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ABSTRACT

Background: To compare 4 different treatment strategies in patients with late whiplash syndrome.

Methods: Patients were randomly assigned to one of the following treatment groups: infiltration, physiotherapy, or medication. Group allocation was stratified according to gender, age, and education. Additionally, patients of each group were randomized 1:1 to cognitive-behavioral therapy (CBT) or no CBT. Patients were assessed at baseline, after an 8-week treatment period, and 3 and 6 months later. Main outcome measures were subjective outcome rating, pain intensity, and working ability.

Results: Of 91 enrolled patients, 73 completed the study; 62% were women. After treatment, 47 patients (64%) were subjectively improved (48%), or free of symptoms (16%), with a preponderance of women (73% vs 50%, $p = 0.047$). There was no difference regarding outcomes among the 3 treatment groups in men and women. The most robust difference was achieved with CBT, associated with a higher rate of recovery (23% vs 9%), and improvement (53% vs 42%) ($p = 0.024$), and with a gender difference ($p = 0.01$). All treatments significantly improved pain intensity and working ability.

Conclusion: Intensive therapy in late whiplash syndrome can achieve improvement of different outcome measures including working ability in two-thirds of patients, more effective in women, persisting beyond 6 months in half. Additional cognitive-behavioral therapy was the most effective treatment modality.

Classification of evidence: This interventional study provides Class III evidence that CBT used as an adjunct to infiltration, medication, or physiotherapy increases improvement rates in persons with late whiplash syndrome. *Neurology*® 2010;74:1223–1230

GLOSSARY

CBT = cognitive-behavioral therapy; **SUVA** = Swiss Accident Insurance Fund; **VAS** = visual analogue scale.

The worldwide annual incidence of symptomatic whiplash injuries varies between 16 and 200/100,000.[1-3] According to the literature, 18%–40% of patients with symptoms assigned to a whiplash injury complain of persistent symptoms for more than 6 months, called chronic or late whiplash syndrome,[4-7] but without a uniform definition. Pain is usually considered the dominant symptom and the duration of persisting symptoms between 3 and 12 months is accepted.[8,9]

There is a disconcerting paucity of randomized controlled or comparative studies that analyze different therapeutic measures in late whiplash. Introducing therapeutic measures which lack scientific support from controlled studies may lead to iatrogenic symptom persistence and further increases treatment costs.[10] Most studies have been conducted with small, usually very selective, sample groups.[11] Phasic exercises improved chronic neck pain after motor vehicle accidents.[12] Subcutaneous sterile water injection above tender neck points showed improved neck mobility and neck pain scores compared to saline water injections in short-term follow-up,[13] whereas intra-articular steroids had no effect in the relief of zygapophyseal neck pain.[14] With radiofrequency neurotomy, significant pain relief persisting for up to 9 months in 80% has been shown in the select subgroup of neck pain sufferers from proven zygapophyseal joint

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pain by repeated cervical medial branch blocks.[15] Therefore, there is no consensus on the optimal management of late whiplash patients and no sound recommendations can be provided to the practitioner.[6]

The present study was designed to compare treatment modalities which are widely used for patients with late whiplash syndrome.

METHODS

Patient recruitment. The principal sources for identifying patients were the Swiss Accident Insurance Fund (SUVA) and the Swiss Insurance Association registers. All patients with a whiplash injury grade I or II (Quebec Task Force Classification) and persistent symptoms for 6 months or longer were candidates for inclusion in the study. Patients were referred to a coordinator who checked for inclusion and exclusion criteria. They were then contacted by the study coordinator. Patients who agreed to participate were randomized to one of the 3 treatment groups and dates for initial assessment, cervical spine X-ray, MRI, and the first treatment session were arranged.

Each patient gave informed consent for participation and agreed to perform only the study treatment for 8 weeks.

Assuming an effect size of 0.6 regarding pain intensity reduction as a main outcome measure with a power of 0.8, α error 0.05, and using a 1-tailed test, the calculated sample size was 72 patients. Assuming a dropout of 20%, we planned to enroll between 90 and 100 patients.

Inclusion criteria. Whiplash injury as defined in previous research[1,16] is considered to be a musculoligamentous strain or sprain of the cervical spine, without fractures or dislocations, due to a hyperextension/hyperflexion injury, without any head trauma, loss of consciousness, or posttraumatic amnesia. The included patients had a whiplash injury grade I or II (Quebec Task Force Classification),[1] and had persistent neck pain or headache 6 to 12 months after the accident.

Exclusion criteria. Patients with injuries to other areas of the body during the accident causing the whiplash were excluded, in order to avoid overlapping of illness behavior due to causes other than whiplash. Patients with actual head injury, previous brain injury, previous neurologic deficits, previous whiplash injury, preexisting neck pain, or previous neck surgery were excluded.

