses", Year: from 2009 to 2011	3
S7	All Fields:"systematic review", Year: from 2009 to 2011	29
S8	All Fields:"systematic reviews", Year: from 2009 to 2011	12
S9	All Fields:search*, Year: from 2009 to 2011	86
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	131
S11	Subject:"Randomized Controlled Trials as Topic", Year: from 2009 to 2011	6
S12	, Year: from 2009 to 2011, Publication Type:Randomized Controlled Trial	24
S13	, Year: from 2009 to 2011, Publication Type:Controlled Clinical Trial	1
S14	All Fields:random*, Year: from 2009 to 2011	128
S15	All Fields:placebo*, Year: from 2009 to 2011	16
S16	All Fields:"double blind", Year: from 2009 to 2011	2
S17	All Fields:"double blinding", Year: from 2009 to 2011	0
S18	All Fields:"double blinded", Year: from 2009 to 2011	3
S19	Article Title:trial*, Year: from 2009 to 2011	48
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	139
S21	Subject:"Cohort Studies", Year: from 1996 to 2011	8
S22	Subject:"Prospective Studies", Year: from 1996 to 2011	3
S23	All Fields:cohort*, Year: from 1996 to 2011	96
S24	All Fields:prospective, Year: from 1996 to 2011	165
S25	S21 OR S22 OR S23 OR S24	231

S26	Subject:"Qualitative Research", Year: from 1996 to 2011	2
S27	Subject:"Interviews as Topic", Year: from 1996 to 2011	10
S28	All Fields:interview*, Year: from 1996 to 2011	131
S29	All Fields:qualitative, Year: from 1996 to 2011	63
S30	S26 OR S27 OR S28 OR S29	174
S31	S10 OR S20 OR S25 OR S30	**593**

ASSIA via CSA Illumina searched on 16/09/2011

(DE=chiropractic) or(KW=(orthopaedic or orthopedic or chiropract* or chirother* or osteopath* or spine or spinal or vertebra* or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint*) within 3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)) or(KW=(manual or manipulat* or mobilis* or mobiliz*) within 3 (therap* or intervention* or treat* or rehab*)) or(DE=("osteopathy" or "cranial osteopathy")) or(KW=("friction massage*" or naprapath* or Rolfing or "myofascial release" or "Bowen technique" or "apophyseal glide*" or "bone setting" or bonesetting or "body work*" or "high-velocity low-amplitude" or HVLA)) or(KW=(Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) within 3 (manipulat* or adjustment* or mobilis* or mobiliz* or traction*)) **308**

Appendix II – Comparison of studies included in the Bronfort report and new / additional studies in the current review

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Conditions / Interventions with high / moderate quality positive evidence in the Bronfort report					
Musculoskeletal					
Non-specific Low Back Pain (LBP)	Chou 2007 Assendelft 2004 van Tulder 2006 Lawrence 2008 Bronfort 2008 Bronfort 2004 Furlan 2009	*Details of RCTs in reviews not listed* Hallegraeff 2009 Rasmussen 2008 Little 2008 NE, not MT Wilkey 2008 Bogefeldt 2008 Hancock 2007 Ferreira 2007 Eisenberg 2007 Hondras 2009 Mohseni-Bandpei 2006 Beyerman 2006 Poole 2007 NE, not MT Zaproudina 2009	Dagenais 2010 Hettinga 2008 Iversen 2010 Kent 2010 Lin 2011 Louw 2007 Luijsterberg 2007 Machado 2009 Maltby 2009 Rajadurai 2009 Reiman 2009 Rubinstein 2010 Rubinstein 2011 Stuber 2009 Walker 2010 ongoing [protocols]: McCarthy 2008	Arribas 2009 Barra Lopez 2007 Bialosky 2009 Bronfort 2011 Cecchi 2010 Cleland 2009 Ghroubi 2007 Hancock 2008 Hough 2007 Juni 2009 Kilpikoski 2009 Konstantinou 2007 Lewis 2011 Mackawan 2007 Marshall 2008 Paatelma 2008 Petersen 2011 Powers 2008 Senna 2011 Skillgate 2007 / 2010 Sutlive 2009 Venegas-Rios 2009 Zaproudina 2007 Zhang 2008	Rowell 2008 (qual) Schneider 2010 (cohort)

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
				ongoing [protocols]: Maiers 2007 Skillgate 2010 (MINT) Westrom 2010 Wilder 2011	
Mechanical neck pain	Hurwitz 2009 Bronfort 2004 Ernst 2003 Gross 2004 Vernon 2005 Ezzo 2007 NE, not MT	*Details of RCTs in reviews not listed* Hakkinen 2007 Gonzales-Iglesias 2009a Gonzales-Iglesias 2009b Walker 2008 Cleland 2007 Zaproudina 2007 Sherman 2009 NE, not MT	D'Sylva 2010 Gross 2010 Leaver 2010 Macaulay 2007 Miller 2010 Mirallas-Martinez 2007 Schellingerhout 2008 Vernon 2007 *Adverse events:* Carlesso 2010	Aquino 2009 Bablis 2008 Blikstad 2008 Borman 2008 Bosmans 2011 Boyles 2010 Briem 2007 Chiu 2011 Cleland 2010 De Hertogh 2009 Escortell-Mayor 2011 Fernandez-de-las-Penas 2009 Gemmell 2010 Gemmell 2008 Graham 2008 Groeneweg 2010 Jensen 2009 Kanlayanaphotpo 2010 Ko 2010 Lau 2011 Leaver 2010 Madson 2010 Maduro 2011 Mai 2010 Maiers 2007	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
				Mansilla-Ferragut 2009 Martel 2011 Murphy 2010 Nagrale 2010 Pool 2010 Puentedura 2011 Rubinstein 2007 Schumacher 2009 Schwerla 2008 Shamsuddin 2010 Sillevis 2010 Skillgate 2010a Skillgate 2010b Ylinen 2007	
Whiplash-associated disorders	Hurwitz 2009 Seferiadis 2004	Fernandez-de-las-Penas 2004a	Conlin 2005 Martin 2007 Mercer 2007 Teasell 2010 a/b Shaw 2010	Fernandez-de-las-Penas 2004b Kongsted 2007 Sterling 2010 Williamson 2009 [prot] Ventegodt 2004	
Adhesive capsulitis		Bulgen 1984 Guler-Uysal 2004 Johnson 2007 Nicholson 1985 Vermeulen 2006	Alvaro 2001 Ortiz-Lucas 2010	Buchbinder 2007 Hsu 1991 Maricar 1999 Thomas 1980 Wies 2003 Yang 2007	Gaspar 2009 (cohort) Jewell 2009 (cohort)

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Hip pain	Brantingham 2009	Hoeksma 2004 Licciardone 2004	French 2011 Toupin-April 2010 Peter 2010	Abbott 2009 Bennell 2010 [prot] Cibulka 1993 de Luca 2011 [prot] French 2009 [prot] Poulsen 2011 [prot] Shearar 2005 Wong 2004	Jarski 2000 (hip arthroplasty) Wright 2010 (cohort)
Knee pain / disorders	Brantingham 2009	Deyle 2000 Deyle 2005 Suter 2000 NE, no relevant outcomes Bennell 2005 Moss 2007 Tucker 2003 Taylor 2003 NE, <20 Pollard 2008 Perlman 2006 NE, not MT Licciardone 2004	Ellis 2007 French 2011 Jansen 2011 Mook 2009 Toupin-April 2010 Peter 2010	Abbott 2009 Fish 2008 Ko 2009 Lu 2007 Pellecchia 1994 van den Dolder 2006	Stoneman 2001
Patello-femoral pain syndrome		Crossley 2002 Rowlands 1999 Stakes 2006	Bizzini 2003 Crossley 2001	Brantingham 2009 Hains 2010	
Headache disorders					
Migraine Headache	Astin 2002 Bronfort 2004	Parker 1980 Tuchin 2000 Nelson 1998 Lawler 2006 NE, not MT	Chaibi 2011 Posadzki 2011 Vernon 2002	Curtis 2011 Voigt 2011	Schabert 2009 (cohort)
Conditions / Interventions with inconclusive or negative evidence in the Bronfort report and additional conditions not covered by Bronfort					
Musculoskeletal					

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Sciatica / radiating leg pain	Chou 2007 Assendelft 2004 Lawrence 2008	*Details of RCTs in reviews not listed*		Paatelma 2008 McMorland 2010 Schulz 2011 [prot]	
Non-specific mid back pain	None	*[not all thoracic back pain]* Schiller 2001 Cleland 2005 Savolainen 2004 Allison 2002 Bergman 2004 Winters 1997 Winters 1999	Vanti 2008	Crothers 2008 [prot]	
Coccydynia	None	Maigne 2006	No additions	No additions	
Shoulder pain	Green 2003 Desmeules 2003	Bang 2000 Bergman 2004 Conroy 1998 NE, <20 Winters 1999 van der Windt 1998 van den Dolder 2003 NE, not MT	Brantingham 2011 Braun 2010 Camarinos 2009 Ellis 2008 Faber 2006 Ho 2009 Kromer 2009 Kuhn 2009 Michener 2004 Pribicevic 2010 Trampas 2006 Verhagen 2007 a Verhagen 2007 b von der Heyde 2011	Bennell 2010 (RC) Bergman 2010 (gen) Bialoszewski 2011 (RC) Bron 2011 (SP) Chen 2009 (gen) Hains 2010 (SP) McClatchie 2009 (gen) Munday 2007 (IS) Senbursa 2007 (IS) Surenkok 2009 (gen) Teys 2008 (SP)	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Lateral epicondylitis	Bisset 2005 McHardy 2008 Smidt 2003	Langen-Pieters 2003 NE, <20 Vicenzino 1996 NE, <20 Paungmali 2003 Struijs 2003 Vicenzino 2001 Smidt 2002 Drechsler 1997 Dwars 1990 Verhaar 1996 Bisset 2006 Nourbakhsh 2008	Aguilera 2009 Barr 2009 Ellis 2008 Herd 2008 Kohia 2008 Nimgade 2005 Pagorek 2009 Trudel 2004	Blanchette 2011 Coombes 2009 [prot] Kochar 2002 Nagrale 2009 Stasinopoulos 2006 Stratford 1989 Vasseljen 1992	Amro 2010 (CCT) Cleland 2004 (cohort) Rompe 2001 (CCT)
Carpal tunnel syndrome	McHardy 2008 O'Connor 2003 Goodyear-Smith 2004 Piazzini 2007	Davis 1998 Tal-Akabi 2000 NE, <20	Ellis 2008 Huisstede 2010 Hunt 2009 Muller 2004	Bialosky 2009 Burke 2007 Hains 2010	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Ankle and foot conditions	Brantingham 2009 van der Wees 2006	Vicenzino 2006 Eisenhart 2003 Green 2001 Pellow 2001 Coetzer 2001 Collins 2004 NE, <20 Lopez-Rodriguez 2007 NE, no relevant outcomes Kohne 2007 Dimou 2004 Govender 2007 Shamus 2004 Brantingham 2005 Brooks 1981 Wynne 2006 Cleland 2009 Lin 2008	Lin 2008 (ankle fracture) Bleakley 2008 (sprains)	Wilson 1991 (ankle fractures) Joseph 2010 (sprains) Davenport 2010 (sprains) [prot] Du Plessis 2001 (hallux) Kuhar 2007 (plantar fasciitis) Renan-Ordine 2011 (plantar heel pain)	
Temporomandibular disorders	McNeely 2006 Medlicott 2006	Taylor 1994 NE, <20 Carmeli 2001 de Laat 2003 NE, not MT Monaco 2008 NE, no relevant outcomes Ismail 2007	De Souza 2008 [protocol]	Cuccia 2010 Kalamir 2010 Yoshida 2005	
Fibromyalgia	Schneider 2009 Ernst 2009 Goldenberg 2004	Blunt 1997 Tyers 2001 Wise 2002 Panton 2009 Gamber 2002 Brattberg 1999 NE, not MT Richards 2000 NE, not MT Ekici 2009 NE, not MT	Baranowsky 2009 Porter 2010	Castro-Sanchez 2011a Castro-Sanchez 2011b	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Myofascial Pain Syndrome Definition	Vernon 2009	Vicenzino 1996 NE, <20 Gam 1998 NE, not MT Dardzinski 2000 NE Greene 1990 Hanten 2000 Jaeger 1986 NE Hong 1993 Hou 2002 Hanten 1997 NE, no relevant outcomes Fernandez-de-las-Penas 2009 Terrett 1984 NE, healthy individuals Vernon 1990 NE, <20 Cote 1994 Atienza-Meseguer 2006 Fryer 2005	de las Peñas 2005 Rickards 2006	Gemmell 2008a Gemmell 2008b Nagrale 2010	
Headache disorders					
Tension-Type Headache	Astin 2002 Bronfort 2004 McCrory 2001 Lenssinck 2004 Fernandez-de-las-Penas 2006	Boline 1995 Bove 1998 Hanten 1999 Demirturk 2002 Donkin 2002 Ahonen 1984 Carlsson 1990 Wylie 1997 NE, not MT Hoyt 1979 NE, <20 Jay 1989 Marcus 1995 NE, not MT Anderson 2006		Anderson 2006 Castien 2011 Van Ettekoven 2006 Vernon 2009	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Cervicogenic Headache	Hurwitz 2009 Astin 2002 Bronfort 2004 Fernandez-de-las-Penas 2005	Bitterli 1977 Howe 1983 Ammer 1990 Jull 2002 Nilsson 1997 Whittingham 1999 Hall 2007	Posadzki 2011	Borusiak 2010 Haas 2004 Haas 2010 von Piekartz 2011	
Miscellaneous Headache	Bronfort 2004	Jensen 1990	Biondi 2005 Bryans 2011 Maltby 2008	de Hertogh 2009 Foster 2004	
Non-musculoskeletal					
ADHD / Learning disorders	*not reported*	*not reported*	Karpouzis 2010	Bierent 2005 Brzozowske 1977 [not available] Hubmann 2006	
Asthma	Ernst 2009 Hondras 2001 Balon 2004 Hawk 2007	Nielsen 1995 Balon 1998 Guiney 2005 Field 1998 NE, not MT Brygge 2001 NE, not MT	Kaminskyj 2010	Mehl-Madrona 2007 Bronfort 2001	Shaw 2006 (qual)
Birth / Pregnancy / Post-natal			Khorsan 2009 Stuber 2008	Cameron 2005	Guthrie 1982 King 2003 Phillips 1995 Pizzolorusso 2011
Cancer care	*not reported*	*not reported*	Alcantara 2011		
Cardiovascular disorders	*not reported*	*not reported*			Lombardini 2009
Cerebral palsy	*not reported*	*not reported*		Duncan 2004 Duncan 2008 Wyatt 2001	
Chronic fatigue	*not reported*	*not reported*	Porter 2010		

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Chronic pelvic pain				Fitzgerald 2009 Heyman 2006 Marx 2009	
Cystic fibrosis	*not reported*	*not reported*		Sandsund 2011	
Diabetes complications	*not reported*	*not reported*		Diaz 2009	
Gastrointestinal	*not reported*	*not reported*	Ernst 2011	Pikula 1999 Hains 2007 Hundscheid 2007	
Pneumonia / respiratory infections	Hawk 2007	Noll 2000	Yang 2010	Kline 1965 Noll 1999 Noll 2008 [prot]	
Vertigo	Hawk 2007 Reid 2005	Karlberg 1996 Reid 2008	Lystad 2011	Hawk 2009	
Infantile Colic	Hawk 2007 Husereau 2003 Brand 2005 Ernst 2003 Gotlib 2008 Ernst 2009	Koonin 2003 NE, conference Mercer 1999 NE, conference Wiberg 1999 Browning 2009 Olafsdottir 2001 Hayden 2006 Huhtala 2000 NE, not MT Arikan 2008 NE, not MT	Alcantara 2011 Perry 2011		Miller 2009 (controlled cohort)
Menopausal symptoms	*not reported*	*not reported*		Cleary 1994	
Insomnia			Kingston 2010		
Nocturnal Enuresis	Hawk 2007 Glazener 2005	Reed 1994 Leboeuf 1991 NE, no control group	Huang 2011		
Parkinson's	*not reported*	*not reported*		Wells 1999	
Paediatric dysfunctional voiding	*not reported*	*not reported*		Nemett 2008	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
Otitis Media	Hawk 2007 Ernst 2008 Gotlib 2008	Mills 2003 Wahl 2008		Steele 2010 [prot]	
Hypertension	Hawk 2007	Goertz 2002 Yates 1988 Bakris 2007	Mangum 2012	Morgan 1985 Plaugher 2002	Cerritelli 2011 (CCT)
Dysmenorrhoea	Hawk 2007 Proctor 2006	Boesler 1993 Snyder 1996 Kokjohn 1992 Tomason 1979 Hondras 1999	No additions	No additions	
Premenstrual Syndrome	Hawk 2007 Stevinson 2001 Fugh-Berman 2003	Walsh 1999 Hernandez-Reif 2000 NE, not MT Oleson 1993 NE, not MT	No additions	No additions	
Surgery rehabilitation and related	*not reported*	*not reported*		Goldstein 2005 (hysterectomy) Hunter 2011 (stroke rehab) Sleszynski 1993 (atelectasis)	Crow 2009 (comparative cohort) Jarski 2000 (CCT) Yurvati 2005 (bypass surgery) (CCT)
Systemic sclerosis	*not reported*	*not reported*		Maddali Bongi 2009 a Maddali Bongi 2009 b	
Adverse events	Ernst 2007 Haldeman 1992 Rubinstein 2005 Rubinstein 2008 Vohra 2007	*Primary studies:* Cassidy 2008 Haldeman 2001 Hurwitz 2004 Hurwitz 2005 Michaeli 1993 Stevinson 2001	Carnes 2010 Gotlib 2002 Gouveia 2009 Haldeman 1999 Humphreys 2010 Inamasu 2005 Miley 2008 Miller 2009 Stevinson 2002	*Primary studies:* Alcantara 2009 Barrett 2000 Boyle 2008 Cagnie 2004 Choi 2011 Dittrich 2007 Dziewas 2003 Ebrall 2000	

Condition	**Bronfort**		**Current review (additional studies)**		
	Systematic reviews	*RCTs*	*Systematic reviews*	*RCTs*	*Other primary study types*
			Walker 2010 Vick 1996	Haldeman 2002a Haldeman 2002b Haldeman 2002c Haneline 2003 Hayes 2006 Klougart 1996a Klougart 1996b Lee 1995 Malone 2002 Miller 2008 Oppenheim 2005 Rajendran 2009 Reuter 2006 Rivett 1996 Rothwell 2001 Senstad 1996 Senstad 1997 Smith 2003 Stevinson 2002 Sweeney 2010 Terrett 1988 Thiel 2007 Thistle 2008 Wolf 1996 Wu 2010	

Abbreviations: NE – not eligible, MT – manual therapy

Appendix III – Quality assessment tables for condition overview

Systematic reviews

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?	Overall
Musculoskeletal												
Mid-back pain												
Vanti 2008	+	?	+	–	–	+	?	?	+	–	–	4/11
Ankle and foot conditions												
Bleakley 2008	+	–	+	?	+/–	+	+	+	+	–	–	6.5/11
Lin 2008	+	+	+	–	+	+	+	+	+	–	+	9/11
Carpal tunnel syndrome												
Ellis 2008	+	+/–	+	?	+/–	+	+	+	+	–	–	7/11
Huisstede 2010	+	+	+	?	+/–	+	+	+	+	–	+	8.5/11
Hunt 2009	+	+	+	–	+/–	+	+	+	+	–	+	8.5/11
Muller 2004	+	+/–	+	+	+	+	+	+	+	–	+/–	9/11

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?	Overall
Lateral epicondylitis												
Herd 2008	+	?	+	–	+	+	+	+	+	–	–	7/11
Kohia 2008	–	?	–	–	+	+	+	+	+	–	–	5/11
Nimgade 2005	+	?	+	–	+	+	+	+	+	–	–	7/11
Trudel 2004	+	?	–	–	+	+	+	+	+	–	+	7/11
Shoulder conditions												
Brantingham 2011	+	+/–	+	?	+/–	+	+	+	+	–	+	8/11
Braun 2009	+	?	+	?	+	+	+	+	+	–	+	8/11
Camarinos 2009	+	+/–	+	?	+/–	+	+	+	+	–	–	7/11
Pribicevic 2010	+	?	+	?	+/–	+	+	+	+	–	+	7.5/11
Headache												
Cervicogenic headache												
Posadzki 2011	+	+	+	–	+	+	+	+	+	–	+	9/11
Miscellaneous headache												
Bryans 2011	+	+	+	–	+	+	+	+	+	–	+	9/11

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?	Overall
Myofascial pain syndrome												
de las Peñas 2005	+	+/–	+	?	+/–	+	+	+	+	–	–	7/11
Richards 1006	+	–	+	?	+/–	+	+	+	+	–	–	6.5/11
Non-musculoskeletal												
Asthma												
Kaminskyi 2010	+	+	+	–	+/–	+	+	+	+	–	–	7.5/11
ADHD / learning disabilities												
Karpouzis 2010	+	+/–	+	–	+	+	+	+	+	–	+	8.5/11
Cancer care												
Alcantara 2011	+	+/–	+	?	–	+/–	–	–	+/–	–	–	3.5/11
Cervicogenic dizziness												
Lystad 2011	+	+	+	?	+	+	+	+	+	–	+	9/11
Chronic fatigue / fibromyalgia												
Porter 2010	+	+	+	–	+	+	+	+	+	–	+	9/11

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?	Overall
Paediatric nocturnal enuresis												
Huang 2011	+	+	+	?	+	+	+	+	+	–	+	9/11
Pneumonia												
Yang 2010	+	+	+	–	+	+	+	+	+	+/–	+	9.5/11
Infantile colic												
Alcantara 2011 (colic)	+	+/–	+	–	–	+/–	–	–	+/–	–	–	3.5/11
Perry 2011	+	+/–	+	?	+/–	+	+	+	+	–	+	8/11
Gastrointestinal disorders												
Ernst 2011	+	+/–	+	–	–	+/–	+	+	+/–	–	+	6.5/11
Hypertension												
Mangum 2012	+	+/–	+	?	+/–	+/–	+	+	+	–	+	7.5/11
Insomnia												
Kingston (2010)	+	+/–	?	?	–	–	–	?	?	–	+	2.5/11

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?	Overall
Pregnancy / obstetric care / neonatal care												
Khorsan 2009	+	?	+	–	+	+	+	+	+	–	–	7/11
Adverse events												
Carlesso 2010	+	+	+	+	–	+	+	+	+	–	–	8/11
Carnes 2009 Carnes 2010	+	+	+	–	+	+	+	+	+	–	+	9/11
Gouveia 2009	+	+	–	–	+	+	–	–	+	–	+	6/11
Haldeman 1999	+	?	+	?	+	+	–	–	?	–	–	4/11
Miley 2008	+	?	+	?	–	–	–	?	+	–	+	4/11
Stevinson 2002	–	?	+	?	+	+	–	–	–	–	–	3/11
Stuber 2012	+	?	+	–	+	+	+	+	+	–	+	8/11

+ 'Yes'; – 'No'; +/– Partial 'Yes'; ? 'Not clear'; *Rating (by criteria fulfilled, i.e. 'yes' response):* 9 to 11 high quality, 5 to 8 medium quality, 0 to 4 low quality.

