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REVIEW

Aris Seferiadis
Mark Rosenfeld
Ronny Gunnarsson

A review of treatment interventions in whiplash-associated disorders

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A. Seferiadis (✉)
Psychiatric Physiotherapy Unit,
Björkängen, Southern Elfsborg Hospital,
Klinikvägen 40, 501 82 Borås, Sweden
e-mail: aris.seferiadis@vgregion.se

M. Rosenfeld
Institute of Occupational Therapy
and Physiotherapy,
Faculty of Health and Caring Sciences,
The Sahlgrenska Academy
at Göteborg University, Göteborg, Sweden

A. Seferiadis
Department of Primary Health Care,
The Sahlgrenska Academy
at Göteborg University, Göteborg, Sweden

R. Gunnarsson
Research and Development Unit
in Primary Health Care,
Southern Elfsborg County, Sweden

Abstract In recent years, there has been much debate on the treatment of whiplash-associated disorders (WAD). It is not clear if the treatments commonly employed are effective, and concerns have been raised on the available scientific evidence of many of these treatments. The aim of this study was to review the literature systematically to analyze the evidence basis of many commonly used treatments for patients suffering from WAD, both in the acute and the chronic state. A computer-assisted search of the databases Medline (from 1962 to May 2003), CINAHL (1960–2003), Embase (1976–2003), and Psychinfo (1960–2003) was conducted as well as a check of the reference lists of relevant studies. All randomized controlled trials (RCTs) were retrieved and systematically analyzed with three common instruments of measurement of methodological quality. A qualitative analysis ("best-evidence synthesis") was performed. The methodological quality of 26 RCTs was analyzed. The median quality scores for all three instruments were poor. Based on the degrees of evidence and the practical obstacles, the following treatments can be recommended: Early physical activity in acute WAD, radiofrequency neurotomy, combination of cognitive behavioral therapy with physical therapy interventions, and coordination exercise therapy in chronic WAD. High-quality RCTs are not common in the field of WAD. More research is needed, particularly on the treatment of chronic WAD.

Keywords Whiplash · Treatment · Review

Introduction

From 1989 to 1994, whiplash-associated disorders (WAD) went from the third most common road traffic injury in Sweden to the most common [17]. Incidence in Sweden has been found to be one per 1,000 inhabitants [4]. Moreover, rear-end collisions resulting in reported WAD seem to have a substantial impact on health complaints in Sweden, even long after collision [3, 8].

There has been much confusion with the term whiplash. It has been used to describe the injury mechanism, the injury itself, and symptoms following injury. The Quebec Task Force (QTF) redefined WAD in 1995. According to the QTF, whiplash is an acceleration-deceleration mechanism of energy transfer to the neck, which may result from rear-end or side-impact motor vehicle collisions but can also occur during diving or other mishaps. The impact may result in bony or soft-tissue injuries (whiplash injury), which in turn may lead to a variety of clinical manifestations (WAD) [47].

Neck pain, headache, and reduction of cervical mobility are cardinal symptoms in the acute phase. WAD can be classified by five grades of initial severity on the modified Quebec classification [15, 47] (Table 1). Exposure without initial symptoms is referred to as grade 0. Hartling et al. have shown that the higher the grade initially, the greater the risk for WAD at 6, 12, 18, and 24 months [15].

Table 1 The modified Quebec classification of whiplash-associated disorders

Grade	Clinical presentation
0	No complaint about the neck
	No physical sign(s)
I	Neck complaint of pain, stiffness or tenderness only
	No physical sign(s)
IIa	Neck complaint and musculoskeletal sign(s):
	These include point tenderness but normal cervical range of motion
IIb	Neck complaint and musculoskeletal sign(s):
	These include point tenderness and abnormal cervical range of motion
III	Neck complaint and neurological sign(s):
	These include decreased or absent deep tendon reflexes, weakness and sensory deficits
IV	Neck complaint and fracture or dislocation

Symptoms and disorders that can appear in all grades include deafness, dizziness, tinnitus, headache, memory loss, dysphagia, and temporomandibular joint pain

Symptoms cover a wide range, particularly in late whiplash syndrome defined as persisting symptoms or residual disability 6 months after the injury [47].

Although the whiplash mechanism potentially injures several structures, objective evidence of such injuries has been scarce. Recent studies have shown that 50% of patients with chronic WAD suffer from zygapophysial joint pain [27] and that the brachial plexus is often involved in the presence of arm symptoms [19, 48]. Instability of the alar ligaments has also been seen in patients with chronic WAD [55].