Standard protocol approvals, registrations, and patient consents. The presented study was approved by the local ethical committee.

All patients included in the study gave written informed consent.

Randomization. Patients were first randomized to 1 of 3 treatment groups: local anesthetic infiltration, physiotherapy, or medication, and stratified according to gender, age, and education (restricted randomization). Thereafter, patients of each treatment group were randomly allocated to cognitive-behavioral therapy (CBT) or no CBT with an allocation ratio of 1:1 (figure).

Assessments. Initial assessment included the following:

1. Detailed analysis of the initial trauma, based on patients' reports, documentation from The Fund's records (SUVA), and interviews with involved physicians
2. Assessment of previous treatments
3. A complete neurologic and physical examination (at baseline and after the study treatment period)
4. Cervical spine MRI
5. Evaluation of psychosocial factors such as marital status, employment status, and pending litigation
6. Evaluation of the level of function, using the German version of the Health Assessment Questionnaire,[17] Well-Being Scale,[18] and cognitive ability (Cognitive Failures Questionnaire)[19]
7. Standardized pain assessment questionnaire concerning headache and neck pain: McGill Pain Questionnaire; visual analogue scale (VAS), where 0 = no pain and 10 = worst pain imaginable[20]

Initial assessment and follow-up after 8 weeks treatment period including neurologic and physical examination were performed by a physician not involved in treatment or treatment allocation or any further assessments. Questionnaires for the subjective ratings (see above) were delivered and explained by another, independent physician, not involved in the treatment.

Radiologic investigations. Cervical spine MRI was performed in every patient except 4 who had contraindications (pacemaker, claustrophobia, metallic elements in the brain or eye). MRI were rated by an independent radiologist according to a defined evaluation form for disc herniation, degenerative changes (disc degeneration, uncarthrosis, spondylosis), and fractures, which were an exclusion criterion. The findings were combined to a semiquantitative degeneration sum score (0 to 4).

Treatment. ***Procedure.*** After initial assessment and randomization, every patient was exclusively treated with the allocated modality for 8 weeks by the same physician or physiotherapist, with or without additional CBT. Each therapeutic intervention was performed twice a week.

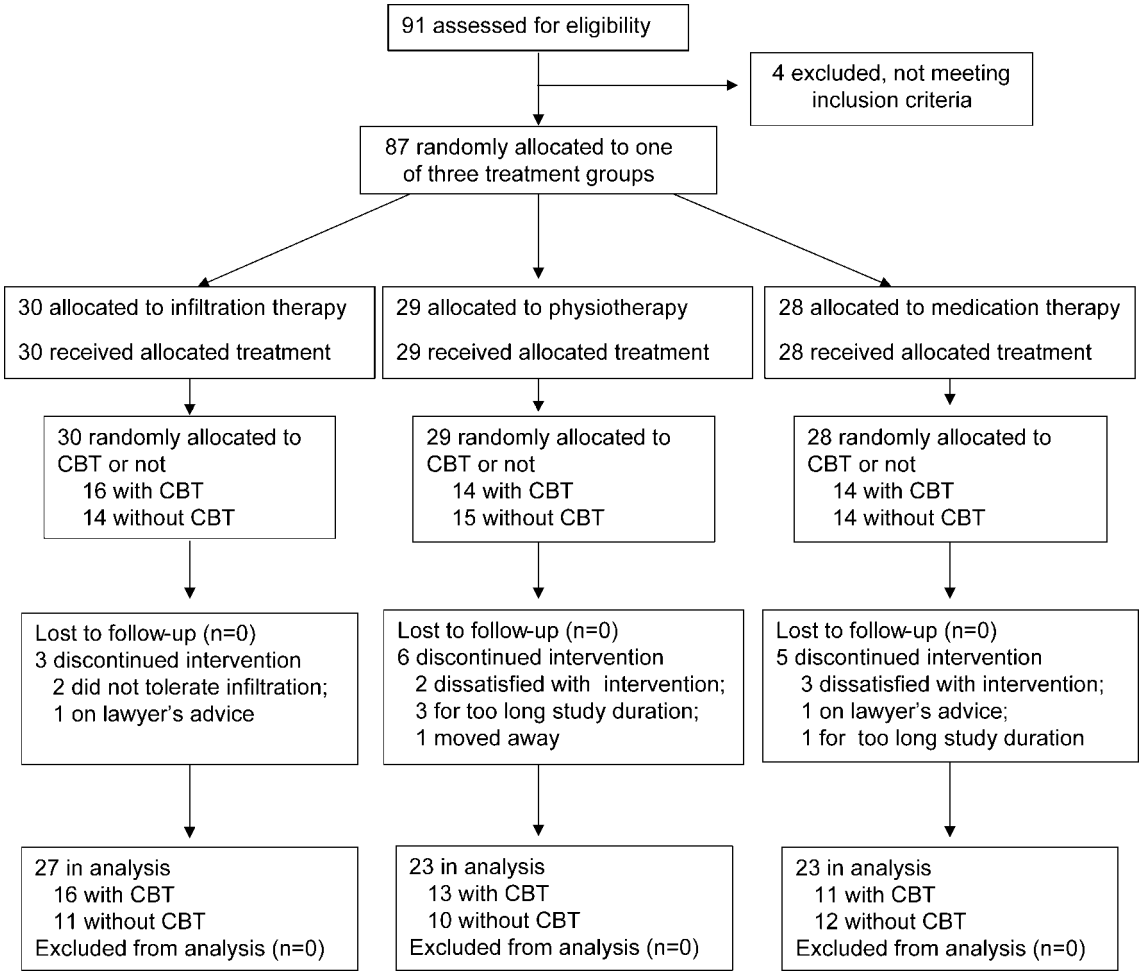
Infiltration. Sixteen experimental sessions for each patient were planned. Patients were examined for the presence of tender points in the neck. Tender points were defined as areas where pain could be evoked by palpation or movement. Each point was infiltrated with an IM injection of bupivacaine 0.25% (Carbostesin®, Astra-Zeneca AG, Zug, Switzerland). A 21-G sharp, beveled needle was inserted 1–3 cm into the point, depth depending on the thickness of the subcutaneous tissue. The volume injected was 1–4 mL, according to the dimension of the tender point. The maximum total volume injected at each session was 30 mL. If no painful or tender point was found at any of the 16 sessions, no infiltration was performed.