RCTs

Study	Adequate sequence generation	Adequate allocation concealment	Blinding (especially outcome assessment)	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)	Overall
Musculoskeletal							
Sciatica							
McMorland 2010	+	?	?	+	+	+	4/6
Paatelma 2008	+	+	?	+	+	+	5/6
Neck pain							
Aquino 2009	+	?	+	+	+	–	4/6
Gemmell 2010	+	+	–	+	+	–	4/6
Leaver 2010	+	+	?	+	+	+	5/6
Martel 2011	?	+	–	+	+	+	4/6
Puentedura 2011	?	+	+	+	+	–	4/6
Schomacher 2009	?	?	?	+	+	?	2/6
Ankle and foot disorders							
Kuhar 2007	–	–	?	?	?	?	0/6
Joseph 2010	+	?	?	?	+	+ / –	2.5/6
du Plessis 2011							
Renan-Ordine 2011	+	?	+ / –	–	+	+	3.5/6
Carpal tunnel syndrome							
Hains 2010	+	+	–	+	+	+ / –	4.5/6
Lateral epicondylitis							

Study	Adequate sequence generation	Adequate allocation concealment	Blinding (especially outcome assessment)	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)	Overall
Blanchette 2011	?	–	–	+	+	?	2/6
Nagrale 2009	?	?	+	+	+	?	3/6
Shoulder disorders							
Bialoszewski 2011	?	?	?	–	+	+ / –	1.5/6
Bron 2011	+	+	+ / –	+	+	+	5.5/6
Temporomandibular disorders							
Cuccia 2010	?	?	?	?	+	–	1/6
Kalamir 2010	+	+	+	+	+	?	5/6
Yoshida 2005	?	?	?	?	+	?	1/6
Headache and other							
Cervicogenic headache							
von Piekartz 2011	+	–	+	+	+	+	5/6
Tension-type headache							
Anderson 2006	+	?	+	+	+	?	4/6
Castien 2011 Castien 2009	?	+	+	+	+	–	4/6
van Ettekoven 2006	+	+	+	+	–	+	5/6
Vernon 2009	?	+	+	–	+	–	3/6
Miscellaneous headache							
de Hertogh 2009	?	+	+	+	+	–	4/6
Foster 2004	?	?	–	+	+	+	3/6
Fibromyalgia							

Study	Adequate sequence generation	Adequate allocation concealment	Blinding (especially outcome assessment)	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)	Overall
Castro-Sanchez 2011a (Clin Rehab)	+	?	+ / –	?	+	+ / –	3/6
Castro-Sanchez 2011b (EB CAM)	?	?	+ / –	–	+	+ / –	2/6
Myofascial pain syndrome							
Gemmell 2008a	+	–	+ / –	+	+	+	4.5/6
Gemmell 2008b	+	?	+ / –	+	+	+	4.5/6
Nagrale 2010	+	?	+ / –	+	+	+ / –	4/6
Non-musculoskeletal							
Asthma							
Mehl-Madrona 2007	+	+	+ / –	–	+ / –	+ / –	3.5/6
ADHD / learning disabilities							
Bierent-Vass 2005	?	?	?	?	?	?	0/6
Hubmann 2006	?	?	?	?	?	?	0/6
Cerebral palsy							
Duncan 2004	?	?	?	–	+	?	1/6
Duncan 2008	+ / –	+	+ / –	+	+	+ / –	4.5/6
Wyatt 2011	+	?	+ / –	?	+	+	3.5/6
Cervicogenic dizziness / balance							
Hawk 2009	?	?	+ / –	+ / –	+	+ / –	2.5/6
Chronic pelvic pain							
FitzGerald 2009	+	?	+ / –	+	+	+	4.5/6
Heyman 2006	?	?	–	?	+	+	2/6
Marx 2009	+	?	?	–	+	+ / –	2.5/6

Study	Adequate sequence generation	Adequate allocation concealment	Blinding (especially outcome assessment)	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)	Overall
Cystic fibrosis							
Sandsund 2011	+	?	+ / –	+	+	?	3.5/6
Dysfunctional voiding							
Nemett 2008	–	–	–	–	+	?	1/6
Menopausal symptoms							
Cleary 1994	–	?	+ / –	?	+	?	1.5/6
Gastrointestinal disorders							
Hundscheid 2006	–	–	–	+	+	?	2/6
Parkinson's disease							
Wells 1999	?	?	+	NA	?	?	1/6
COPD							
Noll 2006	?	?	+	+	+	?	3/6
Pregnancy / obstetric care / neonatal care							
Goldstein 2005	–	–	+	?	+	?	2/6
Rehabilitation							
Hunter 2011	–	+	?	+	+	–	3/6
Sleszynski 1993	–	?	+	+	+	?	3/6
Goldstein 2005	–	–	+	?	+	?	2/6
Systemic sclerosis							
Maddali Bongi 2009 a	+	?	?	NA +	+	+/–	3.5/6
Maddali Bongi 2009 a	+	?	?	NA +	+	+/–	3.5/6

+ 'Yes'; – 'No'; +/– Partial 'Yes'; ? 'Not clear'; *Rating (by criteria fulfilled, i.e. 'yes' response):* 5 to 6 high quality, 3 to 4 medium quality, 0 to 2 low quality

Controlled cohort studies

Study	Sufficient description of the groups and the distribution of prognostic factors?	Groups assembled at a similar point in their disease progression?	Intervention/treatment reliably ascertained?	Groups comparable on all important confounding factors?	Adequate adjustment for the effects of these confounding variables?	Outcome assessment blind to exposure status?	Follow-up long enough for the outcomes to occur?	Adequate proportion of the cohort followed up?	Drop-out rates and reasons for drop-out similar across intervention and unexposed groups?	Overall
Musculoskeletal										
Lateral epicondylitis										
Amro 2010	+	+	+	?	–	–	–	?	?	3/9
Cleland 2004	+	?	+	–	–	–	+	?	?	3/9
Rompe 2001	–	?	+	?	–	–	+	?	?	2/9
Non-musculoskeletal										
Osteosarcoma										
Wu 2010	+	+	+	+	?	–	+	?	?	5/9
Hypertension										
Cerretelli 2011	+	+	+	+	+	–	+	?	?	6/9
Peripheral arterial disease										
Lombardini 2009	+	+	+	+	–	+/–	+	+	?	6.5/9
Pregnancy / obstetric care / neonatal care										
Pizzolorusso 2011	+	+	+	–	?	?	–	+	+	5/9
Rehabilitation										

Study	Sufficient description of the groups and the distribution of prognostic factors?	Groups assembled at a similar point in their disease progression?	Intervention/treatment reliably ascertained?	Groups comparable on all important confounding factors?	Adequate adjustment for the effects of these confounding variables?	Outcome assessment blind to exposure status?	Follow-up long enough for the outcomes to occur?	Adequate proportion of the cohort followed up?	Drop-out rates and reasons for drop-out similar across intervention and unexposed groups?	Overall
Crow 2009	–	+	+	?	–	–	+	?	?	3/9
Yurvati 2005	+	?	+	–	–	–	+	?	?	3/9
Jarski 2000	+	+	+	+	–	?	–	+	+	6/9
Adverse events										
Boyle 2008	–	+	–	?	–	–	+	?	?	2/9
Hayes 2006	–	–	+	–	–	–	+	+	–	3/9
Miller 2008	–	–	+	–	–	–	?	+	–	2/9
Rajendran 2009	–	–	+	–	–	–	–	–	–	1/9

+ 'Yes'; – 'No'; +/– Partial 'Yes'; ? 'Not clear'; *Rating (by criteria fulfilled, i.e. 'yes' response):* 7 to 9 high quality, 4 to 6 medium quality, 0 to 3 low quality

Qualitative studies

Study	Clear statement of the aims of the research?	Qualitative methodology appropriate?	Research design appropriate to address the aims of the research?	Recruitment strategy appropriate to the aims of the research?	Data collected in a way that addressed the research issue?	Relationship between researcher and participants adequately considered?	Ethical issues taken into consideration?	Data analysis sufficiently rigorous?	Clear statement of findings?	Contributions and implications of the research discussed?	Overall
Non-musculoskeletal											
Asthma											
Shaw 2006	+	+	+	+	+	?	?	+	+	+	8/10

+ 'Yes'; – 'No'; +/– Partial 'Yes'; ? 'Not clear'; *Rating (by criteria fulfilled, i.e. 'yes' response):* 8 to 10 high quality, 5 to 7 medium quality, 0 to 4 low quality

Appendix IV – Ongoing studies

Ongoing Systematic reviews

Study and Participants	Inclusion criteria and methodology
Musculoskeletal disorders	
Temporomandibular disorders	
Freitas de Souza 2008[152] **Focus:** effectiveness/safety of any form of non-invasive or surgical treatment in adults adults (> 18 years) with clinical/radiological diagnosis of temporomandibular joint osteoarthritis	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** adults with clinical/radiological diagnosis of temporomandibular joint osteoarthritis **Interventions**: any form of non-invasive or surgical treatment, placebo, no treatment **Outcomes:** pain, extent of mandibular movement, temporomandibular joint sounds, quality of life, number of visits, morphological changes, number of days absent from work, adverse events, and costs **METHODOLOGY** 5 relevant databases will be searched without language restriction; hand search of reference lists; details on study selection, extraction, quality assessment of studies (the Cochrane Collaboration risk of bias tool), and data synthesis will be presented; excluded studies and reasons for exclusions will be listed **Data analysis:** text and tables **Subgroups / sensitivity analyses:** will be reported

Ongoing RCTs

Study and Participants	Interventions	Outcomes
Musculoskeletal disorders		
Sciatica / back-related leg pain		
Schulz 2011 [79] USA RCT **Focus:** RCT to evaluate the effectiveness of adding chiropractic spinal manipulative therapy (SMT) to home exercise program (HEP) in patients with subacute or chronic back-related leg pain **PARTICIPANTS:** **N:** 192 **Age:** >21 years **Inclusion**: Low back pain and related leg pain (sciatica)(sub-acute, chronic) [non-specific] for > 4 wks; pain intensity > 3 (0-10 scale) classified as 2, 3, 4, or 6 according to the Quebec Task Force classification system which includes radiating pain into the proximal or distal part of the lower extremity with/without neurological signs with possible compression of a nerve root **Exclusion**: ongoing treatment for leg or low back pain, progressive neurological deficits, blood clotting disorders, pregnancy, lumbar surgery, uncontrolled hypertension, metabolic disease, drug abuse	**Intervention type:** chiropractic **Intervention 1:** chiropractic spinal manipulative therapy including high velocity, low-amplitude manipulation, low velocity mobilisation, light soft-tissue techniques, and hot/cold packs (up to 20 treatments during 12 weeks; each visit lasts 10-20 minutes) **Intervention 2:** Home exercise program consisting of teaching methods for developing spinal posture awareness for activities of daily living; exercise such as flexion/extension motion cycles, hip/knee stretches, prone press-ups, slow lunges, abdominal curl-ups, leg/arm extension in order to enhance mobility and increase trunk endurance (4 one-hour sessions for 12 weeks) **Dose:** see above **Providers:** chiropractor	**Outcome measures (follow-up: 3, 12, 26, and 52 weeks post-baseline)** **Primary:** Leg pain (11-box scale) **Secondary:** Low back pain (11-box scale), Bothersomeness of symptoms (0-5 scale) Frequency of symptoms (0-5 scale) Disability (Roland-Morris Disability Index) General health status (SF-36) Patient satisfaction (1-7 scale) Medication use (5-point scale) Quality of life (EuroQol 5D) Self-efficacy Straight leg raise test Torso muscle endurance Adverse events

Study and Participants	Interventions	Outcomes
Thoracic back pain		
Crothers 2008[87] Australia **Focus:** effectiveness of spinal manipulation and Graston technique versus placebo for non-specific mid-back pain **Duration:** 3 to 4 weeks **Follow-up:** 1 year **PARTICIPANTS:** **N:** 60 **Age:** adults **Inclusion:** non-specific thoracic spine pain	**Intervention type:** chiropractic **Intervention 1:** spinal manipulative therapy (thoracic spine) **Intervention 2:** Graston Technique (a soft tissue massage therapy using hand-held stainless steel instruments) **Comparison:** placebo (de-tuned ultrasound) **Dose:** spinal manipulation/de-tuned ultrasound: 10 sessions; Graston therapy: 2 treatments/week **Providers:** chiropractors and final year chiropractic students	**Outcome measures:** **Primary:** pain (VAS) **Other:** modified Oswestry Back Pain Disability Index, adverse effects
Ankle sprains		
Davenport 2010[96] USA **Focus:** effectiveness of ankle manual therapy versus placebo for post-acute ankle sprains **Duration:** 4 weeks **Follow-up:** 2 years **PARTICIPANTS:** **N:** 189 **Age:** 16 to 60 years **Inclusion:** onset of ankle sprain at least 2 weeks prior to enrolment, Foot and Ankle Ability Measure Activities of Daily Living (FAAM ADL) score ≤67 points	**Intervention type:** physiotherapy **Intervention 1 (n=63):** talocrural traction manipulation plus range of motion exercises **Intervention 2 (n=63):** talocrural traction mobilisation plus range of motion exercises **Comparison (n=63) :** sham intervention plus range of motion exercises **Dose:** 5 treatment sessions, 2 in the first week and one each in each consecutive week **Providers:** not stated	**Outcome measures:** **Primary:** Foot and Ankle Ability Measure (FAAM) **Other:** anterior drawer test (assessment of integrity of anterior talofibular ligament), inversion stress manoeuvre, volumetric measurement of foot, ankle and lower leg, pain (NRS), Fear Avoidance Beliefs, Lower Extremity Self-Efficacy Scale, Positive and Negative Affect Scale, Patient Global Rating of Change, lower extremity range of motion, lower extremity manual muscle testing, start balance excursion test

Study and Participants	Interventions	Outcomes
Lateral epicondylitis		
Coombes 2009[118] Australia **Focus:** RCT to evaluate the clinical effectiveness, harms, and cost-effectiveness of adding physiotherapy to corticosteroid injections for treatment of adult patients with LE **Duration:** 8 weeks **Follow-up:** 52 weeks **PARTICIPANTS:** **N:** 132 **Age:** 18-70 years **Inclusion:** adults 18-70 years old with unilateral elbow pain for > 6 weeks; pain severity 30mm or greater on a 100mm VAS; pain provoked by at least two of the following: gripping, palpation, stretching of forearm extensor muscles, resisted wrist or middle finger extension; reduced pain-free grip force; willingness to comply; an acceptable understanding of written/spoken English	**Intervention type:** physiotherapy **Intervention:** physiotherapy Education: advice on activity modification, pain management Manipulation: mobilisation with movement, lateral elbow glide, postero-anterior radioulnar glide, de-loading of the common extensor origin Therapeutic/home exercise: sensorimotor retraining of gripping and forearm movement, posture correction, progressive resistance exercise for the wrist extensors, combined concentric eccentric exercise, exercise for arm strengthening **Intervention 1 (n=33):** corticosteroid injection (1 ml lignocaine [1%]) with physiotherapy (education, manipulation/mobilisation with movement, and therapeutic/home exercise) **Intervention 2 (n=33):** corticosteroid injection (1 ml lignocaine [1%]) **Intervention 3 (n=33):** saline injection (0.5 ml isotonic saline [0.9%]) with physiotherapy (education, manipulation, and therapeutic/home exercise) **Comparison (n=33):** saline injection (0.5 ml isotonic saline [0.9%]) **Dose:** physiotherapy (8 sessions), saline injection (0.5 ml isotonic saline), corticosteroid injection (1 ml lignocaine) **Providers:** trained practitioners	Outcomes measured at 4, 8, 12, 26, and 52 weeks post-baseline **Primary** • Global improvement (6-point Likert scale) • Success (success versus no success) • Recurrence (success at 4-8 weeks but no success beyond 8 weeks) **Secondary** • Pain severity (VAS score) • PRTEE (11-point Likert scale) • Pain-free grip force (kg; dynamometer) • Pressure pain threshold • Hospital Anxiety and Depression Scale (HADS) • Quality of life (EuroQol EQ-5D) • Adverse events • Costs

Study and Participants	Interventions	Outcomes
Non-musculoskeletal disorders		
Otitis media		
Steele 2010[207] USA **Focus:** RCT of the effectiveness of an osteopathic manipulative medicine protocol on middle ear effusion after an episode of acute otitis media in young children **Duration:** 5 weeks **Follow-up:** no post-intervention follow-up **PARTICIPANTS:** **N:** 26 **Age:** 6 to 24 months **Inclusion:** acute otitis media, abnormal tympanogram results	**Intervention type:** osteopathy **Intervention:** standardised osteopathic manipulative medicine protocol (using myofascial release, balanced ligamentous tension, suboccipital inhibition, venous sinus drainage, occipital decompression, sphenobasilar symphysis decompression techniques) **Comparison:** no osteopathic manipulation **Dose:** 5 study visits **Providers:** osteopathic physician	**Outcome measures:** Middle ear effusion (tympanograms), interviews with parents, logs completed by parents, adverse events
Pneumonia		
Noll 2008a[210] USA **Focus:** RCT of the effectiveness of osteopathic manipulative treatment in elderly patients with pneumonia (MOPSE trial) **Duration:** 5 weeks **Follow-up:** no post-intervention follow-up **PARTICIPANTS:** **N:** not reported **Age:** ≥50 years **Inclusion:** new pulmonary infiltrate consistent with pneumonia, at least 2 clinical findings consistent with acute pneumonia	**Intervention type:** osteopathy **Intervention:** standardised osteopathic manipulative medicine protocol (using soft tissue techniques (massage across thoracic paraspinal muscle), rib raising, doming the diaphragm, soft tissue massage to cervical paraspinal muscles, myofascial release to the thoracic inlet, thoracic lymphatic pump with activation, pedal lymphatic pump) **Control 1:** light touch **Control 2:** conventional treatment only **Dose:** first session within 24 h of hospital admission, 2 daily treatment sessions at least 6 h apart until discharge, cessation of antibiotic therapy, ventilator-dependent respiratory failure or death **Providers:** osteopathic physician	**Outcome measures:** Length of hospital stay, time to clinical stability, rate of symptomatic and functional recovery, duration of antibiotic use, complications, death, ventilator-dependent respiratory failure, duration and severity of fever, leukocytosis, patient satisfaction