The lack of homogeneity among patients suffering from WAD has led to many treatment options. The Quebec Task Force [47] highlighted the lack of randomized controlled trials (RCTs) in the field.

The RCT is considered the most reliable method to assess the efficacy of treatments. Systematic review of RCTs offers a way to cope with the large number of articles published. An example of such a review in the field of WAD is the investigation of Peeters et al. [34] on the efficacy of conservative treatment.

Assessment of the quality of RCTs included in a review can give an estimate of the likelihood that results are valid [49]. Trial quality is difficult to define. It has been defined as "the confidence that the trial design, conduct and analysis has minimized or avoided biases in its treatment comparisons." This definition covers internal validity, although the concept of quality should also encompass criteria of external validity, statistical analysis and ethics [11, 29, 46].

Several scales and checklists have been created to assess RCT quality, albeit chiefly in a nonscientific manner [33]. The three most widely accepted criteria lists are: an instrument to measure the likelihood of bias in pain research reports (IMLB) by Jadad et al. [20], the Delphi List (DL) by Verhagen et al. [54], and the criteria list for methodological quality assessment also known as Maastricht-Amsterdam List (MAL) by the back review group of the Cochrane Collaboration [51].

The aim of this study was to review the literature systematically using these three instruments to perform a qualitative analysis of the evidence basis of many commonly used treatment options for patients suffering from acute and chronic WAD.

Table 2 Domains included in the three methodological quality lists. *IMLB* likelihood of bias in pain research reports, *DL* Delphi List, *MAL* Maastricht-Amsterdam List

Domains of possible interest		Methodological quality score		
		IMLB	DL	MAL
1	Study question			
2	Population		x	x
3	Sample size and power calculations a priori			
4	Treatment allocation	x	x	x
5	Study design			x
6	Ethics			
7	Intervention			x
8	Outcome measures		x	x
9	Follow-up/withdrawals	x		x
10	Blinding	x	x	x
11	Cointerventions			x
12	Side-effects			x
13	Compliance			x
14	Prognostic comparability			
15	Analysis		x	x
16	Conclusion			
17	Presentation			

Materials and methods

Literature search

The Medline database was searched for articles written 1962 through May 2003. The WebSPIRS 5.02 program was used to search the databases CINAHL (1960–2003), Embase (1976–2003), and Psychinfo (1960–2003). The reference lists of relevant RCTs and controlled clinical trials (CCTs) were checked to identify additional published research not found in the computerized, bibliographic databases. The search was conducted using the MESH term whiplash and the word whiplash in the abstract or title of the study. Titles and abstracts of identified, published articles were initially reviewed by one of the authors (AS). All intervention studies dealing with acute or chronic WAD were retrieved.

Selection for quality assessment

Studies were assessed if they met the following criteria: (1) The intended design was a prospective RCT; (2) the study population included patients with WAD; (3) the publication was in English.

Quality assessment of studies

The methodological quality of the studies was independently assessed by two reviewers (AS and MR). The assessment was not performed under masked conditions. All studies received a score for each of the criteria lists IMLB, DL, and MAL. In case of any disagreement between the two reviewers (AS and MR), a consensus method was used. If disagreement persisted, a third reviewer (RG) would make the final decision. A pilot assessment of one RCT (not included in the study) was conducted to familiarize the reviewers with the quality assessment lists. Prior to scoring, the reviewers discussed the available guidelines to ensure a common interpretation of the lists. After the individual assessment, the reviewers then agreed on a final score for each article.

The IMLB consists of three items directly related to the reduction of bias, treatment allocation, follow-up/withdrawals, and blinding (Tables 2 and 3). The items were presented as questions to elicit yes or no answers. One point was awarded for each affirmative answer. Additionally, one point was added or deducted if the methods used were appropriate or not. This gives a numerical sum score of 0–5.