Appendix V – Additional tables for cost-effectiveness review

Section A

Figure 12. Study Flow Diagram: cost-effectiveness/utility studies

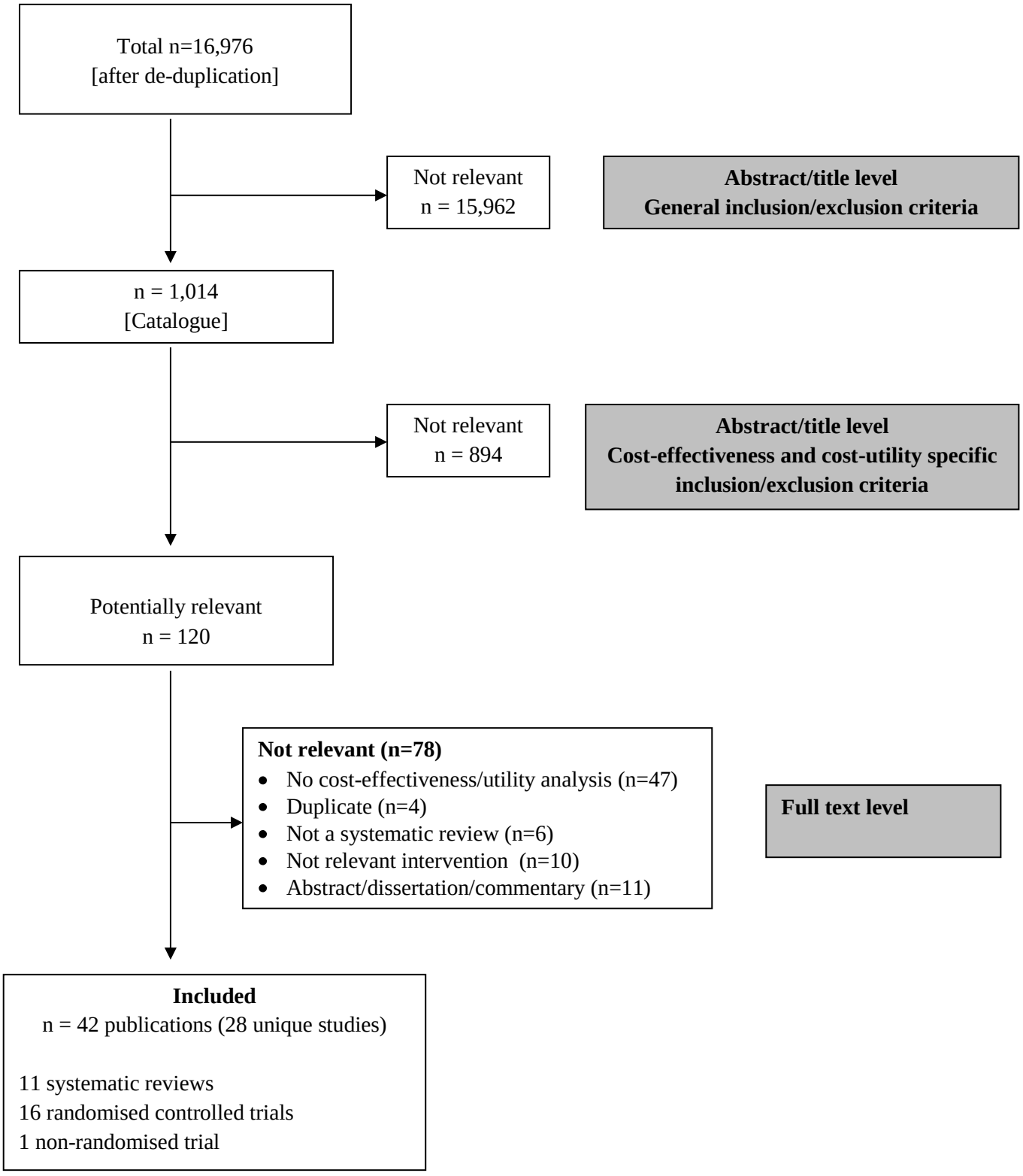


Table 4. List of excluded studies (a sample)

Study (Author, name)	Reference		Reason for exclusion
	Title	Source	
Liliedahl 2010	Cost of care for common back pain conditions initiated with chiropractic doctor vs medical doctor/doctor of osteopathy as first physician: experience of one Tennessee-based general health insurer	Journal of Manipulative & Physiological Therapeutics 33(9), 640-643	Only costs; no cost-effectiveness/utility analysis
Grieves 2009	Cost minimization analysis of low back pain claims data for chiropractic vs medicine in a managed care organization	Journal of Manipulative & Physiological Therapeutics 32(9), 734-739	Only costs; no cost-effectiveness/utility analysis
Schabert 2009	Impact of osteopathic manipulative treatment on cost of care for patients with migraine headache: a retrospective review of patient records	Journal of the American Osteopathic Association 109(8), 403-407	Only costs; no cost-effectiveness/utility analysis
Sharma 2009	Determinants of costs and pain improvement for medical and chiropractic care of low back pain	Journal of Manipulative & Physiological Therapeutics 32(4), 252-261	Non-comparative, prognostic study; no cost-effectiveness
Buchbinder 2007	Efficacy and cost-effectiveness of physiotherapy following glenohumeral joint distension for adhesive capsulitis: a randomized trial	Arthritis & Rheumatism 57(6), 1027-1037	Cost and effect analysed separately; no cost-effectiveness/utility analysis
Gamber 2005	Cost-effective osteopathic manipulative medicine: a literature review of cost-effectiveness analyses for osteopathic manipulative treatment	The Journal of the American Osteopathic Association 105(8), 357-367	Not a systematic review
Kukurin 1995	Chiropractic versus medical management of work-related back injuries: cost comparison studies of workers compensation cases	Dig Chiropractic Econ 37(4), 28-34	Not a systematic review
Canter 2005	Incomplete data render cost comparison of chiropractic with medical care for back pain inconclusive	Focus on Alternative and Complementary Therapies 10(4), 311-312	Commentary
Carey 1995	The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors, and orthopedic surgeons. The North Carolina Back Pain Project	The New England journal of medicine 333(14), 913-917	Cost and effect analysed separately; no cost-effectiveness/utility analysis
Cross 2010	A randomised controlled equivalence trial to determine the effectiveness and cost-utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX)	Health Technology Assessment (Winchester, England) 14(23), 1-147	Not relevant intervention

Study (Author, name)	Reference		Reason for exclusion
	Title	Source	
Rodgers 2003	Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome?	Clinical Rehabilitation 17(6), 579-589	Not relevant intervention
Sullivan 1997	Outcomes and costs of health care for low back pain: a comparison of treatment among provider types	VIRGINIA COMMONWEALTH UNIVERSITY; dissertation	Dissertation abstract; no full text available
Thompson 2005	Costs of chiropractic care in the USA	Focus on Alternative and Complementary Therapies 10(2), 133-135	Commentary
Timm 1994	A randomized-control study of active and passive treatments for chronic low back pain following L5 laminectomy	The Journal of Orthopaedic and Sports Physical Therapy 20(6), 276-286	Average cost effectiveness ratio but not incremental cost-effectiveness ratio
Skouen 2002	Relative cost-effectiveness of extensive and light multidisciplinary treatment programs vesus treatment as usual for patients with chronic low back pain on long-term sick leave	Spine 27(9), 901-910	No manual therapy; cost-benefit analysis
Rosner 2000	Iatrogenesis in medical and chiropractic interventions: a thumbnail cost analysis	Journal of the American Chiropractic Association 37, 41	Letter
Lin 2011	Cost-effectiveness of guideline-endorsed treatments for low back pain: A systematic review	Deutsche Zeitschrift fur Akupunktur 54(2), 26-27	Duplicate
Kominski 2005	Economic evaluation of four treatments for low-back pain: results from a randomized controlled trial	Medical Care 43(5), 428-435	Only costs compared (cost minimisation analysis)
Grieves 2010	Cost minimization analysis of low back pain claims data for chiropractic vs medicine in a managed care organization	Journal of manipulative and physiological therapeutics 33(2), 164	Only costs compared (cost minimisation analysis)
Ernst 1998	The use, efficacy, safety and costs of complementary and alternative therapies for low back pain	European Journal of Physical Medicine and Rehabilitation 8(2), 53-57	Narrative efficacy review
Cook 2008	Manual Therapy Provided by Physical Therapists in a Hospital-Based Setting: A Retrospective Analysis	Journal of manipulative and physiological therapeutics 31(5), 338-343	Cost and effect analysed separately; no cost-effectiveness/utility analysis
Ernst 2003	Doubts about the cost-effectiveness of chiropractic	Focus on Alternative and Complementary Therapies 8(2), 218-219	Commentary
Fritz 2007	Does adherence to the guideline recommendation for active treatments improve the quality of care for patients with acute low back pain delivered by physical therapists?	Medical Care 45(10), 973-980	Cost and effect analysed separately; no cost-effectiveness/utility analysis

Study (Author, name)	Reference		Reason for exclusion
	Title	**Source**	
Shekelle 1995	Comparing the costs between provider types of episodes of back pain care	Spine 20(2), 221-227	Only costs compared (cost minimisation analysis)
Whitehurst 2005	Cost utility analysis of a brief pain management programme and manual therapy for low back pain: An economic evaluation along-side a randomised clinical trial	Arthritis and rheumatism 52(9), S663	Abstract
Xue 2008	Acupuncture, chiropractic and osteopathy use in Australia: a national population survey	BMC Public Health 8, 105	No cost-effectiveness analysis
Wright 2005	Individual active treatment combined with group exercise for acute and subacute low back pain	Spine 30, 1235-1241	Cost and effect analysed separately; no cost-effectiveness/utility analysis
Tuchin 1995	Preliminary findings of analysis of chiropractic utilization and cost in the workers' compensation system of New South Wales, Australia	Journal of manipulative and physiological therapeutics 18(8), 503-511	Only costs compared (cost minimisation analysis)
Waterworth 1985	An open study of diflunisal, conservative and manipulative therapy in the management of acute mechanical low back pain	The New Zealand medical journal 98(779), 372-375	No cost-effectiveness

Section B

Table 5. Systematic reviews reporting economic evaluations for manual therapy compared to other interventions

Author Year	Objectives (condition)	Test interventions	Search strategy	Total n of included manual therapy studies (type of analysis)	Manual therapy studies reporting ICER [Author, year]
Brown 2005[257]	To assess effectiveness, costs, and cost-effectiveness of chiropractic care compared to PT or standard medical care (LBP)	Test: Chiropractic care Control: PT or usual GP care	MEDLINE, Embase, BIOSIS Previews, AMED,™ CINAHL, MANTIS, CAB HEALTH, PASCAL, SPORTDiscus, and ExtraMed, Cochrane Library	n=11 (CEA, CUA, CCA, CMA)	UK BEAM 2004 [268;270]
Canter 2006[258]	To assess cost-effectiveness of complementary therapies in UK (any condition)	Chiropractic spinal manipulation, acupuncture, mobilisation, osteopathic manipulation, usual GP care, exercise	MEDLINE, Embase, CINAHL, AMED, Cochrane Library, NHS EED, HTA	n=4 (CEA, CUA, CCA)	UK BEAM 2004 [268;270] Williams 2004 [271;272]
Cherkin 2003[259]	To assess effectiveness, safety, and costs of the most popular CAM therapies (LBP)	Acupuncture, chiropractic spinal manipulation, massage	MEDLINE, Embase, Cochrane Library	n=2 (CCA)	None
Coon 2005[260]	To assess economic evaluations of CAM therapies (any condition)	Acupuncture, chiropractic spinal manipulation, other types of manual therapy (e.g., mobilisation, PT, osteopathic manipulation), mind-body approaches, hypnosis, plant-based medications, TCM, homeopathy, neuroreflexotherapy	MEDLINE, Embase, CINAHL, Cochrane Library, NHS EED	n=6 (CEA, CUA, CCA, CMA)	Korthals-de Bos 2003 [282]
Dagenais 2009[261]	To assess cost-utility of interventions for LBP (LBP)	Spinal manipulation, exercise, education, surgery, usual GP care	MEDLINE, NHS EED	n=3 (CUA)	Critchley 2007 [293] Rivero-Arias 2006 [294] Whitehurst 2007 [291]

Author Year	Objectives (condition)	Test interventions	Search strategy	Total n of included manual therapy studies (type of analysis)	Manual therapy studies reporting ICER [Author, year]
Furlan 2010[262]	To assess effectiveness, cost-effectiveness, and harms of CAM therapies (LBP, NP)	Spinal manipulation, mobilisation, massage, acupuncture	MEDLINE, Embase, CINAHL, Cochrane Library, AMED, MANTIS, NHS EED, HTA, Acubriefs, LILACS	n=6 (CEA, CUA, CCA, CMA)	Korthals-de Bos 2003 [282] UK BEAM 2004 [268;270] Niemisto 2005 [289] Lewis 2007 [280]
Herman 2005[263]	To assess economic evaluations of CAM therapies (any condition)	Acupuncture, homeopathy, manual therapy, mind-body approaches, hypnosis, plant-based medications, nutritional supplements, biofeedback	MEDLINE, AMED, Alt-Health-Watch, CAM Citation Index	n=7 (CEA, CUA, CCA, CMA)	Korthals-de Bos 2003 [282]
Lin 2011a[264]	To assess economic evaluations of usual GP care compared to other therapies for LBP (LBP)	Usual GP care, massage, chiropractic spinal manipulation, manual therapy, education, exercise, behavioural counselling, PT, advice, clinical rehabilitation, neuroreflexotherapy, acupuncture	MEDLINE, NHS EED, Cochrane Library, Embase, PsychINFO, CINAHL, EconLit, EURONHEED	n=3 (CEA, CUA, CCA, CMA, CBA)	UK BEAM 2004 [268;270]
Lin 2011b[265]	To assess economic evaluations of guideline-endorsed treatments for LBP (LBP)	Chiropractic spinal manipulation, manual therapy, usual GP care, PT, massage, education, acupuncture, behavioural counselling, advice, exercise, clinical or interdisciplinary rehabilitation, back school	MEDLINE, NHS EED, Cochrane Library, Embase, PsychINFO, CINAHL, EconLit, EURONHEED	n=7 (CEA, CUA, CCA, CMA, CBA)	UK BEAM 2004 [268;270] Whitehurst 2007 [291] Niemisto 2005 [289] Critchley 2007 [293]
Van der Roer 2005[266]	To assess economic evaluations of conservative (non-operative) treatments for LBP (LBP)	Chiropractic spinal manipulation, exercise, multidisciplinary rehabilitation, neuroreflexotherapy, ergonomic intervention, bed rest	PUBMED, Embase, Cochrane Library	n=5 (CEA, CCA, CMA)	Niemisto 2005 [289]

Author Year	Objectives (condition)	Test interventions	Search strategy	Total n of included manual therapy studies (type of analysis)	Manual therapy studies reporting ICER [Author, year]
White 2000[267]	To assess economic evaluations of CAM therapies (BP)	Spinal manipulation, acupuncture, homeopathy	MEDLINE, Embase, AMED	n=13 (CEA, CUA, CCA, CMA, CBA)	None

AMED=allied and complementary medicine database; MANTIS=manual, alternative, and natural therapy; LBP=low back pain; BP=back pain; NP=neck pain; PT=physiotherapy; CEA= cost-effectiveness analysis; CUA=cost-utility analysis; CCA=cost-consequence analysis; CMA=cost-minimization analysis; CBA=cost-benefit analysis; ICER=incremental cost-effectiveness ratio; NHS EED=national health service economic evaluation database; HTA=health technology assessment; GP=general practitioner; CAM=complementary alternative medicine; TCM=traditional Chinese medicine; EURONHEED=european network of health economic evaluation databases

Section C

Table 6. Basic characteristics of ongoing studies (protocols) of economic evaluation

Study ID (Author, year, country, and design)	Study participants and eligibility criteria	Condition	Interventions (components) Duration	Study perspective Costs	Analysis/Outcomes Follow-up
Apeldoorn 2010[273] The Netherlands RCT	Planned sample size: 150 Age: 18-65 yrs Gender: male, female LBP (sub-acute, chronic) [non-specific] for > 6 wks Exclusion: specific LBP	LBP	1. Classification-based PT (direction-specific exercise, high velocity manipulation, stabilisation) 2. Usual PT (muscular mobilisation, articular mobilisation, manipulation, exercise, massage, relaxation) > 4 wks	Societal Direct costs (health care, patient/family, out of pocket) Indirect costs (loss of productivity, inactivity days without paid job)	Analysis: CEA, CUA Outcomes: ICER Units: difference in cost per extra person with significant improvement in pain, global perceived recovery, functional status (for CEA), and QALY (for CUA using EuroQoL EQ-5D) 52 wks
Bennell 2007[274] Australia RCT	Planned sample size: 200 Age: > 18 yrs Gender: male, female Rotator cuff pathology, shoulder pain [non-specific] for > 3 mo Exclusion: specific cause of shoulder pain	Rotator cuff pathology	1. PT (shoulder joint and spinal mobilisation, massage, postural taping, home exercise) 2. PL (inactive ultrasound, inert gel) 10 wks	Societal Direct health care costs (health care, patient/family, out of pocket) Direct non-health care costs (use of paid unpaid help, lost time and travel, number of lost days at work)	Analysis: CEA, CUA Outcomes: ICER Units: difference in cost per extra person with significant improvement in pain, perceived recovery (for CEA), and QALY (for CUA using AQoL) 22 wks

Study ID (Author, year, country, and design)	Study participants and eligibility criteria	Condition	Interventions (components) Duration	Study perspective Costs	Analysis/Outcomes Follow-up
Coombes 2009[118] Australia RCT	Planned sample size: 132 Age: 18-70 yrs Gender: male, female Lateral epicondylagia (elbow pain) for > 6 wks Exclusion: specific cause of elbow pain, elbow fracture/surgery, malignancy, arthritis, concomitant neck/arm pain, PT exercise course 3 mo prior, injection within 6 mo of study entry	Lateral epicondylagia	1. CTSD injection + PT (elbow manipulation, exercise) 2. PL (saline injection) + PT 3. CTSD injection 4. PL 8 wks	Societal Direct health care costs (doctor visits, therapists, prescribed medication) Direct non-health care costs (over-the-counter medication, hours of paid and unpaid household help, transportation, out of pocket expenses) Indirect costs (absence from work, housekeeping/other daily activities)	Analysis: CBA, CUA Outcomes: WTP, ICER Units: difference in cost per extra person with significant improvement in QALY (for CUA using EuroQoL EQ-5D) and WTP (for CBA) 52 wks

Study ID (Author, year, country, and design)	Study participants and eligibility criteria	Condition	Interventions (components) Duration	Study perspective Costs	Analysis/Outcomes Follow-up
Maiers 2007[275] USA RCT	Planned sample size: 480 Age: ≥ 65 yrs Gender: male, female LBP (≥ 6 wks; sub-acute, chronic), NP (≥ 12 wks; chronic) [non-specific] Exclusion: baseline pain score < 30 percentage points, pain referred from the joints of the extremities or visceral disease, significant infectious disease, currently receiving treatment for LBP/NP, contraindications to exercise or spinal manipulation	LBP and NP	1. MT (spinal manipulation, mobilisation, flexion, distraction, soft tissue massage) + Home Exercise 2. Rehabilitative Exercise + Home Exercise 3. Home Exercise 12 wks	Societal Direct health care costs (doctor visits, study treatment, non-study health care provider use, medication utilisation, hospitalisation for LBP or NP) Indirect costs (loss of productivity, loss of wage, lost activity days due to LBP or NP)	Analysis: CEA, CUA Outcomes: ICER Units: difference in cost per extra person with significant improvement in pain (for CEA) and QALY (for CUA using EuroQoL EQ-5D) 12 mo