The DL consists of nine items concerning study population, treatment allocation, outcome measures, blinding, and analysis (Tables 2 and 3). All items have a yes/no/don't know option. If bias was unlikely, the item was rated with one point. If information

Table 3 Items included in the three methodological quality lists and the frequency of answers. *IMLB* likelihood of bias in pain research reports, *DL* Delphi List, *MAL* Maastricht-Amsterdam List

Domain[a]	Items	Methodological quality score		
		IMLB	DL[d]	MAL[d]
2	Were the eligibility criteria specified?		20/6/0	8/17/1
4	Was the study described as randomized[b]	25/1		
4	Was a method of randomization performed?		25/1/0	10/2/14
4	Was the method of randomization described and appropriate?[c]	8/17/1		
4	Was the treatment allocation concealed?		4/5/17	4/5/17
5	Were outcome measures relevant?			25/1/0
5	Was the timing of the outcome assessment in both groups comparable?			24/1/1
7	Were the experimental and control interventions explicitly described?			25/1/0
8	Were the groups similar at baseline regarding the most important prognostic indicators?		17/3/6	5/4/17
8	Were point estimates and measures of variability presented for the primary outcome measures?		20/6/0	20/6/0
8	Was the sample size of each group described?			20/5/1
9	Was there a description of withdrawals and/ dropouts?[b]	16/10		
9	Was the withdrawal / drop-out rate described and acceptable?			16/9/1
9	Was a short-term follow-up measurement performed?			22/4/0
9	Was a long-term follow-up measurement performed?			15/11/0
10	Was the care provider blinded to the intervention?		7/18/1	7/18/1
10	Was the patient blinded to the intervention?		8/18/0	8/18/0
10	Was the outcome assessor blinded to the intervention?		16/2/8	16/2/8
10	Was the study described as double blind?[b]	8/18		
10	Was the method of blinding described and appropriate?[c]	6/19/1		
11	Were co-interventions avoided or comparable?			15/8/3
12	Were adverse effects described?			8/18/0
13	Was the compliance acceptable in all groups?			10/0/16
15	Did the analysis include an intention-to-treat analysis?		13/7/6	13/8/5

[a] Domains described in Table 2
[b] Number of Yes (1)/No (0) answers
[c] Number of Appropriate (1)/Nothing (0)/Inappropriate (–1) answers
[d] Number of Yes (1)/No (0)/ Don't know (0) answers

was unavailable or insufficient or if bias was likely, the item was rated with zero points for an overall numerical sum score of 0–9.

The MAL consists of 19 items related to population, treatment allocation, study design, intervention, outcome measures, follow-up/withdrawals, blinding, cointerventions, side-effects, compliance, and analysis (Tables 2 and 3). It includes items similar to the IMLB and DL and unique items. The response options are similar to DL, and the overall numerical score is 0–19.

Detailed instructions on using these assessment scales have been published previously [20, 34, 54]. Differences exist in the assessment guidelines between the DL and MAL in three items. Thus, in these items, the same item on the two lists can have different scores:

– "Were the eligibility criteria specified?" DL requires inclusion and exclusion criteria while MAL only requires that the radiation pattern of back pain and duration of the disorder be described to score a "Yes"
– "Was a method of randomization performed?" DL requires that words such as random and randomization are used. MAL also requires that the randomization procedure is appropriate. This means that articles receiving a "Yes" on DL could score "Don't know" on MAL when a description of the randomization procedure was lacking.
– "Were the groups similar at baseline regarding the most important prognostic indicators?" DL requires the reviewer to determine this item, while MAL specifically requests adequate descriptions of age, duration of complaints, percentage of patients with radiating pain, and main outcome measures to evaluate similarity. Also this item could elicit differing scores, though it exists on both lists.

Best-evidence synthesis

A qualitative analysis ("best-evidence synthesis") was conducted using a rating system utilized by the Cochrane Collaboration Back Group [52]. It consists of the following degrees of evidence:

1. Strong evidence: generally consistent findings in multiple high quality RCTs
2. Moderate evidence: generally consistent findings in multiple low quality RCTs and/or one high quality RCT

3a. Limited evidence: only one low quality RCT
3b. Conflicting evidence: inconsistent findings in multiple RCTs
4. No evidence: no RCTs and no double-blind trials.

A study was arbitrarily judged to be of high quality if the sum score in all three scales (IMLB, DL, and MAL) was at least 50% of the total score.

Statistical methods

The outcome of quality assessment and best-evidence synthesis is presented. Kappa is calculated to estimate interobserver reliability of quality assessment.

Table 4 Scores received on the instrument for measurement of likelihood of bias (IMLB) stratified after type of study

IMLB[b] scoring	Type of study[a]				
	Chiropractic intervention	Drug therapy	Orthopedic surgery	Physical therapy	Multimodal intervention[c]
0–25%	0/2	0/1	0/0	3/2	0/1
26–50%	0/0	0/1	0/0	5/1	0/1
51–75%	0/0	0/1	0/0	2/0	0/0
76–100%	0/0	1/1	0/3	1/0	0/0
Total	0/2	1/4	0/3	11/3	0/2

[a] In each column studies focusing on acute/chronic whiplash-associated disorders (WAD)
[b] Instrument for measuring the likelihood of bias
[c] Combination of physical therapy and psychological support

Table 5 Scores received on the Delphi List (DL) stratified after type of study

DL[b] scoring	Type of study[a]				
	Chiropractic intervention	Drug therapy	Orthopedic surgery	Physical therapy	Multimodal intervention[c]
0–25%	0/0	0/0	0/0	1/0	0/1
26–50%	0/1	0/1	0/0	3/2	0/0
51–75%	0/1	0/2	0/1	5/1	0/1
76–100%	0/0	1/1	0/2	2/0	0/0
Total	0/2	1/4	0/3	11/3	0/2

[a] In each column studies focusing on acute/chronic whiplash-associated disorders (WAD)
[b] Delphi List
[c] Combination of physical therapy and psychological support

Table 6 Scores received on the Maastricht-Amsterdam List (MAL) stratified after type of study

MAL[b] scoring	Type of study[a]				
	Chiropractic intervention	Drug therapy	Orthopedic surgery	Physical therapy	Multimodal intervention[b]
0–25%	0/0	0/0	0/0	0/0	0/0
26–50%	0/1	0/1	0/0	6/3	0/2
51–75%	0/1	0/3	0/1	4/0	0/0
76–100%	0/0	1/0	0/2	1/0	0/0
Total	0/2	1/4	0/3	11/3	0/2

[a] In each column studies focusing on acute/chronic whiplash-associated disorders (WAD)
[b] Combination of physical therapy and psychological support

Results

In the literature search, 1,726 studies were found. 56 were intervention studies and 33 were CCTs. Seven CCTs did not use randomization, while 26 studies were RCTs that subsequently were quality assessed. The interobserver reliability in quality assessment between the two independent reviewers was very good (κ=1) for IMLB and good for DL (κ=0.76) and MAL (κ=0.74). There was no need for the third reviewer to arbitrate. Median scores (interquartile range) were for IMLB 2 (1–3), for DL 5 (4–6), and for MAL 9.5 (8–12). Studies evaluating orthopedic surgery were often scored higher than studies investigating effects of chiropractic, drug therapy, physical therapy, or multimodal interventions (Tables 4, 5, and 6). The three most prevalent shortcomings were lack of information on patient and/or care provider blinding, lack of information on concealment of treatment allocation, and lack of description of adverse effects (Table 3).

Evaluated therapeutic interventions and their degree of evidence according to the Cochrane Collaboration Back Group system [52] are presented in Table 7. An overview of all references is presented in Table 8.

Discussion

The main finding of this review was the large number of physical therapy articles on the subject. Apparently, this profession is often called upon to treat patients with WAD. The interventions for acute WAD that have the strongest scientific support are: early physical activity [5, 6, 14, 31, 32, 35, 39, 40, 45] (degree 2), electromagnetic-field therapy [13, 50] (degree 2), and high-dose methyl-

Table 7 Treatment interventions and the degrees of evidence in their support. *WAD* whiplash-associated disorders