Study ID (Author, year, country, and design)	Study participants and eligibility criteria	Condition	Interventions (components) Duration	Study perspective Costs	Analysis/Outcomes Follow-up
Westrom 2010[276] USA RCT	Planned sample size: 200 Age: ≥ 18 yrs Gender: male, female LBP (≥ 6 wks; chronic) [non-specific] Exclusion: baseline pain score < 3 points (0-10 numerical rating scale), inflammatory or destructive tissue changes of the spine, lumbar surgery, progressive neurological deficits, pregnancy, severe osteoporosis, blood clotting disorder, currently receiving treatment for LBP by non-study provider, or contraindications to spinal manipulation	LBP	1. Monodisciplinary chiropractic care (high velocity low amplitude spinal manipulation, low velocity low amplitude mobilisation, soft tissue massage, flexion, distraction, hot/cold packs) 2. Multidisciplinary integrative care (high velocity low amplitude spinal manipulation, low velocity low amplitude mobilisation, flexion, distraction, cognitive behavioral therapy, soft tissue massage, myofascial technique, trigger point therapy, Swedish massage, medication, self-care education, and/or traditional Chinese medicine) 12 wks	Societal Direct health care costs (pain/disease related medical cost including those for the study treatment, non-study health care provider use, prescription medication, advanced imaging, hospitalisation) Direct non-health care costs (out of pocket expenses, informal care, travel expenses) Indirect costs (loss of productivity, absence from work, or days of inactivity)	Analysis: CEA, CUA Outcomes: ICER Units: difference in cost per extra person with significant improvement in pain (for CEA) and QALY (for CUA using EuroQoL EQ-5D) 12 mo

RCT=randomised controlled trial; wk(s)=week(s); mo=month(s); yrs=years; PT=physiotherapy/physical therapy; PL=placebo; CEA= cost-effectiveness analysis; CUA= cost-utility analysis; CBA=cost-benefit analysis; ICER=incremental cost-effectiveness ratio; AQoL= assessment of quality of life; LBP=low back pain; NP=neck pain; QALY=quality adjusted life years; CTSD=corticosteroid; WTP=willingness to pay; MT=manual treatment

Table 7. Included studies and their characteristics

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Spinal (upper/low back, neck, or both) pain				
Williams 2004[271;272] UK RCT	**Sample size:** 201 pts **Age (mean):** NR **Male (%):** NR **Inclusion:** pts aged 16-65 yrs with non-specific neck or back pain for 2-12 wks **Exclusion:** pts with serious spinal pathology, nerve root pain, previous spinal surgery, or major psychological disorder	**Intervention 1:** OSM (osteopathic manipulation + advice on keeping active, exercise regularly, and avoiding excessive rest) + Usual GP care [3-4 sessions] **Intervention 2:** Usual GP care [3-4 sessions] **Duration:** 2 mo	**Perspective:** Primary care organization (NHS) **Currency:** GBP (£) **Direct medical costs**: Consultations, investigations, prescribing, hospital stay **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (study duration < 1 yr) **Health outcome used in economic analysis:** EuroQoL EQ-5D **Statistical analysis:** Non-parametric bootstrap (1,000 simulations)	**Analysis:** CUA, CU plane **Analysed sample size:** 136 pts **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D) **Outcomes:** within-group mean QALY gained, between-group difference in mean QALY gained, ICER **Last follow-up:** 6 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Low Back Pain				
Critchley 2007[293] UK RCT	**Sample size:** 212 pts **Age (mean):** 44 yrs **Male (%):** 50 **Inclusion:** pts aged ≥18 yrs referred by GP with non-specific LBP >12 wks **Exclusion:** previous spinal surgery, PT for LBP within 6 mo prior to enrolment, chronic conditions such as rheumatoid arthritis or disabilities rendering unsuitable for the treatment	**Intervention 1:** Individual PT (joint manipulation, mobilisation, massage, back care advice, individual exercises including trunk muscle retraining, stretches, and general spinal mobility) [12 sessions] **Intervention 2:** spinal stabilisation PT (transverses abdominis and lumbar multifidus muscle training, exercise for spinal stability) [8 sessions] **Intervention 3:** Pain management (back pain education, strengthening, stretching, aerobic exercise, cognitive behavioural approach) [8 sessions] **Duration:** NR	**Perspective:** Primary care organization (NHS) **Currency:** GBP (£) **Direct medical costs**: public health service utilisation (NHS) **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: 3.5% **Health outcome used in economic analysis:** EuroQoL EQ-5D **Statistical analysis:** ANOVA, non-parametric bootstrap (number of simulations: NR)	**Analysis:** CUA, CU acceptability curves, sensitivity analysis **Analysed sample size:** 148 pts **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D) **Outcomes:** within-group mean QALY gained, between-group difference in mean QALY gained, ICER **Last follow-up:** 18 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Haas 2005[296] USA Non-RCT (Prospective cohort study)	**Sample size:** 2,780 **Age (mean):** 40 yrs **Male (%):** 50 **Inclusion:** pts 18 yrs or older with acute or chronic non-specific LBP **Exclusion:** pts who had received similar care 6 wks prior to trial, pregnant, or contraindications to spinal manipulation	**Intervention 1:** Chiropractic care (spinal manipulation, physical modalities, exercise plan, and self-care education) [number of sessions NR] **Intervention 2:** GP care [number of sessions NR] **Duration:** 12 mo	**Perspective:** Public payer (Medicare) **Currency:** US Dollar ($) **Direct medical costs**: Office costs (visits, x-ray, prescribed medication), advanced imaging, surgical consultation, referrals to physical therapists **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (<12 mo study) **Health outcome used in economic analysis:** Pain (VAS score) and disability (RODQ) **Statistical analysis:** Regression models separately for chronic and acute pts adjusted for age, sex, baseline pain/disability scores, co-morbidity, depression, health insurance, marital status, and income; dependent variables were mean change in pain, disability, and costs; α level of statistical significance of 0.01	**Analysis:** CEA **Analysed sample size:** 1,290 pts **Units:** Difference in cost ($) per score improvement in pain and disability **Outcomes:** Within-group improvement in pain and disability, between-group mean difference in improved pain and disability, ICER **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Niemisto 2005[289;290] Finland RCT	**Sample size:** 204 pts **Age (mean):** 37 yrs **Male (%):** 46 **Inclusion:** pts 24-46 yrs of age with non-specific LBP ≥ 3 mo and disability measured with ODI of 16% **Exclusion:** malignancies, ankylosing spondylitis, severe osteoporosis, osteoarthritis, paralysis, progressive neurologic disorder, hemophilia, spinal infection, spinal operation, vertebral fracture within 6 mo of trial, pregnancy, severe sciatica, and psychiatric disease	**Intervention 1:** Manipulative combination treatment (manipulation with muscle energy technique to correct any biomechanical dysfunction in the lumbar or pelvic segments, stabilizing exercise to correct the lumbopelvic rhythm, GP advice) [4 sessions] **Intervention 2:** GP advice (booklet, advice on exercise, muscle stretch, and stability) [1 session] **Duration:** 4 wks	**Perspective:** Societal **Currency:** US Dollar ($) **Direct medical costs**: Health services utilisation, drug costs **Direct non-medical costs:** Traveling costs **Indirect costs:** Productivity loss costs **Discounting**: None **Health outcome used in economic analysis:** pain (VAS score), disability (ODI score) **Statistical analysis:** Repeated measures ANOVA, ITT, bootstrapping technique (5,000 simulations), two-tailed p values, α level of statistical significance of 0.05	**Analysis:** CEA, CE plane, acceptability curve **Analysed sample size:** 138 pts **Units:** Difference in cost ($) per score improvement in pain and disability **Outcomes:** Within-group endpoint mean pain and disability scores, between-group mean difference in pain and disability (incremental effectiveness), ICER **Last follow-up:** 24 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Rivero-Arias 2006[294;295] UK RCT	**Sample size:** 286 pts **Age (mean):** 41 yrs **Male (%):** 47.5 **Inclusion:** pts ≥18 yrs with LBP ≥ 6 wks **Exclusion:** pts with systemic rheumatological disease, gynecological problems, ankylosing spondylitis, tumours, infections, past spinal surgery, or treatment for physical problems	**Intervention 1:** PT (joint manipulation, mobilisation, massage, stretching, spinal mobility and strengthening exercise, heat/cold therapy) + advice to remain active (back book) [5 sessions] **Intervention 2:** Advice to remain active (back book)[1 session] **Duration:** NR	**Perspective:** Societal, public payer (NHS) **Currency:** GBP (£) **Direct medical costs**: NHS costs (intervention, GP visits, hospitalisations, prescribed items), health care purchased by pt (private consultations with osteopaths, chiropractors, over the counter drugs) **Direct non-medical costs:** NR **Indirect costs:** employment costs (number of days off work) **Discounting**: None (12 mo follow-up) **Health outcome used in economic analysis:** quality of life (EuroQoL EQ-5D) **Statistical analysis:** Mean difference and 95% CI using independent sample t test (for costs) and ANCOVA (for QALYs), multiple imputation for missing values using linear regression technique	**Analysis:** CUA, CU plane, CU acceptability curves, sensitivity analysis **Analysed sample size:** 286 **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D) **Outcomes:** within-group mean QALY gained, between-group difference in mean QALY gained, ICER **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
UK BEAM 2004[268-270] UK RCT	**Sample size:** 1,334 pts **Age (mean):** 43.1 yrs **Male (%):** 44 **Inclusion:** pts 18-65 yrs of age with non-specific LBP ≥ 1 mo and RDQ ≥ 4 **Exclusion:** pts with malignancies, ankylosing spondylitis, osteoporosis, infections, past spinal surgery, psychiatric disease, treatment for physical problems 3 mo before trial, chronic use of steroids, cardiovascular condition, or previous attendance to pain management clinic	**Intervention 1:** GP care **Intervention 2:** Exercise + GP care [9 sessions] **Intervention 3:** Manipulation (a multidisciplinary group developed a package of techniques representative of those used by the UK chiropractic, osteopathic, and physiotherapy professions) + GP care [9 sessions] **Intervention 4:** Manipulation + exercise + GP care [9 sessions] **Duration:** 12 wks	**Perspective:** Public payer (NHS) **Currency:** GBP (£) **Direct medical costs**: GP care/consultations, visits, outpatient attendance, hospital stay, programmes of exercise, manipulation **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (12 mo follow-up) **Health outcome used in economic analysis:** quality of life (EuroQoL EQ-5D) **Statistical analysis:** Bayesian Markov Chain Monte Carlo multilevel analysis	**Analysis:** CUA, CU plane, CU acceptability curves, sensitivity analysis **Analysed sample size:** 1,287 pts **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D) **Outcomes:** within-group mean QALY gained, between-group difference in mean QALY gained, ICER **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Whitehurst 2007[291;292] UK RCT	**Sample size:** 402 pts **Age (mean):** 41 yrs **Male (%):** 47 **Inclusion:** pts 18-64 yrs of age with non-specific LBP < 12 wks **Exclusion:** serious spinal or systemic disorders, long-term sick leave (> 12 wks), osteoporosis, inflammatory arthritis, steroid treatment (> 12 wks), pregnancy, previous hip/back surgery or fracture, abdominal surgery, back pain treatment by another professional	**Intervention 1:** Manual PT (articulatory mobilisation, manipulation, or soft tissue techniques, spinal stabilisation, back exercise, ergonomic advice, back education) [7 sessions] **Intervention 2:** BPM (general fitness, exercise for spinal mobility, explanation about pain mechanisms, distress, coping strategies) [2-day course plus clinical tutoring] **Duration:** NR	**Perspective:** Public payer (NHS) **Currency:** GBP (£) **Direct medical costs**: treatment sessions (PT and BPM), outpatient attendance, inpatient attendance, primary care contacts, other health professionals (e.g., acupuncture, chiropractic, osteopathy, physiotherapy) **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (12 mo follow-up) **Health outcome used in economic analysis:** disability (RMDQ score), quality of life (EuroQoL EQ-5D) **Statistical analysis:** ITT analysis, multiple imputation based on multiple linear regression models, 95% CIs based on parametric tests if normal distribution, and if skewed, bootstrapping technique (5,000 simulations)	**Analysis:** CUA, CEA, CU plane, sensitivity analysis, threshold analysis for ICER using utility acceptability curve **Analysed sample size:** 402 pts **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D); difference in cost (£) per score improvement in RMDQ **Outcomes:** cost-utility (within-group mean QALY gained, between-group difference in mean QALY gained and ICER), cost-effectiveness (within-group mean RMDQ score change, between-group difference in mean RMDQ score change, ICER) **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Neck Pain				
Bosmans 2011[284-286] The Netherlands RCT	**Sample size:** 146 pts **Age (mean):** 45 yrs **Male (%):** 40 **Inclusion:** pts 18-70 yrs of age with non-specific neck pain (4-12 wks) **Exclusion:** malignancy, neurologic disease, herniated disc, or systemic rheumatic disease	**Intervention 1:** SMT (manipulation using passive movement of a joint beyond its active and passive limit of motion with a localized thrust of small amplitude to regain motion, restore function, and reduce pain; mobilisation using skilled low grade passive movement with large amplitude to restore movement and relieve pain) [6 sessions] **Intervention 2:** BGA (gradually increasing exercise program) [18 sessions] **Duration:** 6 wks	**Perspective:** Societal **Currency:** Euro (€) **Direct medical costs**: Primary care (GP, SMT, BGA, massage, homeopathy, outpatient visit, x-ray, tomography, MRI), supportive care **Direct non-medical costs:** Informal care, paid home help **Indirect costs:** Absenteeism from paid/unpaid work **Discounting**: adjusted to 2004 **Health outcome used in economic analysis:** Pain (VAS), disability (NDI), perceived recovery, and quality of life (SFHS-12) **Statistical analysis:** ITT analysis, multiple imputation, CIs based on bootstrapping (5,000 simulations)	**Analysis:** CE plane, threshold analysis for ICER using acceptability curves, sensitivity analysis **Analysed sample size:** 146 pts **Units:** difference in cost (€) per QALY gained (based on SFHS-12); difference in cost (€) per score improvement in NDI, pain intensity (VAS), or perceived recovery **Outcomes:** cost-utility (within-group mean QALY gained, between-group difference in mean QALY gained), cost-effectiveness (within-and between-group difference in NDI, VAS, or perceived recovery, ICER) **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Korthals-de Bos 2003[282;283] The Netherlands RCT	**Sample size:** 183 pts **Age (mean):** 45 yrs **Male (%):** 40 **Inclusion:** pts 18-70 yrs of age with non-specific neck pain (≥ 2 wks) **Exclusion:** previous neck surgery, malignancy, neurologic disease, fracture, herniated disc, or systemic rheumatic disease	**Intervention 1:** SMT (combination of techniques described by Cyriax, Kaltenborn, Maitland, and Mennel using hands-on muscular and articular mobilisation techniques, coordination or stabilisation techniques, and joint mobilisation with low-velocity passive movements) [6 sessions] **Intervention 2:** PT (active, postural, or relaxation exercises, stretching, massage, manual traction) [12 sessions] **Intervention 3:** GP care (standard care, advice on self-care, education, ergonomic issues, paracetamol or NSAIDs, if necessary) [1 session and optional biweekly follow-up visits] **Duration:** 6 wks	**Perspective:** Societal **Currency:** Euro (€) **Direct medical costs**: GP, SMT, PT, outpatient appointments, hospitalisation, exercise, home care **Direct non-medical costs:** Alternative therapy, home care, friend's or partner's help, travel **Indirect costs:** Absenteeism from paid/unpaid work **Discounting**: None (trial duration: 12 mo) **Health outcome used in economic analysis:** Pain (VAS), disability (NDI), perceived recovery, and quality of life (EuroQoL EQ-5D) **Statistical analysis:** ITT analysis, CIs based on bootstrapping (500 simulations), ICERs based on bootstrapping (5,000 simulations)	**Analysis:** CUA, CEA, CE plane, sensitivity analysis, threshold analysis for ICER acceptability curves **Analysed sample size:** 178 pts **Units:** difference in cost (€) per QALY gained (based on EuroQoL EQ-5D); difference in cost (€) per score improvement in NDI, pain intensity (VAS), or perceived recovery **Outcomes:** cost-utility (within-group mean QALY gained, between-group difference in mean QALY gained and ICER), cost-effectiveness (within-and between-group difference in NDI, VAS, or perceived recovery, ICER) **Last follow-up:** 12 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Lewis 2007[280;281] UK RCT	**Sample size:** 350 pts **Age (mean):** 51 yrs **Male (%):** 37 **Inclusion:** pts ≥ 18 yrs with non-specific neck pain who consulted only primary care team in the previous 6 mo **Exclusion:** weight loss, fever, progressive neurologic signs, muscle weakness, sensation disturbance, malignancy, systemic rheumatic disease, osteoporosis, contraindications to the study treatments, taking anticoagulants	**Intervention 1:** A & E [8 sessions] **Intervention 2:** A & E + SMT (passive/active assisted hands-on movements, joint and soft tissue mobilisations or manipulations graded as appropriate to the patient's signs and symptoms) [8 sessions] **Intervention 3:** A & E + PSWD [8 sessions] **Duration:** 6 wks	**Perspective:** Societal and public payer (NHS) **Currency:** GBP (£) **Direct medical costs**: Study intervention sessions, GP consultations, outpatient attendance (e.g., rheumatology, physiotherapist, neurologist, emergency, radiographer, acupuncturist), patient expenses (e.g., prescription drugs, over-the-counter medicines, devices) **Direct non-medical costs:** NR **Indirect costs:** Absenteeism from paid work **Discounting**: None (trial duration: 6 mo) **Health outcome used in economic analysis:** Disability (NPQ) and quality of life (EuroQoL EQ-5D) **Statistical analysis:** ITT analysis, CIs for differences in means using parametric methods, CIs for uncertainty in cost estimates were based on bootstrapping (5,000 simulations), linear regression to adjust for baseline covariates, multiple imputation technique to account for missing data	**Analysis:** CUA, CEA, CE plane, sensitivity analysis, threshold analysis for ICER using acceptability curves **Analysed sample size:** 346 pts **Units:** difference in cost (£) per QALY gained (based on EuroQoL EQ-5D); difference in cost (£) per score improvement in NPQ **Outcomes:** cost-utility (within-group mean QALY gained, between-group difference in mean QALY gained), cost-effectiveness (within-and between-group difference in NPQ) **Last follow-up:** 6 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Shoulder Pain				
Bergman 2010[136;277-279] The Netherlands RCT	**Sample size:** 150 pts **Age (mean):** 48 yrs **Male (%):** 49 **Inclusion:** pts ≥ 18 yrs with non-specific shoulder pain without shoulder treatment in the past 3 mo **Exclusion:** fractures, ruptures or dislocations in the shoulder region, previous orthopedic surgery, contraindications for manipulative therapy, cervical nerve root compression, rheumatic disorder, dementia, psychiatric disorder, or abdominal pathology	**Intervention 1:** SMT (high velocity low amplitude manipulation and passive low velocity mobilisation within the range of joint motion) [6 sessions] + Usual GP care (advice on daily living, if needed analgesics, NSAIDs, corticosteroid injections, or PT including massage and exercise) **Intervention 2:** Usual GP care [number sessions: NR] **Duration:** 12 wks	**Perspective:** Societal **Currency:** Euro (€) **Direct medical costs**: treatment by GP, physiotherapist, manual, occupational, exercise or complementary health therapists, visits to consultant in orthopedic surgery, acupuncturist, neurology, rheumatology, rehabilitation medicine, and hospitalisation **Direct non-medical costs:** out-of-pocket expenses, costs for paid/unpaid help **Indirect costs:** loss of production due to sick leave from paid/unpaid work **Discounting**: None (trial duration: 6 mo) **Health outcome used in economic analysis:** perceived recovery (%), shoulder pain, shoulder disability, general health **Statistical analysis:** paired sample t-test (two sided at α=0.05), 95% CIs for the differences between the groups, bootstrapping (2,000 replications) to compare mean costs between the groups and estimate 95% CIs, ITT analysis	**Analysis:** CEA, CE plane, sensitivity analysis, threshold analysis for ICER using acceptability curves **Analysed sample size:** 140 pts (excluding 2 cost outliers) **Units:** difference in cost (€) per pt recovered, per score improvement in disability, pain, or general health **Outcomes:** cost-effectiveness, within-and between-group difference in perceived recovery, shoulder pain, shoulder disability, or general health **Last follow-up:** 6 mo

Study ID Design	Study participants Eligibility criteria	Interventions (components) Duration	Study perspective Costs Health outcomes Methods	Analysis/Outcomes Last Follow-up (Post baseline)
Ankle Fracture				
Lin 2008[287;288] Australia RCT	**Sample size:** 94 pts **Age (mean):** 41.5 yrs **Male (%):** 54 **Inclusion:** pts ≥ 18 yrs with ankle fractures treated with cast immobilisation with cast removed the week before the trial entry, pain VAS ≥ 2, approved to weight-bear as tolerated or partial weight-bear **Exclusion:** pts with significant pathologies	**Intervention 1:** MT (large amplitude oscillatory anterior-posterior glides of the talus) + PT (exercise, gait retraining, walking aids, advice, ice, elevation and progression if required) [8 sessions] **Intervention 2:** PT [5 sessions] **Duration:** 4 wks	**Perspective:** Public payer, patient **Currency:** Australian dollar (AU$) **Direct medical costs**: outpatient physiotherapy, medical specialists, GP, emergency department, hospitalisation, medication, investigations, private health providers, **Direct non-medical costs:** public transport, private vehicle **Indirect costs:** None **Discounting**: None (trial duration: 6 mo) **Health outcome used in economic analysis:** quality of life (AQoL), activity limitation (LEFS) **Statistical analysis:** ITT analysis, ANCOVA for group-differences, imputation of missing values (LKVCF), hypothesis testing at α=0.05, two sample t-test and bootstrapping (1,000 replications) 95% CIs for group-differences in costs	**Analysis:** CUA **Analysed sample size:** 92 pts **Units:** difference in cost (AU$) per QALY gained (based on AQoL) **Outcomes:** between-group difference in quality of life (AQoL) and activity limitation (LEFS) **Last follow-up:** 6 mo

NA=not applicable; RCT=randomised controlled trial; pts=patients; wk(s)=week(s); mo=month(s); yrs=years; PT=physiotherapy/physical therapy; PL=placebo; CE=cost-effectiveness; CU=cost-utility; CEA=cost-effectiveness analysis; CUA= cost-utility analysis; CBA=cost-benefit analysis; ICER=incremental cost-effectiveness ratio; AQoL= assessment of quality of life; LBP=low back pain; NP=neck pain; QALY=quality adjusted life years; CTSD=corticosteroid; WTP=willingness to pay; MT=manual treatment; OSM=osteopathic spinal manipulation; GP=general practitioner; NHS=national health service; NR=not reported; MD=mean difference; RODQ=revised Oswestry disability questionnaire; VAS=visual analogue scale; ODI=Oswestry disability index; ITT=intention to treat; ANOVA=analysis of variance; RDQ=Roland disability questionnaire; BPM=brief pain management; SMT=spinal manual therapy; NSAID=non-steroidal anti-inflammatory drug; NDI=neck disability index; SFHS=short form health survey; BGA=behavioral graded activity; PSWD=pulsed shortwave diathermy; A & E=advice and exercise; NPQ=Northwick Park Neck Pain Questionnaire; LEFS=lower extremity functional scale; LKVCF=last known value carried forward

Table 8. Interventions in the included cost-effectiveness/cost-utility studies

Study	*Test Treatment*						*Comparator Treatment 1*						*Comparator Treatment 2*					*Comparator Treatment 3*	
	Manual therapy*	GP care	Advice	Exercise	Mobilisation	Massage	PSWD	Spinal stabilisation	Manipulation	Advice	Exercise	GP care	Spinal pain education	Advice	Exercise	GP care	Cognitive behavioural approach	Advice	GP care
Bergman 2010[136;277-279]	X	X	X	X	-	-	-	-	-	X	X	X	-	-	-	-	-	-	-
Bosmans 2011[284-286]	X	-	-	-	-	-		-	-	-	X	-	-		-	-	-	-	-
Critchley 2007[293]	X	-	X	-	-	X		X	-	-	X	-	X		X	-	X	-	-
Haas 2005[296]	X	-	-	-	-	-		-	-	X	X	X	-		-	-	-	-	-
Korthals-de Bos 2003[282;283]	-	-	-	-	X	-		-	-	-	X	-	X		-	X	-	-	-
Lewis 2007[280;281]	X	-	X	X	-	-	X	-	-	X	X	-	-	X	X	-	-	-	-
Lin 2008[287;288]	X		X	X	-	-	-	-	-	X	X	-	-	-	-	-	-	-	-
Niemisto 2005[289;290]	X	-	X	X	-	-		-	-	-	-	-	-		-	-	-	X	-
Rivero-Arias 2006[294;295]	X	-	X	X	-	X		-			-	-	-		-		-	X	-
UK BEAM 2004[268-270]	X	X	-	X	-	-		-	X	-	-	X	-		X	X	-	-	X
Whitehurst 2007[291;292]	X	-	X	X	-	X		-	-	X	X	-	-		-	-	-	-	-
Williams 2004[271;272]	X	X	-	-	-	-		-	-	-	-	X	-		-	-	-	-	-
GP=general practitioner; PSWD=pulsed shortwave diathermy																			

*Manual therapy may consist of manipulation, mobilisation, or a combination of the two

Table 9. Methodological quality of economic evaluations in included studies

Item#*	Bergman 2010	Bosmans 2011	Critchley 2007	Haas 2005	Korthals-de Bos 2003	Lewis 2007	Lin 2008	Niemisto 2005	Rivero-Arias 2006	UK BEAM 2004	Whitehurst 2007	Williams 2004	Proportion of studies with 'Yes' (%)
Item 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Item 2	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Item 3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Item 4	Yes	Yes	Can't Tell (costs)	Yes	Yes	No (costs)	Yes	Yes	Yes	Yes	Yes	Yes	83.3
Item 5	Can't Tell (costs)	Yes	Can't Tell (costs)	Can't Tell (costs)	Can't Tell (costs)	Can't Tell (costs)	Can't Tell (costs)	Can't Tell (costs)	Yes	Yes	Yes	Yes	41.6
Item 6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Item 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Item 8	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	91.6
Item 9	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	83.3
Item 10	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	91.6

*Responses to items: Yes, No, Can't Tell

The Drummond checklist for critical appraisal of economical evaluation (Drummond et al. Methods for the economic evaluation of health care programmes 3rd Ed. Oxford: Oxford University Press; 2005**)**

Item 1: Was a well defined question posed in answerable form?
Item 2: Was a comprehensive description of the competing alternatives given?
Item 3: Was the effectiveness of the programmes or services established?
Item 4: Were all the important and relevant costs and consequences for each alternative identified?
Item 5: Were costs and consequences measured accurately in appropriate physical units (e.g. number of physician visits, lost work-days, gained life-years)?
Item 6: Were costs and consequences valued credibly?
Item 7: Were costs and consequences adjusted for differential timing?
Item 8: Was an incremental analysis of costs and consequences of alternatives performed?
Item 9: Was allowance made for uncertainty in the estimates of costs and consequences?
Item 10: Did the presentation and discussion of study results include all issues of concern to users?

Table 10. Results of the included cost-effectiveness/cost-utility studies

Study	Monetary unit (study-based)	Treatments	Costs (Total)	Difference in costs (MT - comparator)	Effectiveness	Utility (QALY)	Incremental ratio (MT versus comparator)	
							Cost-effectiveness (cost per unit outcome improved)	**Cost-utility** (cost per QALYs gained)
Spinal (low back, neck, or both) Pain								
Williams 2004[271;272] UK RCT	British Pounds (£)	OSM + Usual GP care	£303.00	£88.00 95% CI: -3, -239	NR	0.056	NR	£3,560.00 [80% CI: 542-77,100]
		Usual GP care	£215.00			0.031		
Low Back Pain								
Critchley 2007[293] UK RCT	British Pounds (£)	Individual PT	£474.00	£309.00 [NS]	NR	0.990	NR	£1,055.00 [CI: NR]
		Spinal stabilisation PT	£379.00	£214.00 [NS]		0.900		
		Pain management	£165.00	-		1.000		Dominant over both other treatments
Haas 2005[296] USA Non-RCT	US Dollar ($) Converted to £ (December 31, 1995)	Chiropractic care	*Unadjusted* $450.00 £292.95	*Adjusted* $1.00 [NS] £0.65 (Chronic) $43.00 [NS] £28.00 (Acute)	*Pain (VAS)-MD* 7.3 (chronic) 3.6 (acute) *Disability (RODQ)-MD* 5.4 (chronic) 2.7 (acute)	NR	*Pain (VAS)-MD* $0.10 (chronic) £0.06 $12.0 (acute) £7.80 *RODQ-MD* $0.10 (chronic) £0.06 $16.1 (acute) £10.50	NR
		Usual GP care	*Unadjusted* $457.00 £297.50					

Study	Monetary unit (study-based)	Treatments	Costs (Total)	Difference in costs (MT - comparator)	Effectiveness	Utility (QALY)	Incremental ratio (MT versus comparator)	
							Cost-effectiveness (cost per unit outcome improved)	**Cost-utility** (cost per QALYs gained)
Niemisto 2005[289;290] Finland RCT	US Dollar ($) Converted to £ (December 31, 2002)	Manipulative treatment	NR	$1,662.00 95% CI: 1637, 1687 £1,032.10 95% CI: 1016, 1047	*Pain (VAS)-MD* 4.97 *Disability (ODI)-MD* 1.24	NR	*Pain (VAS)* $512.00 95% CI: 77, 949 £318.00 95% CI: 48, 589 *Disability (ODI)* $78.00 95% CI: -655, 499 £48.40 95% CI: -406, 310	NR
		GP advice	NR					
Rivero-Arias 2006[294;295] UK RCT	British Pounds (£)	PT + advice	£264.00	£60.00 [95% CI: -5, 126]	NR	0.740	NR	£3,010.00 [CI: NR]
		Advice	£204.00			0.690		
UK BEAM 2004[268-270] UK RCT	British Pounds (£)	GP (Best) care + manipulation	£541.00	£195.00 95% CI: 85, 308	NR	0.659	NR	£4,800.00 [CI: NR]
		GP (Best) care + manipulation + exercise	£471.00	£125.00 95% CI: 21, 228		0.651		£3,800.00 [CI: NR] Dominant over exercise
		GP (Best) care + exercise	£486.00	£140.00 95% CI: 3, 278		0.635		£8,300.00 [CI: NR]
		GP (Best) care	£346.00	-		0.618		-

Study	Monetary unit (study-based)	Treatments	Costs (Total)	Difference in costs (MT - comparator)	Effectiveness	Utility (QALY)	Incremental ratio (MT versus comparator)	
							Cost-effectiveness (cost per unit outcome improved)	**Cost-utility** (cost per QALYs gained)
Whitehurst 2007[291;292] UK RCT	British Pounds (£)	Manual PT	£194.52	£52.19 95% CI: -19.2, 123.6	**Mean change disability (**RMDQ): 8.88	0.777	£156.00 [CI: NR]	£2,362.00 [CI: NR]
		Brief pain management (BPM)	£142.33		**Mean change disability (**RMDQ): 8.55	0.755		
Neck Pain								
Bosmans 2011[284-286] The Netherlands RCT	Euro (€) Converted to £ (December 31, 2004)	SMT (MOB + MAN)	€613.00 £433.00	-€260.00 95% CI: -107, 825	**Mean change** Pain (VAS): 3.5 Disability (NDI): 8.3 Recovery: 0.76	0.770	**BGA versus SMT** [% Bootstrap ratios] Recovery: €13,083.00 [NR] £9,236.60 Pain: €296.00 [86%] £209.00 NDI: €110.00 [85%] £77.70	**BGA versus SMT** [% Bootstrap ratios] €13,000.00 [NR] £9,178.00
		BGA (increasing exercise program)	€873.00 £616.30	-£183.60 95% CI: -75.55, 582.45	**Mean change** Pain (VAS): 4.4 Disability (NDI): 10.6 Recovery: 0.78	0.750		
Korthals-de Bos 2003[282;283] The Netherlands RCT	Euro (€) Converted to £ (December 31, 2000)	SMT (mobilisation)	€447.00 £281.61	-€932.00 95% CI: -1932, -283 -£587.20 95% CI: -	**Mean change** Pain (VAS): 4.2 Disability (NDI): 7.2 Recovery: 71.7	0.820	**Dominance of SMT** [% Bootstrap ratios] Over PT Pain -€757.00 [98%]	**Dominance of SMT [% Bootstrap ratios]** Over PT -€31,144.00 [87%] -£19,620.00 Over GP care

Study	Monetary unit (study-based)	Treatments	Costs (Total)	Difference in costs (MT - comparator)	Effectiveness	Utility (QALY)	Incremental ratio (MT versus comparator)	
							Cost-effectiveness (cost per unit outcome improved)	**Cost-utility** (cost per QALYs gained)
				1217, -178.30			-£477.00 Recovery - €9,488.00 [85%] -£5,977.00 Over GP care Recovery - €6,041.00 [96%] -£3,805.00	-€15,505.00 [97%] -£9,768.15
		PT	€1,297.00 £817.10	-€82.00 95% CI: -1063, 1446 -£51.66 95% CI: -670, 911	**Mean change** Pain (VAS): 3.1 Disability (NDI): 6.3 Recovery: 62.7	0.790		
		GP care	€1,379.00 £868.77	-	**Mean change** Pain (VAS): 4.1 Disability (NDI): 8.5 Recovery: 56.3	0.770		
Lewis 2007[280;281] UK RCT	British Pounds (£)	SMT (MOB + MAN) + A&E	£303.31	-£69.41 [NS]	Disability (NPQ): 10.2	0.342	£53.10.00 [CI: NR]	£3,450.00 [CI: NR]
		PSWD + A&E (advice + exercise)	£338.40	-£34.32 [NS]	Disability (NPQ): 10.3	0.360		
		A&E (advice + exercise)	£372.72	-	Disability (NPQ): 11.5	0.362		
Shoulder Pain								
Bergman 2010 [136;277-279] The Netherlands RCT	Euro (€) Converted to £ (December 31, 2000)	SMT (MOB + MAN) + GP care	€676.00 £425.88	€121.00 95% CI: -340, 581	Recovery: 41% Pain: 5.9 Disability: 33.0 General health: 0.11	NR	Recovery: €2,876.00 £1,811.88 Pain: €175.00 £110.25 Disability: €5.00 £3.15 General health:	NR
		GP care	€555.00 £349.65	£76.23 95% CI: -214, 366	Recovery: 35% Pain: 5.2 Disability: 20.3			

Study	Monetary unit (study-based)	Treatments	Costs (Total)	Difference in costs (MT - comparator)	Effectiveness	Utility (QALY)	Incremental ratio (MT versus comparator)	
							Cost-effectiveness (cost per unit outcome improved)	**Cost-utility** (cost per QALYs gained)
					General health: 0.08		€2,952.00 £1,859.76	
Ankle Fracture								
Lin 2008[287;288] Australia RCT	Australian dollar (AU$) Converted to £ (December 31, 2005)	MT + PT	AU$828.99 £352.32	AU$187.66 95% CI: -124, 539 £80.00 95% CI: -53, 230	LEFS: -1.0, 95% CI: -5.9, 3.9 [between-group difference] AQoL: 1.3, 95% CI: 0.1, 2.5 [between-group difference]	-0.09, 95% CI: -0.6, 0.4 [between-group]	NR	NR Analysis not performed
		PT	AU$641.33 £272.56					

LY=life years; QALY=quality-adjusted life years; CE=cost-effectiveness; CU=cost-utility; MT=manual therapy; OSM=osteopathic manual therapy; GP=general practitioner; CI=confidence interval; NR=not reported; RODQ=revised Oswestry disability questionnaire; VAS=visual analogue scale; MD=mean difference; PT=physiotherapy; SMT=spinal manual therapy; MAN=manipulation; MOB=mobilisation; BGA=behavioural graded activity; A&E=advice and exercise; PSWD=pulsed shortwave diathermy; NPQ=Northwick Park Neck Pain Questionnaire; NS=statistically non-significant; MT=manual therapy; LEFS=lower extremity functional scale

Appendix VI – Feedback information (flipchart /questionnaires) from group work at University of Warwick Dissemination Event

1. What do the findings mean to you?
    - It provides a baseline for future research
    - Confirms cost-effectiveness – cost-effectiveness study helpful
    - I feel the findings are reasonably similar to what we know already/ no real difference
    - I think that the non-musculoskeletal research should be dictated by the profession and a focus on musculoskeletal conditions to be prioritised
    - At the time, the Bronfort Report was fair and complete, despite the controversy that occurred
    - Bronfort was criticised unfairly for only including RCTs (few other studies found)
    - Beefed up Bronfort – up to date (qualitatively)
    - Huge amount of evidence, but concluding anything from it is very difficult
    - No new strong evidence to change current practice – "we are where we were"
    - There is a low quality favourable evidence for a few new conditions
    - It highlights the pointlessness of low quality research
    - It highlights the diversity of manual therapy treatment modality (i.e. what is chiropractic)
    - Diversity of conditions recorded suggested lack of coherence in defining chiropractic
    - Independent and comprehensive
    - Important for credibility of profession
    - More work/research is needed – good quality, specific and direct
    - In order to be a platform for funding (e.g. RFPB)
    - Clear statement of current evidence-base
    - Increases our knowledge of what evidence base is (quality of methods of this review)
    - Unsurprising that findings from non-musculoskeletal conditions have not changed
    - Evidence for only part of chiropractic package looked only at manual therapy, not psychosocial, rehabilitation exercises – whole package. Tease out other components
    - Damages of limiting score of practice to manipulation. Rod for own back
    - More high quality research needed
    - Researchers unaware of criteria to be included in a systematic review

2. What would you like to happen with these findings?
    - Stimulate further high quality research
    - Publish in quality journals
    - Ignore them
    - Make the database available to encourage further research
    - Widespread dissemination to clinicians (publication and conferences etc.)
    - Open and transparent about results (regardless)
    - Focus on strengths
    - Published in the context of the Bronfort findings to collaborately address the question "what works"
    - Accessibility e.g. findings and database
    - Presented to students are college to encourage the right sort of research

3. What are the important areas for further research?
    - Cost effectiveness = particularly on LBP not improved after 6 week GP care (NICE guidelines)
    - Cost-effectiveness of chiropractic (musculoskeletal) back, neck, MA.
    - Low back pain subsets/mechanism of low back pain
    - Mobilisation/manipulation – low back pain
    - Patients exploration/experience - qualitative
    - Chronic illness
    - Neck Pain
    - Headaches
    - Musculoskeletal research
    - Cost comparisons – societal costs
    - Do we need another RCT – possibly chiropractics versus usual GP care – costs
    - Pragmatic approaches/ don't look at specifics of treatment
    - Focus on strengths
    - Compare difficult treatment modalities with a chiropractic treatment/package of care.
    - Anything high quality
    - Not important to research specific treatment modalities
    - Safety
    - What kind of research/what constitutes good quality research
    - Classification of back pain
    - Delve deeper into database and trial evidence – not just abstracts

4. What was the most surprising finding that you heard today?
    - Not surprised
    - Consistency of cost-effectiveness for studies of low back pain
    - Outcomes for shoulders - good
    - Trial on osteosarcoma/ that somebody felt that manipulation will possibly help Osteosarcoma
    - Lack of non-RCT evidence
    - Lack of any new evidence/change
    - Limitations of Bronfort

5. What were you expecting to be told?
    - More research would have been published
    - Good and bad
    - Good news
    - Nothing new
    - More about cumulative weight of non-RCT (SRs) studies

6. How would you like the findings to be reported?
    - Published papers
    - Positive findings to press
    - Conferences
    - Digest for CoC members
    - Published in the context of the Bronfort findings to collaborately address the question "what works"

- Published in unbiased way
- Widely (not just chiropractic)
- Quality publications of the positive findings –patients

7. What would you like to happen to the materials – e.g. how do you think the catalogue can be sustained?
    - Kept up-to-date with CoC findings and made available to chiropractors on a subscription basis
    - Open access
    - Regular updates – cost? Findings?
    - CoC lead next steps
    - Rolling programme of updating catalogue/database – cost?
    - 3 undergraduate colleges working together
    - Set in place mechanism to maintain catalogue
    - Available to colleges
    - Wiki

References

(1) Hoving JL, Koes BW, de Vet HC, van der Windt DA, Assendelft WJ, Van MH et al. Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial. *Ann Intern Med* 2002; 136(10):713-722.

(2) Farrell JP, Jensen GM. Manual therapy: a critical assessment of role in the profession of physical therapy. *Phys Ther* 1992; 72(12):843-852.

(3) Fitzgerald GK, McClure PW, Beattie P, Riddle DL. Issues in determining treatment effectiveness of manual therapy. *Phys Ther* 1994; 74(3):227-233.

(4) Jette AM, Delitto A. Physical therapy treatment choices for musculoskeletal impairments. *Phys Ther* 1997; 77(2):145-154.

(5) Bergmann TF, Peterson DH. Chiropractic technique: principles and procedures. 3rd edition ed. Elsevier; 2011.

(6) International Federation of Orthopaedic Manipulative Therapists (IFOMT). 2012.

(7) DeStefano LA, Greenman PE. Greenman's principles of manual medicine. 4th ed. Lippincott Williams & Wilkins; 2010.