Degree of evidence[a]	Claim	References[b]
1	Radiofrequency neurotomy reduces pain and psychological distress in patients with chronic WAD and zygapophysial joint pain	**Lord 1996** [27], **Wallis 1997** [55]
2	Melatonin therapy advances melatonin onset and sleep-wake rhythm in patients with chronic WAD and delayed melatonin onset	**van Wieringen 2001** [52]
2	High-dose methylprednisolone therapy administered within 8 h of injury reduces sick leave	**Pettersson 1998** [36]
2	Intra-articular corticosteroid therapy lacks effect in patients with chronic WAD and zygapophysial joint pain	**Barnsley 1994** [1]
2	Electromagnetic Field therapy reduces pain and increases cervical range of motion in patients with acute WAD	**Foley-Nolan 1992** [13], Thuile 2002 [50][c]
2	Early physical activity reduces pain, increases cervical range of motion and reduces sick leave in patients with acute WAD	Bonk 2000 [5], Borchgrevink 1998 [6], Gennis 1996 [14}[d], McKinney 1989 [30], Mealy 1986 [32], Pennie 1990 [35], Söderlund 2000 [45], Rosenfeld 2000 [39][e], **Rosenfeld 2003** [40][e]
2	Cognitive behavioural therapy combined with Physical therapy reduce pain and sick leave in patients with chronic WAD	Johansson 1998 [21}, Provinciali 1996 [37], Söderlund 2001 [44]
2	Coordination exercise therapy reduces pain in patients with chronic WAD	Fitz-Ritson 1995 [12][f], Humphreys 2002 [18]
3a	Ultra-reiz current therapy combined with physical therapy reduces pain and cervical range of motion in patients with acute WAD	Hendriks 1996 [16]
3a	Spinal manipulation therapy reduces pain and increases cervical range of motion in patients with neck pain with radiation to the trapezius muscle[f]	Cassidy 1992 [10]
3a	Fluoxetine therapy provides similar pain reduction to that of Amitriptyline therapy in patients with chronic WAD	Schreiber 2001 [43]
3b	Subcutaneous sterile water injection therapy reduces pain and increases cervical range of motion in patients with chronic WAD	Byrn 1993 [9], Sand 1992[41][h]

[a] Rating system derived from the system utilized by the Cochrane Collaboration Back Group [52] (See "Methods"-section)
[b] Studies presented by first author in alphabetical order where appropriate. ***Bold*** references denote studies defined as high quality
[c] It was unclear if patients in this randomized controlled trial (RCT) suffered from acute or chronic whiplash-associated disorders (WAD)
[d] The results of this RCT conflict with the claim
[e] The two articles by Rosenfeld are based on the same data and should therefore be regarded as one RCT
[f] The groups in this RCT were different at baseline
[g] The claim refers to effects immediate following treatment. Long-term effects have not been studied
[h] This RCT conflicts with the claim, and the study population is heterogeneous

Table 8 Overview of all evaluated randomized controlled trials (RCTs). *T* Timing when intervention is initiated, *IMLB* instrument for measuring the likelihood of bias, *DL* Delphi List, *MAL* Maastricht-Amsterdam List.

Articles sorted after first author	T	Scales		
		IMLB	DL	MAL
Barnsley et al. [1]	C	5	8	16
Double-blind comparison of intraarticular corticosteroid (Betamethasone) injection therapy with local anesthetic (bupivacaine) injection therapy. Neither treatment provided lasting pain-relief. The median time for return to 50% preinjection level of pain was 3 days in the betamethasone group and 3.5 days in the bupivacaine group				
Bonk et al. [5]	A	2	3	8
Comparison of active therapy (3 weeks of active and passive mobilization, postural exercises and advice) with collar therapy (3 weeks wearing collar). Patients receiving active therapy were significantly improved in pain intensity and cervical range of motion and comparable to a control group of unexposed individuals at 6 weeks. At 12 weeks, the collar-therapy group did not differ from the control group of unexposed individuals either. Outcome assessors were not blinded				
Borchgrevink et al. [6]	A	2	6	11
Single-blind comparison. All patients received instructions for self-training of the neck beginning on the first day of treatment and a 5-day prescription of NSAIDs before being randomized to "act-as-usual" group (advice to act as usual, no sick-leave, no collar) or immobilized group (14 days sick-leave, soft neck collar). Patients in the "act-as-usual" group had greater improvements in subjective symptoms, including pain localization, pain during daily activities, neck stiffness, memory and concentration, and pain and headache intensity				
Byrn et al. [9]	C	1	5	11
Double-blind comparison of subcutaneous sterile water injection therapy with saline injection therapy. Patients receiving active treatment improved in minimum and maximum pain intensity, neck mobility, and self-assessment of improvement. Therapist blinding failed because sterile water injection therapy was painful to the patient. The eligibility criteria for inclusion were not specified				
Cassidy et al. [10]	C	1	5	13
Single-blind comparison of manipulation with mobilization of the neck. Patients receiving manipulation had greater improvements in pain intensity and cervical range of motion. Evaluation was conducted immediately posttreatment without long-term follow-up				
Fitz-Ritson [12]	C	1	3	9
Comparison of chiropractic therapy plus either standard exercise program or "phasic" exercise program. Patients doing "phasic" exercises improved in measures of Neck Disability Index. The groups were dissimilar in age, gender distribution, and previous injuries. Blinding of the outcome assessor inadequate				
Foley-Nolan et al. [13]	A	4	7	15
Placebo-controlled double-blind trial of high-frequency pulsed electromagnetic therapy. Patients receiving active treatment improved in measures of pain intensity at 2 and 4 weeks but not at 12. Cervical range of motion was initially worse in the active treatment group but became significantly better than that of the placebo treatment group at 12 weeks. Patients in the active treatment group used significantly less analgesics at 2, 4, and 12 weeks				
Gennis et al. [14]	A	1	3	6
Trial of the effect of soft cervical collars. Patients were assigned to either soft cervical collar or no collar groups. Both groups were advised to rest. The groups showed no difference in pain scores at 6 months. The randomization procedure was flawed, and blinding of the outcome assessor unknown				
Hendriks et al. [16]	A	1	4	8
Comparison of ice treatment, neck exercises, and advice on neck care, posture and use of collar with/without ultrareiz current therapy. Patients receiving ultrareiz current therapy significantly improved in pain intensity and cervical range of motion at 6 weeks. Blinding of outcome assessor unknown				
Humphreys et al. [18]	C	1	4	8
Trial of the effect of coordination exercises. Four groups: chronic neck pain or asymptomatic individuals assigned to coordination exercises or nonexercise group. Individuals with chronic neck pain assigned to coordination exercise group experienced reduction in pain intensity. Both coordination exercise groups exhibited an increase in head-repositioning accuracy. Blinding of outcome assessor unknown				
Johansson et al. [21]	C	2	2	8
Trial of the effect of a 4-week cognitive behavioral pain management program. Patients were randomized to treatment group or waiting list control group. Patients participating in the program had decreased catastrophizing and pain behaviors and greater activity level in the spare time post-treatment. At the 1-month follow-up, they still had greater activity level in the spare time and were more often in occupational training. Not reported whether the outcome assessors were blinded and whether the groups were similar at baseline				