(8) Dvorak J, Schneider W, Dvorak V, Gilliar W. Musculoskeletal manual medicine: diagnosis and treatment. 1st ed. Thieme Medical Pub; 2008.

(9) Kaltenborn FM, Evjenth O, Frisch H, Hinsen W, Robinson BE. Manual Therapy for the Extremity Joints: Specialized Techniques, Tests and Joint-mobilisation. A. Norlis; 1976.

(10) Cook C. Orthopedic Manual Therapy: An Evidence-Based Approach. 2nd ed. Pearson/Prentice Hall; 2011.

(11) Mintken PE, DeRosa C, Little T, Smith B. A model for standardizing manipulation terminology in physical therapy practice. *J Man Manip Ther* 2008; 16(1):50-56.

(12) Mintken PE, DeRosa C, Little T, Smith B. AAOMPT clinical guidelines: A model for standardizing manipulation terminology in physical therapy practice. *J Orthop Sports Phys Ther* 2008; 38(3):A1-A6.

(13) Homola S. Chiropractic: history and overview of theories and methods. *Clin Orthop Relat Res* 2006; 444:236-242.

(14) Kaptchuk TJ, Eisenberg DM. Chiropractic: origins, controversies, and contributions. *Arch Intern Med* 1998; 158(20):2215-2224.

(15) Meeker WC, Haldeman S. Chiropractic: a profession at the crossroads of mainstream and alternative medicine. *Ann Intern Med* 2002; 136(3):216-227.

(16) Keating JC, Jr., Charlton KH, Grod JP, Perle SM, Sikorski D, Winterstein JF. Subluxation: dogma or science? *Chiropr Osteopat* 2005; 13:17.

(17) Gatterman MI, Hansen DT. Development of chiropractic nomenclature through consensus. *J Manipulative Physiol Ther* 1994; 17(5):302-309.

(18) Pettman E. A history of manipulative therapy. *J Man Manip Ther* 2007; 15(3):165-174.

(19) Ernst E, White A. The BBC survey of complementary medicine use in the UK. *Complement Ther Med* 2000; 8(1):32-36.

(20) Cameron-Blackie G, Mouncer Y. Complementary therapies in the NHS. 10. 1993. United Kingdom, National Association of Health Authorities and Trusts (NAHAT), Birmingham (United Kingdom).

(21) British Medical Association.Board of Science. Complementary medicine: new approaches to good practice. Oxford University Press, USA; 1993.

(22) Cookson JC. Orthopedic manual therapy--an overview. Part II: the spine. *Phys Ther* 1979; 59(3):259-267.

(23) Paris SV. Mobilization of the spine. *Phys Ther* 1979; 59(8):988-995.

(24) Maitland GD, Brewerton DA, Graham J, Edwards BC. Vertebral manipulation. Butterworths London; 1986.

(25) Paris SV. Spinal manipulative therapy. *Clin Orthop Relat Res* 1983;(179):55-61.

(26) American Chiropractic Association. Policy statement on spinal manipulation. American Chiropractic Association; 1999.

(27) Garofalo JP, Polatin P. Low back pain: an epidemic in industrialized countries. *Psychosocial factors in pain: Critical perspectives* 1999;164-174.

(28) Rosen M, Breen A, Hamann W, Harker P, Jayson MIV, Kelly E. Report of a clinical standards advisory group committee on back pain. *Her Majesty's Stationary Office, London, UK* 1994.

(29) Ong CK, Doll H, Bodeker G, Stewart-Brown S. Use of osteopathic or chiropractic services among people with back pain: a UK population survey. *Health Soc Care Community* 2004; 12(3):265-273.

(30) Lawrence DJ, Meeker WC. Chiropractic and CAM utilization: a descriptive review. *Chiropr Osteopat* 2007; 15:2.

(31) Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report* 2008;(12):1-23.

(32) Gross AR, Aker PD, Goldsmith CH, Peloso P. Physical medicine modalities for mechanical neck disorders. *Cochrane Database Syst Rev* 2000;(2):CD000961.

(33) Hoving JL, Gross AR, Gasner D, Kay T, Kennedy C, Hondras MA et al. A critical appraisal of review articles on the effectiveness of conservative treatment for neck pain. *Spine* 2001; 26(2):196-205.

(34) Furlan AD, Yazdi F, Tsertsvadze A, Gross A, van TM, Santaguida L et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012; 2012:953139.

(35) Shekelle PG. The appropriateness of spinal manipulation for low-back pain: project overview and literature review. 1 ed. Rand Corp; 1991.

(36) Shekelle PG, Adams AH, Chassin MR, Hurwitz EL, Brook RH. Spinal manipulation for low-back pain. *Ann Intern Med* 1992; 117(7):590-598.

(37) Bigos SJ, United States.Agency for Health Care Policy and Research, American HC. Acute low back problems in adults. US Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994.

(38) Di Fabio RP. Clinical assessment of manipulation and mobilization of the lumbar spine. A critical review of the literature. *Phys Ther* 1986; 66(1):51-54.

(39) Ottenbacher K, DiFabio RP. Efficacy of spinal manipulation/mobilization therapy. A meta-analysis. *Spine (Phila Pa 1976)* 1985; 10(9):833-837.

(40) Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropr Osteopat* 2010; 18:3.

(41) Assendelft WJ, Morton SC, Yu EI, Suttorp MJ, Shekelle PG. Spinal manipulative therapy for low back pain. A meta-analysis of effectiveness relative to other therapies. *Ann Intern Med* 2003; 138(11):871-881.

(42) Bronfort G, Haas M, Evans RL, Bouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. *Spine J* 2004; 4(3):335-356.

(43) Cherkin DC, Deyo RA, Battie M, Street J, Barlow W. A comparison of physical therapy, chiropractic manipulation, and provision of an educational booklet for the treatment of patients with low back pain. *N Engl J Med* 1998; 339(15):1021-1029.

(44) Ernst E. Adverse effects of spinal manipulation: a systematic review. *J R Soc Med* 2007; 100(7):330-338.

(45) Ernst E. Deaths after chiropractic: a review of published cases. *Int J Clin Pract* 2010; 64(8):1162-1165.

(46) Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. *Man Ther* 2010; 15(4):355-363.

(47) Cassidy JD, Boyle E, Cote P, He Y, Hogg-Johnson S, Silver FL et al. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. *J Manipulative Physiol Ther* 2009; 32(2 Suppl):S201-S208.

(48) Hurwitz EL, Morgenstern H, Vassilaki M, Chiang LM. Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA Neck Pain Study. *J Manipulative Physiol Ther* 2004; 27(1):16-25.

(49) Gouveia LO, Castanho P, Ferreira JJ. Safety of chiropractic interventions: a systematic review. *Spine (Phila Pa 1976)* 2009; 34(11):E405-E413.

(50) Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. *Stroke* 2005; 36(7):1575-1580.

(51) Vohra S, Johnston BC, Cramer K, Humphreys K. Adverse events associated with pediatric spinal manipulation: a systematic review. *Pediatrics* 2007; 119(1):e275-e283.

(52) Stevinson C, Ernst E. Risks associated with spinal manipulation. *Am J Med* 2002; 112(7):566-571.

(53) Carlesso LC, Gross AR, Santaguida PL, Burnie S, Voth S, Sadi J. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. *Man Ther* 2010; 15(5):434-444.

(54) Petersen T, Larsen K, Nordsteen J, Olsen S, Fournier G, Jacobsen S. The McKenzie method compared with manipulation when used adjunctive to information and advice in low back pain patients presenting with centralization or peripheralization. A randomized controlled trial. *Spine (Phila Pa 1976)* 2011.

(55) Voigt K, Liebnitzky J, Burmeister U, Sihvonen-Riemenschneider H, Beck M, Voigt R et al. Efficacy of osteopathic manipulative treatment of female patients with migraine: results of a randomized controlled trial. *J Altern Complement Med* 2011; 17(3):225-230.

(56) Chiu TT, Ng JK, Walther-Zhang B, Lin RJ, Ortelli L, Chua SK. A randomized controlled trial on the efficacy of intermittent cervical traction for patients with chronic neck pain. *Clin Rehabil* 2011; 25(9):814-822.

(57) Wyatt K, Edwards V, Franck L, Britten N, Creanor S, Maddick A et al. Cranial osteopathy for children with cerebral palsy: a randomised controlled trial. *Arch Dis Child* 2011; 96(6):505-512.

(58) Martel J, Dugas C, Dubois JD, Descarreaux M. A randomised controlled trial of preventive spinal manipulation with and without a home exercise program for patients with chronic neck pain. *BMC Musculoskelet Disord* 2011; 12:41.

(59) Alcantara J, Alcantara JD, Alcantara J. The Chiropractic Care of Patients With Cancer: A Systematic Review of the Literature. *Integr Cancer Ther* 2011.

(60) Brantingham JW, Cassa TK, Bonnefin D, Jensen M, Globe G, Hicks M et al. Manipulative therapy for shoulder pain and disorders: expansion of a systematic review. *J Manipulative Physiol Ther* 2011; 34(5):314-346.

(61) Bryans R, Descarreaux M, Duranleau M, Marcoux H, Potter B, Ruegg R et al. Evidence-based guidelines for the chiropractic treatment of adults with headache. *J Manipulative Physiol Ther* 2011; 34(5):274-289.

(62) Alcantara J, Alcantara JD, Alcantara J. The chiropractic care of infants with colic: a systematic review of the literature. *Explore (NY)* 2011; 7(3):168-174.

(63) Posadzki P, Ernst E. Spinal manipulations for the treatment of migraine: a systematic review of randomized clinical trials. *Cephalalgia* 2011; 31(8):964-970.

(64) Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. *J Headache Pain* 2011; 12(2):127-133.

(65) Ernst E. Chiropractic treatment for gastrointestinal problems: a systematic review of clinical trials. *Can J Gastroenterol* 2011; 25(1):39-40.

(66) Walker BF, French SD, Grant W, Green S. A Cochrane review of combined chiropractic interventions for low-back pain. *Spine (Phila Pa 1976)* 2011; 36(3):230-242.

(67) Ernst E, Posadzki P. An independent review of NCCAM-funded studies of chiropractic. *Clin Rheumatol* 2011; 30(5):593-600.

(68) Alcantara J, Davis J. The chiropractic care of children with "growing pains": a case series and systematic review of the literature. *Complement Ther Clin Pract* 2011; 17(1):28-32.

(69) Posadzki P, Ernst E. Osteopathy for musculoskeletal pain patients: a systematic review of randomized controlled trials. *Clin Rheumatol* 2011; 30(2):285-291.

(70) Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007; 2(12):e1350.

(71) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7:10.

(72) Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009; 62(10):1013-1020.

(73) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011. The Cochrane Collaboration.

(74) Khan KS, Ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for Carrying Out or Commissioning Reviews. 2nd Edition[CRD Report No. 4.]. 2001. York, NHS Centre for Reviews and Dissemination (CRD), University of York.

(75) CASP. 10 questions to help you make sense of qualitative research. http://www sph nhs uk/sph-files/Qualitative%20Appraisal%20Tool pdf [2006

(76) Drummond MF, Sculpher MJ, Torrance GW. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford University Press, USA; 2005.

(77) McMorland G, Suter E, Casha S, du Plessis SJ, Hurlbert RJ. Manipulation or microdiskectomy for sciatica? A prospective randomized clinical study. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(8):576-584.

(78) Paatelma M, Kilpikoski S, Simonen R, Heinonen A, Alen M, Videman T. Orthopaedic manual therapy, McKenzie method or advice only for low back pain in working adults: a randomized controlled trial with one year follow-up. *J Rehabil Med* 2008; 40(10):858-863.

(79) Schulz CA, Hondras MA, Evans RL, Gudavalli MR, Long CR, Owens EF et al. Chiropractic and self-care for back-related leg pain: Design of a randomized clinical trial [randomized controlled trial]. *Chiropr & Manual Ther* 2011; 19(8):Online.

(80) Schomacher J. The effect of an analgesic mobilization technique when applied at symptomatic or asymptomatic levels of the cervical spine in subjects with neck pain: A randomized controlled trial. *J Man Manip Ther* 2009; 17(2):101-108.

(81) Puentedura EJ, Landers MR, Cleland JA, Mintken PE, Huijbregts P, Fernandez-de-Las-Penas C. Thoracic spine thrust manipulation versus cervical spine thrust manipulation in patients with acute neck pain: a randomized clinical trial. *Journal of Orthopaedic & Sports Physical Therapy* 2011; 41(4):208-220.

(82) Aquino RL, Caires PM, Furtado FC, Loureiro AV, Ferreira PH, Ferreira ML. Applying joint mobilization at different cervical vertebral levels does not influence immediate pain reduction in patients with chronic neck pain: A randomized clinical trial. *J Man Manip Ther* 2009; 17(2):95-100.

(83) Gemmell H, Miller P. Relative effectiveness and adverse effects of cervical manipulation, mobilisation and the activator instrument in patients with sub-acute non-specific neck pain: Results from a stopped randomised trial. *Chiropr Osteopathy* 2010; 18.

(84) Leaver AM, Maher CG, Herbert RD, Latimer J, McAuley JH, Jull G et al. A randomized controlled trial comparing manipulation with mobilization for recent onset neck pain. *Archives of Physical Medicine & Rehabilitation* 2010; 91(9):1313-1318.

(85) Martel J, Dugas C, Dubois JD, Descarreaux M. A randomised controlled trial of preventive spinal manipulation with and without a home exercise program for patients with chronic neck pain. *BMC Musculoskelet Disord* 2011; 12:41.

(86) Vanti C, Ferrari S, Morsillo F, Tosarelli D, Pillastrini P. Manual therapy for non-specific thoracic pain in adults: Review of the literature. *J Back Musculoskeletal Rehabil* 2008; 21(3):143-152.

(87) Crothers A, Walker B, French SD. Spinal manipulative therapy versus Graston Technique in the treatment of non-specific thoracic spine pain: Design of a randomised controlled trial. *Chiropr Osteopathy* 2008; 16.

(88) Schiller L. Effectiveness of spinal manipulative therapy in the treatment of mechanical thoracic spine pain: a pilot randomized clinical trial. *J Manipulative Physiol Ther* 2001; 24(6):394-401.

(89) Bleakley CM, McDonough SM, MacAuley DC. Some conservative strategies are effective when added to controlled mobilisation with external support after acute ankle sprain: a systematic review. [Review] [75 refs]. *Aust J Physiother* 2008; 54(1):7-20.

(90) Lin CW, Moseley AM, Refshauge KM. Rehabilitation for ankle fractures in adults. [Review] [112 refs]. *Cochrane Database of Systematic Reviews (3):CD005595, 2008* 2008;(3):CD005595.

(91) du Plessis M., Zipfel B, Brantingham JW, Parkin-Smith GF, Birdsey P, Globe G et al. Manual and manipulative therapy compared to night splint for symptomatic hallux abducto valgus: An exploratory randomised clinical trial. *Foot* 2011; 21(2):71-78.

(92) Joseph LC, de BN, Brantingham JW, Globe G, Cassa TK, Korporaal C et al. The comparative effect of muscle energy technique vs. manipulation for the treatment of chronic recurrent ankle sprain [randomized controlled trial]. *JACA Online* 2010; 47(7):Online-22.

(93) Kuhar S, Subhash K, Chitra J. Effectiveness of myofascial release in treatment of plantar fasciitis: A rct. *Indian Journal of Physiotherapy and Occupational Therapy* 2007; 1(3):3-9.

(94) Renan-Ordine R, Alburquerque-Sendin F, de Souza DP, Cleland JA, Fernandez-de-Las-Penas C. Effectiveness of myofascial trigger point manual therapy combined with a self-stretching protocol for the management of plantar heel pain: a randomized controlled trial. *Journal of Orthopaedic & Sports Physical Therapy* 2011; 41(2):43-50.

(95) Wilson FM. Manual therapy versus traditional exercises in mobilisation of the ankle post-ankle fracture. *New Zealand Journal Physiotherapy* 1991; 19:11-16.

(96) Davenport TE, Kulig K, Fisher BE. Ankle manual therapy for individuals with post-acute ankle sprains: description of a randomized, placebo-controlled clinical trial. *BMC Complementary & Alternative Medicine* 2010; 10:59.

(97) Brantingham JW, Bonnefin D, Perle SM, Cassa TK, Globe G, Pribicevic M et al. Manipulative therapy for lower extremity conditions: update of a literature review. *J Manipulative Physiol Ther* 2012; 35(2):127-166.

(98) Ellis RF, Hing WA. Neural mobilization: A systematic review of randomized controlled trials with an analysis of therapeutic efficacy. *J Man Manip Ther* 2008; 16(1):8-22.

(99) Huisstede BM, Hoogvliet P, Randsdorp MS, Glerum S, van MM, Koes BW. Carpal Tunnel Syndrome. Part I: Effectiveness of Nonsurgical Treatments-A Systematic Review. *Arch Phys Med Rehabil* 2010; 91(7):981-1004.

(100) Hunt KJ, Hung SK, Boddy K, Ernst E. Chiropractic manipulation for carpal tunnel syndrome: a systematic review. *Hand Ther* 2009; 14(4):89-94.

(101) Muller M, Tsui D, Schnurr R, Biddulph-Deisroth L, Hard J, Macdermid JC. Effectiveness of hand therapy interventions in primary management of carpal tunnel syndrome: a systematic review. *J Hand Ther* 2004; 17:210-228.

(102) Bialosky JE, Bishop MD, Price DD, Robinson ME, Vincent KR, George SZ. A randomized sham-controlled trial of a neurodynamic technique in the treatment of carpal tunnel syndrome. *Journal of Orthopaedic & Sports Physical Therapy* 2009; 39(10):709-723.

(103) Burke J, Buchberger DJ, Carey-Loghmani MT, Dougherty PE, Greco DS, Dishman JD. A pilot study comparing two manual therapy interventions for carpal tunnel syndrome. *Journal of Manipulative & Physiological Therapeutics* 2007; 30(1):50-61.

(104) Hains G, Descarreaux M, Lamy A-M, Hains F. A randomized controlled (intervention) trial of ischemic compression therapy for chronic carpal tunnel syndrome [randomized controlled trial]. *J Can Chiropr Assoc* 2010; 54(3):155-163.

(105) Aguilera Eguia RA. Manual therapy in lateral epicondylalgia (systematic review). *Rev Soc Esp Dolor* 2009; 16(2):112-115.

(106) Barr S, Cerisola FL, Blanchard V. Effectiveness of corticosteroid injections compared with physiotherapeutic interventions for lateral epicondylitis: A systematic review. *Physiotherapy* 2009; 95(4):251-265.

(107) Herd CR, Meserve BB. A systematic review of the effectiveness of manipulative therapy in treating lateral epicondylalgia. *J Man Manip Ther* 2008; 16(4):225-237.

(108) Kohia M, Brackle J, Byrd K, Jennings A, Murray W, Wilfong E. Effectiveness of physical therapy treatments on lateral epicondylitis. *J Sport Rehabil* 2008; 17:119-136.

(109) Nimgade A, Sullivan M, Goldman R. Physiotherapy, steroid injections, or rest for lateral epicondylosis? What the evidence suggests. *Pain Pract* 2005; 5(3):203-215.

(110) Pagorek S. Effect of manual mobilization with movement on pain and strength in adults with chronic lateral epicondylitis. *J Sport Rehabil* 2009; 18:448-457.

(111) Trudel D, Duley J, Zastrow I, Kerr EW, Davidson R, Macdermid JC. Rehabilitation for patients with lateral epicondylitis: a systematic review. *J Hand Ther* 2004; 17:243-266.

(112) Blanchette MA, Normand MC. Augmented soft tissue mobilization vs natural history in the treatment of lateral epicondylitis: A pilot study. *J Manipulative Physiol Ther* 2011; 34(2):123-130.

(113) Kochar M, Dogra A. Effectiveness of a specific physiotherapy regimen on patients with tennis elbow: Clinical study. *Physiotherapy* 2002; 88(6):333-341.

(114) Nagrale AV, Herd CR, Ganvir S, Ramteke G. Cyriax physiotherapy versus phonophoresis with supervised exercise in subjects with lateral epicondylalgia: A randomized clinical trial. *J Man Manip Ther* 2009; 17(3):171-178.

(115) Stasinopoulos D, Stasinopoulos I. Comparison of effects of Cyriax physiotherapy, a supervised exercise programme and polarized polychromatic non-coherent light (Bioptron light) for the treatment of lateral epicondylitis. *Clin Rehabil* 2006; 20(1):12-23.

(116) Vasseljen O. Low-level laser versus traditional physiotherapy in the treatment of tennis elbow. *Physiotherapy* 1992; 78(5):329-334.

(117) Stratford PW, Levy DR, Gauldie S, Miseferi D, Levy K. The evaluation of phonophoresis and friction massage as treatments for extensor carpi radialis tendinitis: A randomized controlled trial. *PHYSIOTHER CAN* 1989; 41(2):93-99.

(118) Coombes BK, Bisset L, Connelly LB, Brooks P, Vicenzino B. Optimising corticosteroid injection for lateral epicondylalgia with the addition of physiotherapy: A protocol for a randomised control trial with placebo comparison. *BMC Musculoskelet Disord* 2009; 10(1).

(119) Amro A, Diener I, Bdair WO, Hameda IM, Shalabi AI, Ilyyan DI. The effects of Mulligan mobilisation with movement and taping techniques on pain, grip strength, and function in patients with lateral epicondylitis. *Hong Kong Physiother J* 2010; 28:19-23.

(120) Cleland JA, Whitman JM, Fritz JM. Effectiveness of manual physical therapy to the cervical spine in the management of lateral epicondylalgia: a retrospective analysis. *J Orthop Sports Phys Ther* 2004; 34(11):713-714.

(121) Rompe JD, Riedel C, Betz U, Fink C. Chronic lateral epicondylitis of the elbow: A prospective study of low-energy shockwave therapy and low-energy shockwave therapy plus manual therapy of the cervical spine. *Arch Phys Med Rehabil* 2001; 82(5):578-582.

(122) Brantingham JW, Cassa TK, Bonnefin D, Jensen M, Globe G, Hicks M et al. Manipulative therapy for shoulder pain and disorders: Expansion of a systematic review. *J Manipulative Physiol Ther* 2011; 34(5):314-346.

(123) Braun C, Hanchard NC. Manual therapy and exercise for impingement-related shoulder pain. *Phys Ther Rev* 2010; 15(2):62-83.

(124) Camarinos J, Marinko L. Effectiveness of manual physical therapy for painful shoulder conditions: A systematic review. *J Man Manip Ther* 2009; 17(4):206-215.

(125) Faber E, Kuiper JI, Burdorf A, Miedema HS, Verhaar JA. Treatment of impingement syndrome: a systematic review of the effects on functional limitations and return to work. [Review] [50 refs]. *J Occup Rehabil* 2006; 16(1):7-25.

(126) Ho CY, Sole G, Munn J. The effectiveness of manual therapy in the management of musculoskeletal disorders of the shoulder: a systematic review. [Review] [38 refs]. *Manual Ther* 2009; 14(5):463-474.

(127) Kromer TO, Tautenhahn UG, de Bie RA, Staal JB, Bastiaenen CH. Effects of physiotherapy in patients with shoulder impingement syndrome: a systematic review of the literature. [Review] [41 refs]. *J Rehabil Med* 2009; 41(11):870-880.

(128) Kuhn JE. Exercise in the treatment of rotator cuff impingement: A systematic review and a synthesized evidence-based rehabilitation protocol. *J Shoulder Elbow Surg* 2009; 18(1):138-160.

(129) Michener LA, Walsworth MK, Burnet EN. Effectiveness of rehabilitation for patients with subacromial impingement syndrome: a systematic review. *J Hand Ther* 2004; 17(2):152-164.

(130) Pribicevic M, Pollard H, Bonello R, de LK. A systematic review of manipulative therapy for the treatment of shoulder pain. [Review]. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(9):679-689.

(131) Trampas A, Kitsios A. Exercise and Manual Therapy for the Treatment of Impingement Syndrome of the Shoulder: a Systematic Review. *Phys Ther Rev* 2006; 11(2):125-142.

(132) Verhagen AP, Karels C, Bierma-Zeinstra SM, Feleus A, Dahaghin S, Burdorf A et al. Ergonomic and physiotherapeutic interventions for treating work-related complaints of the arm, neck or shoulder in adults. A Cochrane systematic review. [Review] [36 refs]. *Eur Medicophys* 2007; 43(3):391-405.

(133) Verhagen AP, Karels C, Bierma-Zeinstra SM, Feleus A, Dahaghin S, Burdorf A et al. Exercise proves effective in a systematic review of work-related complaints of the arm, neck, or shoulder. [Review] [42 refs]. *J Clin Epidemiol* 2007; 60(2):110-117.

(134) von der Heyde RL. Occupational therapy interventions for shoulder conditions: a systematic review. [Review]. *Am J Occup Ther* 2011; 65(1):16-23.

(135) Bennell K, Wee E, Coburn S, Green S, Harris A, Staples M et al. Efficacy of standardised manual therapy and home exercise programme for chronic rotator cuff disease: randomised placebo controlled trial. *BMJ* 2010; 340:c2756.

(136) Bergman GJ, Winters JC, Groenier KH, Meyboom-de JB, Postema K, van der Heijden GJ. Manipulative therapy in addition to usual care for patients with shoulder complaints: results of physical examination outcomes in a randomized controlled trial. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(2):96-101.

(137) Bialoszewski D, Zaborowski G. Usefulness of manual therapy in the rehabilitation of patients with chronic rotator cuff injuries. Preliminary report. *Ortop Traumatol Rehab* 2011; 13(1):9-20.

(138) Bron C, de Gast A, Dommerholt J, Stegenga B, Wensing M, Oostendorp RAB. Treatment of myofascial trigger points in patients with chronic shoulder pain: a randomized, controlled trial. *BMC Med* 2011; 9.

(139) Chen JF, Ginn KA, Herbert RD. Passive mobilisation of shoulder region joints plus advice and exercise does not reduce pain and disability more than advice and exercise alone: a randomised trial. *Aust J Physiother* 2009; 55(1):17-23.

(140) Hains G, Descarreaux M, Hains F. Chronic Shoulder Pain of Myofascial Origin: A Randomized Clinical Trial Using Ischemic Compression Therapy. *J Manipulative Physiol Ther* 2010; 33(5):362-369.

(141) McClatchie L, Laprade J, Martin S, Jaglal SB, Richardson D, Agur A. Mobilizations of the asymptomatic cervical spine can reduce signs of shoulder dysfunction in adults. *Manual Ther* 2009; 14(4):369-374.

(142) Munday SL, Jones A, Brantingham JW, Globe G, Jensen M, Price JL. A randomized, single-blinded, placebo-controlled clinical trial to evaluate the efficacy of chiropractic shoulder girdle adjustment in the treatment of shoulder impingement syndrome. *Journal of the American Chiropractic Association* 2007; 44:6-15.

(143) Senbursa G, Baltaci G, Atay A. Comparison of conservative treatment with and without manual physical therapy for patients with shoulder impingement syndrome: a prospective, randomized clinical trial. *Knee Surg Sports Traumatol Arthroscopy* 2007; 15(7):915-921.

(144) Surenkok O, Aytar A, Baltaci G. Acute effects of scapular mobilization in shoulder dysfunction: a double-blind randomized placebo-controlled trial. *J Sport Rehabil* 2009; 18(4):493-501.

(145) Teys P, Bisset L, Vicenzino B. The initial effects of a Mulligan's mobilization with movement technique on range of movement and pressure pain threshold in pain-limited shoulders. *Manual Ther* 2008; 13(1):37-42.

(146) Conroy DE, Hayes KW. The effect of joint mobilization as a component of comprehensive treatment for primary shoulder impingement syndrome. *J Orthop Sports Phys Ther* 1998; 28(1):3-14.

(147) Guler-Uysal F, Kozanoglu E. Comparison of the early response to two methods of rehabilitation in adhesive capsulitis. *Swiss Med Wkly* 2004; 134(23-24):353-358.

(148) Johnson AJ, Godges JJ, Zimmerman GJ, Ounanian LL. The effect of anterior versus posterior glide joint mobilization on external rotation range of motion in patients with shoulder adhesive capsulitis. *Journal of Orthopaedic & Sports Physical Therapy* 2007; 37(3):88-99.

(149) Kachingwe AF, Phillips B, Sletten E, Plunkett SW. Comparison of manual therapy techniques with therapeutic exercise in the treatment of shoulder impingement: a randomized controlled pilot clinical trial. *J Man Manip Ther* 2008; 16(4):238-247.

(150) Vermeulen HM, Rozing PM, Obermann WR, le CS, Vliet Vlieland TP. Comparison of high-grade and low-grade mobilization techniques in the management of adhesive capsulitis of the shoulder: randomized controlled trial. *Phys Ther* 2006; 86(3):355-368.

(151) Yang JI, Chang CW, Chen SY, Wang SF, Lin JJ. Mobilization Techniques in Subjects with Frozen Shoulder-Syndrome: Randomized Multiple-Treatment Trial. *Phys Ther* 2007; 87(10):1307-1315.

(152) De Souza RF, Lovato Da Silva CH, Nasser M, Fedorowicz Z. Interventions for the management of temporomandibular joint osteoarthritis. *Cochrane Database Syst Rev* 2008;(3).

(153) Cuccia AM, Caradonna C, Annunziata V, Caradonna D. Osteopathic manual therapy versus conventional conservative therapy in the treatment of temporomandibular

disorders: a randomized controlled trial. *Journal of Bodywork & Movement Therapies* 2010; 14(2):179-184.

(154) Kalamir A, Pollard H, Vitiello A, Bonello R. Intra-oral myofascial therapy for chronic myogenous temporomandibular disorders: A randomized, controlled pilot study. *J Man Manip Ther* 2010; 18(3):139-146.

(155) Yoshida H, Fukumura Y, Suzuki S, Fujita S, Kenzo O, Yoshikado R et al. Simple manipulation therapy for temporomandibular joint internal derangement with closed lock. *Asian J Oral Maxillofac Surg* 2005; 17(4):256-260.

(156) Posadzki P, Ernst E. Spinal manipulations for cervicogenic headaches: A systematic review of randomized clinical trials. *Headache: The Journal of Head & Face Pain* 2011; 51(7):1132-1139.

(157) von Piekartz H., Ludtke K. Effect of treatment of temporomandibular disorders (TMD) in patients with cervicogenic headache: a single-blind, randomized controlled study. *Cranio* 2011; 29(1):43-56.

(158) Chaibi A, Russell MB. Manual therapies for cervicogenic headache: a systematic review. *J Headache Pain* 2012; 13(5):351-359.

(159) Anderson RE, Seniscal C. A comparison of selected osteopathic treatment and relaxation for tension-type headaches. *Headache: The Journal of Head & Face Pain* 2006; 46(8):1273-1280.

(160) Castien RF, van der Windt DA, Grooten A, Dekker J. Effectiveness of manual therapy for chronic tension-type headache: a pragmatic, randomised, clinical trial. *Cephalalgia* 2011; 31(2):133-143.

(161) Castien RF, van der Windt DA, Dekker J, Mutsaers B, Grooten A. Effectiveness of manual therapy compared to usual care by the general practitioner for chronic tension-type headache: design of a randomised clinical trial. *BMC Musculoskelet Disord* 2009; 10:21.

(162) van Ettekoven H., Lucas C. Efficacy of physiotherapy including a craniocervical training programme for tension-type headache; a randomized clinical trial. *Cephalalgia* 2006; 26(8):983-991.

(163) Vernon. A Randomized, Placebo-Controlled Clinical Trial of Chiropractic and Medical Prophylactic Treatment of Adults With Tension-Type Headache: Results From a Stopped Trial (vol 32, pg 344, 2009). *J Manipulative Physiol Ther* 2009; 32(9):804.

(164) Bryans R, Descarreaux M, Duranleau M, Marcoux H, Potter B, Ruegg R et al. Evidence-based guidelines for the chiropractic treatment of adults with headache. *J Manipulative Physiol Ther* 2011; 34(5):274-289.

(165) Maltby JK, Harrison DD, Harrison DE, Betz JW, Ferrantelli JR, Clum GW. Frequency & duration of chiropractic care for headaches, neck and upper back pain. *Journal of Vertebral Subluxation Research (JVSR)* 2008;1-12.

(166) De Hertogh W., Vaes P, Devroey D, Louis P, Carpay H, Truijen S et al. Preliminary results, methodological considerations and recruitment difficulties of a randomised clinical trial comparing two treatment regimens for patients with headache and neck pain. *BMC Musculoskelet Disord* 2009; 10:115.

(167) Foster KA, Liskin J, Cen S, Abbott A, Armisen V, Globe D et al. The Trager approach in the treatment of chronic headache: A pilot study. *Altern Ther Health Med* 2004; 10(5):40-46.

(168) Baranowsky J, Klose P, Musial F, Hauser W, Dobos G, Langhorst J. Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia. [Review][Erratum appears in Rheumatol Int. 2009 Nov;30(1):23 Note: Haeuser, Winfried [corrected to Hauser, Winfried].]. *Rheumatol Int* 2009; 30(1):1-21.

(169) Porter NS, Jason LA, Boulton A, Bothne N, Coleman B. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. *J Altern Complement Med* 2010; 16(3):235-249.

(170) Castro-Sanchez AM, Mataran-Penarrocha GA, Sanchez-Labraca N, Quesada-Rubio JM, Granero-Molina J, Moreno-Lorenzo C. A randomized controlled trial investigating the effects of craniosacral therapy on pain and heart rate variability in fibromyalgia patients. *Clin Rehabil* 2011; 25(1):25-35.

(171) Castro-Sanchez AM, Mataran-Pearrocha GA, Granero-Molina J, Aguilera-Manrique G, Quesada-Rubio JM, Moreno-Lorenzo C. Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia. *Evid -Based Complement Altern Med* 2011; 2011.

(172) de las Penas CF, Sohrbeck CM, Fernandez CJ, Miangolarra Page JC. Manual therapies in myofascial trigger point treatment: A systematic review. *J Bodywork Mov Ther* 2005; 9(1):27-34.

(173) Rickards LD. The effectiveness of non-invasive treatments for active myofascial trigger point pain: A systematic review of the literature. *Int J Ostheopath Med* 2006; 9(4):120-136.

(174) Gemmell H, Allen A. Relative immediate effect of ischaemic compression and activator trigger point, therapy on active upper trapezius trigger points: A randomised trial. *Clin Chiropractic* 2008; 11(4):175-181.

(175) Gemmell H, Miller P, Nordstrom H. Immediate effect of ischaemic compression and trigger point pressure release on neck pain and upper trapezius trigger points: A randomised, controlled trial. *Clin Chiropractic* 2008; 11(1):30-36.

(176) Nagrale AV, Glynn P, Joshi A, Ramteke G. The efficacy of an integrated neuromuscular inhibition technique on upper trapezius trigger points in subjects with non-specific neck pain: A randomized controlled trial. *J Man Manip Ther* 2010; 18(1):37-43.

(177) Kaminskyj A, Frazier M, Johnstone K, Gleberzon BJ. Chiropractic care for patients with asthma: A systematic review of the literature. *J Can Chiropr Assoc* 2010; 54(1):24-32.

(178) Mehl-Madrona L, Kligler B, Silverman S, Lynton H, Merrell W. The impact of acupuncture and craniosacral therapy interventions on clinical outcomes in adults with asthma. *Explore: The Journal of Science & Healing* 2007; 3(1):28-36.

(179) Shaw A, Thompson EA, Sharp D. Complementary therapy use by patients and parents of children with asthma and the implications for NHS care: A qualitative study. *BMC Health Serv Res* 2006; 6.

(180) Kaminskyj A, Frazier M, Johnstone K, Gleberzon BJ. Chiropractic care for patients with asthma: A systematic review of the literature. *J Can Chiropr Assoc* 2010; 54(1):24-32.

(181) Karpouzis F, Bonello R, Pollard H. Chiropractic care for paediatric and adolescent Attention-Deficit/Hyperactivity Disorder: A systematic review. *Chiropr Osteopathy* 2010; 18.

(182) Bierent-Vass A. [Has osteopathic treatment a positive influence on children with ADD/ADHD?]. *Osteopath Med* 2005; 6:4-8.

(183) Hubmann B. The influence of osteopathy on ADHD [Donau Universität Krems; 2006.

(184) Alcantara J, Alcantara JD, Alcantara J. The Chiropractic Care of Patients With Cancer: A Systematic Review of the Literature. *Integr Cancer Ther* 2011.

(185) Wu PK, Chen WM, Lee OK, Chen CF, Huang CK, Chen TH. The prognosis for patients with osteosarcoma who have received prior manipulative therapy. *Journal of Bone & Joint Surgery - British Volume* 2010; 92(11):1580-1585.

(186) Duncan B, Barton L, Edmonds D, Blashill BM. Parental perceptions of the therapeutic effect from osteopathic manipulation or acupuncture in children with spastic cerebral palsy. *Clin Pediatr (Phila)* 2004; 43(4):349-353.

(187) Duncan B, McDonough-Means S, Worden K, Schnyer R, Andrews J, Meaney FJ. Effectiveness of osteopathy in the cranial field and myofascial release versus acupuncture as complementary treatment for children with spastic cerebral palsy: a pilot study. *J Am Osteopath Assoc* 2008; 108(10):559-570.

(188) Wyatt K, Edwards V, Franck L, Britten N, Creanor S, Maddick A et al. Cranial osteopathy for children with cerebral palsy: a randomised controlled trial. *Arch Dis Child* 2011; 96(6):505-512.

(189) Lystad RP, Bell G, Bonnevie-Svendsen M, Carter CV. Manual therapy with and without vestibular rehabilitation for cervicogenic dizziness: a systematic review. *Chiropr Man Therap* 2011; 19(1):21.

(190) Hawk C, Cambron JA, Pfefer MT. Pilot Study of the Effect of a Limited and Extended Course of Chiropractic Care on Balance, Chronic Pain, and Dizziness in Older Adults. *J Manipulative Physiol Ther* 2009; 32(6):438-447.

(191) FitzGerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. *J Urol* 2009; 182(2):570-580.

(192) Heyman J, Ohrvik J, Leppert J. Distension of painful structures in the treatment for chronic pelvic pain in women. *Acta Obstet Gynecol Scand* 2006; 85(5):599-603.

(193) Marx S, Cimniak U, Beckert R, Schwerla F, Resch KL. [Chronic prostatitis/chronic pelvic pain syndrome. Influence of osteopathic treatment - a randomized controlled study]. [German]. *Urologe (Ausg A)* 2009; 48(11):1339-1345.

(194) Sandsund CA, Roughton M, Hodson ME, Pryor JA. Musculoskeletal techniques for clinically stable adults with cystic fibrosis: a preliminary randomised controlled trial. *Physiotherapy* 2011; 97(3):209-217.

(195) Nemett DR, Fivush BA, Mathews R, Camirand N, Eldridge MA, Finney K et al. A randomized controlled trial of the effectiveness of osteopathy-based manual physical therapy in treating pediatric dysfunctional voiding. *J Pediatr Urol* 2008; 4(2):100-106.

(196) Huang T, Shu X, Huang YS, Cheuk DK. Complementary and miscellaneous interventions for nocturnal enuresis in children. *Cochrane Database Syst Rev* 2011;(12):CD005230.

(197) Alcantara JD, Alcantara J. The chiropractic care of infants with colic: A systematic review of the literature. *Explor J Sci Heal* 2011; 7(3):168-174.

(198) Perry R, Hunt K, Ernst E. Nutritional supplements and other complementary medicines for infantile colic: A systematic review. *Pediatrics* 2011; 127(4):720-733.

(199) Miller JE, Phillips HL. Long-term effects of infant colic: a survey comparison of chiropractic treatment and nontreatment groups. *Journal of Manipulative & Physiological Therapeutics* 2009; 32(8):635-638.

(200) Cleary C, Fox JP. Menopausal symptoms: An osteopathic investigation. *Complement Ther Med* 1994; 2(4):181-186.

(201) Ernst E. Chiropractic treatment for gastrointestinal problems: a systematic review of clinical trials. [Review]. *Can J Gastroenterol* 2011; 25(1):39-40.

(202) Hundscheid HW, Pepels MJ, Engels LG, Loffeld RJ. Treatment of irritable bowel syndrome with osteopathy: results of a randomized controlled pilot study. *Journal of Gastroenterology & Hepatology* 2007; 22(9):1394-1398.

(203) Mangum K, Partna L, Vavrek D. Spinal manipulation for the treatment of hypertension: a systematic qualitative literature review. *J Manipulative Physiol Ther* 2012; 35(3):235-243.

(204) Cerritelli F, Carinci F, Pizzolorusso G, Turi P, Renzetti C, Pizzolorusso F et al. Osteopathic manipulation as a complementary treatment for the prevention of cardiac complications: 12-Months follow-up of intima media and blood pressure on a cohort affected by hypertension. *Journal of Bodywork & Movement Therapies* 2011; 15(1):68-74.