Table 8 (continued)

Articles sorted after first author	T	Scales		
		IMLB	DL	MAL
Lord et al. [28]	C	5	8	17
Placebo-controlled double-blind trial of percutaneous radiofrequency neurotomy. Patients receiving active treatment improved in measures of McGill Neck Pain Questionnaire and pain intensity				
McKinney et al. [30]	A	3	5	10
Single-blind comparison of outpatient physiotherapy (treatment could include heat, cold, short-wave diathermy, hydrotherapy, traction, McKenzie assessment and treatment, Maitland mobilization, postural correction and home exercises) with standard therapy (rest and analgesia, general advice on mobilization after 10–14 days), and home mobilization (instructions on postural correction, use of analgesia and collar, use of heat sources and muscle relaxation, mobilizing exercises). Both patients receiving outpatient physiotherapy and patients receiving home mobilization improved in cervical range of motion and pain intensity more than patients with standard therapy. There was no difference in effectiveness between outpatient physiotherapy and home mobilization				
Mealy et al. [32]	A	2	5	8
Single-blind comparison of standard treatment (rest, initial immobilization with soft cervical collar for 2 weeks, gradual mobilization) with early active mobilization (ice in the first 24 h, Maitland mobilization, daily neck exercises every hour). Patients in the early active mobilization group had greater improvements in pain intensity and cervical range of motion at 8 weeks				
Pennie et al. [35]	A	1	1	6
Comparison of standard treatment (2 weeks of rest in soft collar, then exercise therapy) with active treatment (traction, advice on neck care and sleeping posture, neck and shoulder exercises). No differences were found between the two treatments at 6–8 weeks or 5 months in pain intensity, neck mobility, or time off work. The randomization procedure was flawed and blinding of the outcome assessor unknown				
Pettersson et al. [36]	A	4	8	16
Placebo-controlled double-blind trial of high-dose methylprednisolone therapy administered within 8 h of injury. Patients receiving active treatment exhibited reduction in sick leave at the 6-month follow-up				
Provinciali et al. [37]	C	1	5	8
Single-blind comparison of multimodal treatment (postural training, manual technique, psychological support) with control treatment (physical agents only, such as electrical or sonic modalities). Patients receiving multimodal treatment had greater improvement in pain levels, return to work delay, and self-rating scores of treatment efficacy. Neck mobility increased equally in both groups				
Rosenfeld et al. [39]	A	2	5	8
Single-blind comparison of standard intervention (initial rest, recommended use of soft collar, gradual mobilization) with active intervention (frequent active cervical rotation, McKenzie assessment and treatment) either within 96 h or after 14 days. Patients receiving active intervention had a greater reduction in pain intensity at the 6-month follow-up. There were no differences in cervical range of motion. Active intervention gave better results when administered within 96 h. Standard intervention gave better results when administered after 14 days				
Rosenfeld et al. [40]	A	3	7	12
Single-blind comparison of standard intervention (initial rest, recommended use of soft collar, gradual mobilization) with active intervention (frequent active cervical rotation, McKenzie assessment, and treatment) either within 96 h or after 14 days. Pain intensity, cervical range of motion, and sick leave were significantly lower for patients receiving active intervention at the 6-month and 3-year follow-up. Cervical range of motion at the 3-year follow-up was similar to that of a control group of unexposed individuals if active intervention was received within 96 h				
Sand et al. [41]	C	2	3	8
Double-blind comparison of subcutaneous sterile water injection therapy with saline injection therapy in patients with cervicogenic headache. No benefit was observed for either treatment on either pain or neck mobility. Not all patients in the sample suffered from whiplash-associated disorders				
Schreiber et al. [43]	C	3	5	11
Single-blind comparison of fluoxetine therapy with amitriptyline therapy. Both groups decreased in pain intensity. The between-group differences were not significant. Not all patients in the sample suffered from whiplash-associated disorders. No long-term follow-up				
Söderlund et al. [45]	A	2	5	11
Single-blind comparison of coordination exercise therapy. Patients were randomized to regular treatment (advice on posture and being active, neck and shoulder exercises) or additional treatment group (as previous plus a coordination exercise). Patients in the additional treatment group had not improved more than patients with regular treatment at 6 months				