(205) Lombardini R, Marchesi S, Collebrusco L, Vaudo G, Pasqualini L, Ciuffetti G et al. The use of osteopathic manipulative treatment as adjuvant therapy in patients with peripheral arterial disease. *Manual Ther* 2009; 14(4):439-443.

(206) Kingston J, Raggio C, Spencer K, Stalaker K, Tuchin PJ. A review of the literature on chiropractic and insomnia. *J Chiropractic Med* 2010; 9:121-126.

(207) Steele KM, Viola J, Burns E, Carreiro JE. Brief report of a clinical trial on the duration of middle ear effusion in young children using a standardized osteopathic manipulative medicine protocol. *J Am Osteopath Assoc* 2010; 110(5):278-284.

(208) Wells MR, Giantinoto S, D'Agate D, Areman RD, Fazzini EA, Dowling D et al. Standard osteopathic manipulative treatment acutely improves gait performance in patients with Parkinson's disease. *J Am Osteopath Assoc* 1999; 99(2):92-98.

(209) Yang M, Yuping Y, Yin X, Wang BY, Wu T, Liu GJ et al. Chest physiotherapy for pneumonia in adults. *Cochrane Database Syst Rev* 2010; 2:CD006338.

(210) Noll DR, Degenhardt BF, Fossum C, Hensel K. Clinical and research protocol for osteopathic manipulative treatment of elderly patients with pneumonia.[Erratum appears

in J Am Osteopath Assoc. 2008 Nov;108(11):670]. *J Am Osteopath Assoc* 2008; 108(9):508-516.

(211) Noll DR, Degenhardt BF, Johnson JC, Burt SA. Immediate effects of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease. *J Am Osteopath Assoc* 2008; 108(5):251-259.

(212) Khorsan R, Hawk C, Lisi AJ, Kizhakkeveettil A. Manipulative therapy for pregnancy and related conditions. *Obstet Gynecol Surv* 2009; 64(6):416-427.

(213) Cameron EC, Maehle V, Reid J. The effects of an early physical therapy intervention for very preterm, very low birth weight infants: a randomized controlled clinical trial. *PEDIATR PHYS THER* 2005; 17(2):107-119.

(214) Pizzolorusso G, Turi P, Barlafante G, Cerritelli F, Renzetti C, Cozzolino V et al. Effect of osteopathic manipulative treatment on gastrointestinal function and length of stay of preterm infants: An exploratory study. *Chiropr & Manual Ther* 2011; 19(15):Online.

(215) Goldstein FJ, Jeck S, Nicholas AS, Berman MJ, Lerario M. Preoperative intravenous morphine sulfate with postoperative osteopathic manipulative treatment reduces patient analgesic use after total abdominal hysterectomy. *J Am Osteopath Assoc* 2005; 105(6):273-279.

(216) Hunter SM, Hammett L, Ball S, Smith N, Anderson C, Clark A et al. Dose-response study of mobilisation and tactile stimulation therapy for the upper extremity early after stroke: a phase I trial. *Neurorehabil Neural Repair* 2011; 25(4):314-322.

(217) Sleszynski SL, Kelso AF. Comparison of thoracic manipulation with incentive spirometry in preventing postoperative atelectasis. *J Am Osteopath Assoc* 1993; 93(8):834-835.

(218) Crow WT, Gorodinsky L. Does osteopathic manipulative treatment (OMT) improves outcomes in patients who develop postoperative ileus: A retrospective chart review. *Int J Ostheopath Med* 2009; 12(1):32-37.

(219) Jarski RW, Loniewski EG, Williams J, Bahu A, Shafinia S, Gibbs K et al. The effectiveness of osteopathic manipulative treatment as complementary therapy following surgery: a prospective, match-controlled outcome study. *Altern Ther Health Med* 2000; 6(5):77-81.

(220) Yurvati AH, Carnes MS, Clearfield MB, Stoll ST, McConathy WJ. Hemodynamic effects of osteopathic manipulative treatment immediately after coronary artery bypass graft surgery. *J Am Osteopath Assoc* 2005; 105(10):475-481.

(221) Maddali BS, Del RA, Galluccio F, Sigismondi F, Miniati I, Conforti ML et al. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. *Clin Rheumatol* 2009; 28(10):1167-1173.

(222) Maddali BS, Del RA, Galluccio F, Tai G, Sigismondi F, Passalacqua M et al. Efficacy of a tailored rehabilitation program for systemic sclerosis. *Clin Exp Rheumatol* 2009; 27:44-50.

(223) Dagenais S, Gay RE, Tricco AC, Freeman MD, Mayer JM. NASS Contemporary Concepts in Spine Care: spinal manipulation therapy for acute low back pain. [Review]. *Spine Journal: Official Journal of the North American Spine Society* 2010; 10(10):918-940.

(224) Kent P, Mjosund HL, Petersen DH. Does targeting manual therapy and/or exercise improve patient outcomes in nonspecific low back pain? A systematic review. [Review] [74 refs]. *BMC Med* 2010; 8:22.

(225) Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. *Spine* 2011; 36:E825-E846.

(226) Walker BF, French SD, Grant W, Green S. A cochrane review of combined chiropractic interventions for low-back pain. *Spine* 2011; 36(3):230-242.

(227) Leaver AM, Refshauge KM, Maher CG, McAuley JH. Conservative interventions provide short-term relief for non-specific neck pain: a systematic review. [Review] [54 refs]. *J Physiother* 2010; 56(2):73-85.

(228) Gross A, Miller J, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N et al. Manipulation or mobilisation for neck pain: a Cochrane Review. [Review]. *Manual Ther* 2010; 15(4):315-333.

(229) D'Sylva J, Miller J, Gross A, Burnie SJ, Goldsmith CH, Graham N et al. Manual therapy with or without physical medicine modalities for neck pain: a systematic review. [Review]. *Manual Ther* 2010; 15(5):415-433.

(230) Miller J, Gross A, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N et al. Manual therapy and exercise for neck pain: a systematic review. [Review]. *Manual Ther* 2010; 15(4):334-354.

(231) Shaw L, Descarreaux M, Bryans R, Duranleau M, Marcoux H, Potter B et al. A systematic review of chiropractic management of adults with Whiplash-Associated Disorders: recommendations for advancing evidence-based practice and research. [Review] [77 refs]. *Work* 2010; 35(3):369-394.

(232) Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 4 - noninvasive interventions for chronic WAD. [Review]. *Pain Research & Management* 2010; 15(5):313-322.

(233) Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 3 - interventions for subacute WAD. [Review]. *Pain Research & Management* 2010; 15(5):305-312.

(234) Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 2 - interventions for acute WAD. *Pain Res Manag* 2010; 15(5):295-304.

(235) Maund E, Craig D, Suekarran S, Neilson A, Wright K, Brealey S et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2012; 16(11):1-264.

(236) Wies JT, Asher SN, Latham M, Hazleman BL, Speed CA. A Pilot Randomised Placebo-Controlled Trial of Physiotherapy and Osteopathic Treatment for Frozen Shoulder. *Rheumatology (UK)* 2003; 42:146.

(237) French HP, Brennan A, White B, Cusack T. Manual therapy for osteoarthritis of the hip or knee - a systematic review. [Review]. *Manual Ther* 2011; 16(2):109-117.

(238) Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. [Review]. *J Physiother* 2011; 57(1):11-20.

(239) van Baar ME, Dekker J, Oostendorp RA, Bijl D, Voorn TB, Lemmens JA et al. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. *J Rheumatol* 1998; 25(12):2432-2439.

(240) Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Ann Intern Med* 2000; 132(3):173-181.

(241) Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: A systematic review. *J Headache Pain* 2011; 12(2):127-133.

(242) Posadzki P, Ernst E. Spinal manipulations for the treatment of migraine: A systematic review of randomized clinical trials. *Cephalalgia* 2011; 31(8):964-970.

(243) Nelson CF, Bronfort G, Evans R, Boline P, Goldsmith C, Anderson AV. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. *J Manipulative Physiol Ther* 1998; 21(8):511-519.

(244) Parker GB, Tupling H, Pryor DS. A controlled trial of cervical manipulation of migraine. *Aust N Z J Med* 1978; 8(6):589-593.

(245) Tuchin PJ, Pollard H, Bonello R. A randomized controlled trial of chiropractic spinal manipulative therapy for migraine. *J Manipulative Physiol Ther* 2000; 23(2):91-95.

(246) Carnes D MTMBUM. Adverse Events in manual therapy: a systematic review. 2009. Barts and The London, School of Medicine and Dentistry.

(247) Stuber KJ, Wynd S, Weis CA. Adverse events from spinal manipulation in the pregnant and postpartum periods: a critical review of the literature. *Chiropr Man Therap* 2012; 20:8.

(248) Haldeman S, Kohlbeck FJ, McGregor M. Risk factors and precipitating neck movements causing vertebrobasilar artery dissection after cervical trauma and spinal manipulation. *Spine* 1999; 24(8):785-794.

(249) Miley ML, Wellik KE, Wingerchuk DM, Demaerschalk BM. Does cervical manipulative therapy cause vertebral artery dissection and stroke?. [Review] [28 refs]. *Neurologist* 2008; 14(1):66-73.

(250) Boyle E, Cote P, Grier AR, Cassidy JD. Examining vertebrobasilar artery stroke in two Canadian provinces. *Spine* 2008; 33(4 SUPPL.):S170-S175.

(251) Hayes NM, Bezilla TA. Incidence of iatrogenesis associated with osteopathic manipulative treatment of pediatric patients. *J Am Osteopath Assoc* 2006; 106(10):605-608.

(252) Alcantara J, Ohm J, Kunz D. The safety and effectiveness of pediatric chiropractic: a survey of chiropractors and parents in a practice-based research network. *EXPLORE* 2009; 5(5):290-295.

(253) Choi S, Boyle E, Cote P, Cassidy JD. A population-based case-series of Ontario patients who develop a vertebrobasilar artery stroke after seeing a chiropractor. *Journal of Manipulative & Physiological Therapeutics* 2011; 34(1):15-22.

(254) Miller JE, Benfield K. Adverse effects of spinal manipulative therapy in children younger than 3 years: a retrospective study in a chiropractic teaching clinic. *Journal of Manipulative & Physiological Therapeutics* 2008; 31(6):419-423.

(255) Rajendran D, Mullinger B, Fossum C, Collins P, Froud R. Monitoring self-reported adverse events: A prospective, pilot study in a UK osteopathic teaching clinic. *Int J Osteopath Med* 2009; 12(2):49-55.

(256) Sweeney A, Doody C. Manual therapy for the cervical spine and reported adverse effects: A survey of Irish Manipulative Physiotherapists. *Manual Ther* 2010; 15(1):32-36.

(257) Brown A, Angus D, Chen S, Tang Z, Milne S, Pfaff J et al. Costs and outcomes of chiropractic treatment for low back pain (Structured abstract). *Ottawa : Canadian Coordinating Office for Health Technology Assessment* 2005;88.

(258) Canter PH, Coon JT, Ernst E. Cost-effectiveness of complementary therapies in the United Kingdom - A systematic review. *Evid -Based Complement Altern Med* 2006; 3(4):425-432.

(259) Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med* 2003; 138(11):898-906.

(260) Coon JT, Ernst E. A systematic review of the economic evaluation of complementary and alternative medicine. *Perfusion* 2005; 18(6):202-214.

(261) Dagenais S, Roffey DM, Wai EK, Haldeman S, Caro J. Can cost utility evaluations inform decision making about interventions for low back pain?. [Review] [69 refs]. *Spine Journal: Official Journal of the North American Spine Society* 2009; 9(11):944-957.

(262) Furlan AD, Yazdi F, Tsertsvadze A, Gross A, van TM, Santaguida L et al. Complementary and alternative therapies for back pain II (Provisional abstract). *Agency for Healthcare Research and Quality* 2010;1.

(263) Herman PM, Craig BM, Caspi O. Is complementary and alternative medicine (CAM) cost-effective? A systematic review. *BMC Altern Med* 2005; 5:11.

(264) Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW. Cost-effectiveness of general practice care for low back pain: a systematic review. *Eur Spine J* 2011; 20(7):1012-1023.

(265) Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW. Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review. *Eur Spine J* 2011; 20(7):1024-1038.

(266) Van Der Roer N, Goossens MEJB, Evers SMAA, van Tulder MW. What is the most cost-effective treatment for patients with low back pain? A systematic review. *Best Practice and Research in Clinical Rheumatology* 2005; 19(4):671-684.

(267) White AR, Ernst E. Economic analysis of complementary medicine: a systematic review. *Complement Ther Med* 2000; 8(2):111-118.

(268) UK BEAM Trial Team. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. *BMJ (Clinical research ed)* 2004; 329(7479):1381.

(269) UK BEAM Trial Team. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. *BMJ (Clinical research ed)* 2004; 329(7479):1377.

(270) UK BEAM Trial Team. UK Back pain Exercise And Manipulation (UK BEAM) trial--national randomised trial of physical treatments for back pain in primary care: objectives, design and interventions [ISRCTN32683578]. BMC Health Serv Res [101088677] 2003 3(1):[16]

(271) Williams NH, Wilkinson C, Russell I, Edwards RT, Hibbs R, Linck P et al. Randomized osteopathic manipulation study (ROMANS): pragmatic trial for spinal pain in primary care. *Fam Pract* 2003; 20(6):662-669.

(272) Williams NH, Edwards RT, Linck P, Muntz R, Hibbs R, Wilkinson C et al. Cost-utility analysis of osteopathy in primary care: results from a pragmatic randomized controlled trial. *Fam Pract* 2004; 21(6):643-650.

(273) Apeldoorn AT, Ostelo RW, van HH, Fritz JM, de Vet HC, van Tulder MW. The cost-effectiveness of a treatment-based classification system for low back pain: design of a randomised controlled trial and economic evaluation. *BMC Musculoskelet Disord* 2010; 11(1):58.

(274) Bennell K, Coburn S, Wee E, Green S, Harris A, Forbes A et al. Efficacy and cost-effectiveness of a physiotherapy program for chronic rotator cuff pathology: a protocol for a randomised, double-blind, placebo-controlled trial. *BMC Musculoskelet Disord* 2007; 8:86.

(275) Maiers MJ, Hartvigsen J, Schulz C, Schulz K, Evans RL, Bronfort G. Chiropractic and exercise for seniors with low back pain or neck pain: the design of two randomized clinical trials. *BMC Musculoskelet Disord* 2007; 8:94.

(276) Westrom KK, Maiers MJ, Evans RL, Bronfort G. Individualized chiropractic and integrative care for low back pain: the design of a randomized clinical trial using a mixed-methods approach. *Trials [Electronic Resource]* 2010; 11:24.

(277) Bergman GJ, Winter JC, van Tulder MW, Meyboom-de JB, Postema K, van der Heijden GJ. Manipulative therapy in addition to usual medical care accelerates recovery of shoulder complaints at higher costs: economic outcomes of a randomized trial. *BMC Musculoskelet Disord* 2010; 11:200.

(278) Bergman GJD, Winters JC, van der Heijden GJMG, Postema K, Meyboom-de Jong B. Groningen Manipulation Study. The effect of manipulation of the structures of the shoulder girdle as additional treatment for symptom relief and for prevention of chronicity or recurrence of shoulder symptoms. Design of a randomized controlled trial within a

comprehensive prognostic cohort study. *J Manipulative Physiol Ther* 2002; 25(9):543-549.

(279) Bergman GJD, Winters JC, Groenier KH, Pool JJM, Meyboom-de Jong B, Postema K et al. Manipulative therapy in addition to usual medical care for patients with shoulder dysfunction and pain: a randomized, controlled trial. *Ann Intern Med* 2004; 141(6):432-439.

(280) Lewis M, James M, Stokes E, Hill J, Sim J, Hay E et al. An economic evaluation of three physiotherapy treatments for non-specific neck disorders alongside a randomized trial. *Rheumatology (UK)* 2007; 46(11):1701-1708.

(281) Dziedzic K, Hill J, Lewis M, Sim J, Daniels J, Hay EM. Effectiveness of manual therapy or pulsed shortwave diathermy in addition to advice and exercise for neck disorders: a pragmatic randomized controlled trial in physical therapy clinics. *Arthritis Rheum* 2005; 53(2):214-222.

(282) Korthals-de Bos IBC, Hoving JL, van Tulder MW, Rutten-van Molken MPMH, Ader HJ, de Vet HCW et al. Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial. *BMJ (Clinical research ed)* 2003; 326(7395):911.

(283) Hoving JL, Koes BW, de Vet HCW, van der Windt DAWM, Assendelft WJJ, van Mameren H et al. Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial. *Ann Intern Med* 2002; 136(10):713-722.

(284) Bosmans JE, Pool JJM, de Vet HCW, van Tulder MW, Ostelo RWJG. Is Behavioral Graded Activity Cost-Effective in Comparison With Manual Therapy for Patients With Subacute Neck Pain? An Economic Evaluation Alongside a Randomized Clinical Trial. *Spine* 2011; 36(18):E1179-E1186.

(285) Pool JJ, Ostelo RW, Koke AJ, Bouter LM, de Vet HC. Comparison of the effectiveness of a behavioural graded activity program and manual therapy in patients with sub-acute neck pain: design of a randomized clinical trial. *Manual Ther* 2006; 11(4):297-305.

(286) Pool JJ, Ostelo RW, Knol DL, Vlaeyen JW, Bouter LM, de Vet HC. Is a behavioral graded activity program more effective than manual therapy in patients with subacute neck pain? Results of a randomized clinical trial. *Spine* 2010; 35(10):1017-1024.

(287) Lin CW, Moseley AM, Haas M, Refshauge KM, Herbert RD. Manual therapy in addition to physiotherapy does not improve clinical or economic outcomes after ankle fracture. *J Rehabil Med* 2008; 40(6):433-439.

(288) Lin CC, Moseley AM, Refshauge KM, Haas M, Herbert RD. Effectiveness of joint mobilisation after cast immobilisation for ankle fracture: a protocol for a randomised controlled trial [ACTRN012605000143628]. *BMC Musculoskelet Disord* 2006; 7:46.

(289) Niemisto L, Rissanen P, Sarna S, Lahtinen-Suopanki T, Lindgren KA, Hurri H. Cost-effectiveness of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain: a prospective randomized trial with 2-year follow-up. *Spine* 2005; 30(10):1109-1115.

(290) Niemisto L, Lahtinen-Suopanki T, Rissanen P, Lindgren KA, Sarna S, Hurri H. A randomized trial of combined manipulation, stabilizing exercises, and physician

consultation compared to physician consultation alone for chronic low back pain. *Spine* 2003; 28(19):2185-2191.

(291) Whitehurst DG, Lewis M, Yao GL, Bryan S, Raftery JP, Mullis R et al. A brief pain management program compared with physical therapy for low back pain: results from an economic analysis alongside a randomized clinical trial. *Arthritis Rheum* 2007; 57(3):466-473.

(292) Hay EM, Mullis R, Lewis M, Vohora K, Main CJ, Watson P et al. Comparison of physical treatments versus a brief pain-management programme for back pain in primary care: a randomised clinical trial in physiotherapy practice. *Lancet* 2005; 365(9476):2024-2030.

(293) Critchley DJ, Ratcliffe J, Noonan S, Jones RH, Hurley MV. Effectiveness and cost-effectiveness of three types of physiotherapy used to reduce chronic low back pain disability: a pragmatic randomized trial with economic evaluation. *Spine (Phila Pa 1976)* 2007; 32(14):1474-1481.

(294) Rivero-Arias O, Gray A, Frost H, Lamb SE, Stewart-Brown S. Cost-utility analysis of physiotherapy treatment compared with physiotherapy advice in low back pain. *Spine (Phila Pa 1976)* 2006; 31(12):1381-1387.

(295) Frost H, Lamb SE, Doll HA, Carver PT, Stewart-Brown S. Randomised controlled trial of physiotherapy compared with advice for low back pain. *BMJ (Clinical research ed)* 2004; 329(7468):708.

(296) Haas M, Sharma R, Stano M. Cost-effectiveness of medical and chiropractic care for acute and chronic low back pain. *J Manipulative Physiol Ther* 2005; 28(8):555-563.

(297) Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; 337(sep29_1):a1655.

(298) Pran Manga and Associates. The Effectiveness and Cost Effectiveness of Chiropractic Management of Low-Back Pain (The Manga Report). 1993. Ottawa, Canada, University of Ottawa.

(299) Hasselberg PD. Chiropractic in New Zealand: Report of the Commission of Inquiry. 1979. Wellington, New Zealand, Government Printer.

(300) Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol Assess* 1999; 3(2):1-134.

(301) O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. *Statistical Methods in Medical Research* 2002; 11(6):455-468.