Table 8 (continued)

Articles sorted after first author	T	Scales		
		IMLB	DL	MAL
Söderlund et al. [44]	C	2	5	9
Single-blind comparison of individualized physiotherapy management (treatment could include stabilization exercises, coordination exercises, muscle stretching, body posture training, strengthening exercises, relaxation training, TENS, acupuncture, heat) with individualized physiotherapy management integrating cognitive behavioral components (learning, application and generalization of basic skills in everyday activities). Basic skills could include muscle stabilization techniques, relaxation training, reeducation of humeroscapular rhythm, and exercises aimed to increase neck range of motion, coordination, and endurance of neck muscles. Patients whose physiotherapy included cognitive behavioral components reported less pain and better performance of daily activities at 3 months				
Thuile et al. [50]	C?	1	4	7
Comparison of low-energy, low-frequency magnetic-field treatment. Patients received standard treatment (diclofenac and tizanidine therapy) with or without magnetic field treatment. Patients receiving magnetic-field treatment improved in pain intensity and neck mobility. Blinding of outcome assessor unknown. Uncertain whether the patients suffered from acute or chronic whiplash-associated disorder (WAD)				
Van Wieringen et al. [53]	C	5	8	14
Placebo-controlled double-blind trial of melatonin treatment. Patients with delayed melatonin onset receiving active treatment exhibited advances in melatonin onset and sleep-wake rhythm. Other sleep parameters, pain, quality of life, cognitive processing speed, and vigilance were not influenced by 1 month of treatment				
Wallis et al. [56]	C	4	6	12
Double-blind placebo-controlled trial of percutaneous radiofrequency neurotomy. Patients receiving active treatment improved in measures of pain intensity and exhibited resolution of their preoperative psychological distress. No report on whether the groups were similar at baseline				

A = Acute (whiplash-associated disorder persisting <3 months)

C = Chronic (whiplash-associated disorders persisting ≥3 months)

prednisolone therapy [36] (degree 2). Interventions for chronic WAD with the strongest scientific support are: radiofrequency neurotomy [28, 56] (degree 1), combined cognitive behavioral therapy with physical therapy interventions [21, 37, 44] (degree 2), melatonin therapy [53] (degree 2), and coordination exercise therapy [12, 18] (degree 2).

Methodological aspects

The inherent risk of bias must be considered in this review. The selection process was limited to articles published in the English language. Therefore, it is possible that relevant articles published in other languages have been missed. Trials with positive outcomes are more likely to be published; however, it was noted that articles both in favor and in disfavor of interventions were identified.

It is the purpose of systematic reviews to pool, if possible, the results of trials. This can provide valuable information on size of treatment effect and clinical relevance. Nevertheless, intervention trials on WAD display heterogeneity of patient populations. This is, in part, due to differences in the definition of WAD, making pooling of results, in practice, impossible.

Scientific shortcomings with some types of interventions

The lists commonly used for measuring methodological quality of RCTs have been developed for drug therapy rather than health sciences. This could lead to bias towards interventions of health sciences. In this review, physical therapy RCTs achieved consistently lower methodological scores compared to drug therapy and orthopedic surgery RCTs (Tables 4, 5, and 6). Interventions used by several health professions often cannot be administered in a double-blind fashion. Therefore, they can never achieve full score.

Acute and chronic WAD

Patients suffering from acute WAD differ from those suffering from chronic WAD. It is currently not possible to identify the injured structures in the acute stage. The available data [6, 23, 25, 45] lead to the suggestion that the combination of the injury with psychological factors such as coping style [7] and explanatory style [24] may lead to chronic WAD. With this in mind and the evidence available, this review recommends that patients suffering from acute WAD be prescribed advice to “act as usual” and early, controlled, physical activity to tolerance level.

Treatment of acute WAD

Early physical activity reduces pain, increases cervical range of motion, and reduces sick leave in patients with acute WAD. This is supported by one high-quality study [40] and several low-quality studies [5, 6, 30, 32, 35, 39, 45].

One high-quality RCT suggests that high-dose methylprednisolone therapy within 8 h of injury should be prescribed [36]. In the authors' view, however, the practical difficulties of this treatment (8-h limitation, 23-h infusion, need for hospitalization, cost) only warrant its use on patients that run higher risk of developing chronic WAD. Findings associated with increased risk are neurological signs, initially reduced cervical range of motion [15], and brachial plexus tension signs [19].

The use of magnetic fields is not recommended by this review on the basis that the equipment used in the high-quality RCT by Foley-Nolan [13] was collar-mounted, thus conflicting with the advice on early activity, and negative effects of collars. It is possible that magnetic-field therapy administered by other equipment is equally efficient, but the authors did not locate any RCTs on the subject.

Treatment of chronic WAD

Knowledge of the origin of symptoms in the late stage is increasing. Thus, treatment interventions can be directed or developed in a purposeful manner. The identification of cervical zygapophysial joints as the symptom-giving structure in approximately 50% of patients suffering from chronic WAD [2, 27] is an example. Interventions were evaluated on this condition, and intraarticular corticosteroid injection therapy was discarded [1] in favor of radiofrequency neurotomy. This review recommends that patients suffering from chronic WAD be examined for cervical zygapophysial joint pain. In cases of such findings, radiofrequency neurotomy could be considered on the basis of two high-quality RCTs [28, 56]. However, the technique is difficult, even for experienced personnel [26].

The prescription of combined, cognitive, behavioral therapy and physical therapy interventions in chronic WAD could be recommended on the basis of three low-quality RCTs [21, 37, 44]. These interventions have respectively strong and moderate evidence of significant reductions in neck pain and sick leave.

Abnormalities in sleep quality have been reported in patients suffering from chronic WAD [42]. Melatonin therapy could be considered to improve melatonin onset and sleep/wake rhythm in patients exhibiting delayed melatonin onset and chronic WAD. This recommendation is based on one high-quality RCT [53], although 1 month of treatment did not influence other sleep parameters, pain, quality of life, cognitive processing speed, or vigilance.

This review also cautiously recommends including coordination exercises in physical therapy interventions on the basis of two low-quality RCTs. There is moderate evidence that coordination exercises significantly reduce neck pain in patients suffering from chronic WAD.

Need for future research

Since the consequences of WAD may be great for the patient and the economical costs for society large, WAD prevention should be exhaustively researched. Moreover, refinement of the acute care of WAD is needed to reduce the amount of patients developing chronic symptoms. Future RCTs should focus on evaluating treatment interventions that lack evidence such as surgical stabilization and discectomy.

Since positive brachial plexus tension signs indicate poor prognosis [19, 22, 38, 48], the evaluation of interventions on adverse peripheral nerve tension is urgent. This dysfunction may explain the continuing suffering of patients with chronic WAD that do not suffer from zygapophysial joint pain.

Conclusions

Based on the degrees of evidence and the practical obstacles, the following treatments can be recommended: Early physical activity in acute WAD, radiofrequency neurotomy, combination of cognitive behavioral therapy with physical therapy interventions, and coordination exercise therapy in chronic WAD. High-quality RCTs are not common in the field of WAD. More research is needed, particularly on the treatment of chronic WAD.

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