Physiotherapy. Patients were seen by their physiotherapist twice a week. They received massage, learned relaxation techniques of myogelotic muscles, and were instructed in a detailed program of isometric and low intensity active isotonic training of their neck muscles, which they had to regularly practice at home daily and to record.

Medication. Patients in this group received 200 mg flurbiprophen (Froben®, Abbott, Baar, Switzerland) in its slow release preparation once a day. To maintain a similar relationship with the therapy group, patients were seen twice a week by the same study physician during the 8 weeks.

Cognitive-behavioral therapy. In all patients, CBT was always performed by the same (male) psychologist twice weekly for 8 weeks (16 sessions). Each single session lasted 60 minutes. During the sessions, the therapist followed a therapy manual, and each patient received a step-by-step manual that covered the material presented in sessions and the home exercises. CBT focused on those pain aspects that may be behavioral in nature

Figure Study flow diagram



CBT = cognitive-behavioral therapy.

(e.g., what we think, feel, and do). It was designed to teach control of pain by controlling the physical reactions to stress and pain through relaxation, stress reduction, and chronic pain management techniques. Specific skills taught during the sessions were imagery, cognitive therapy for stressful situations, progressive muscle relaxation training, and application of guided mastery for stress/pain management.[21]

Follow-up. Evaluations were performed immediately after the 8-week study treatment period (T2), then, at 3 (T3) and 6 months (T4) later. Primary outcome measures were subjective outcome rating (free of symptoms, improved, unchanged, worse), pain rating (McGill pain questionnaire, VAS), and working capacity (as a %, determined by the family physician). Secondary outcome measures were 1) activities of daily living (HAQ); 2) Well-Being Scale (Zerssen); and 3) cognitive ability (Cognitive Failures Questionnaire).

Outcome measures were evaluated at T2, T3, and T4 for influence of gender, employment status, marital status, fault (liability), lawyer involvement, and degenerative spine changes on MRI.

Statistical analysis. Statistical analysis was performed using SPSS 12.0. Categorical data were analyzed using the χ^2 test if dichotomous, or Mann-Whitney test if ranked. Ordinal data were analyzed using analysis of variance.

Primary research questions were to compare 3 in real world practice used treatments and to evaluate efficacy of additional CBT.

RESULTS Ninety-one patients were enrolled over a 3-year period and 18 dropped out during follow-up. The reasons were as follows: 2 patients did not tolerate the infiltration therapy, 4 patients were excluded because they did not fulfill all inclusion criteria, 4 patients resigned because the study took too long, 1 patient unexpectedly moved away, 5 patients were dissatisfied with their randomization to the treatment group, and 2 patients stopped participating on their lawyer's advice.

Of the remaining 73 patients, 45 (62%) were women and 28 (38%) were men. All had previously used intermittent NSAIDs and received passive physical therapy; none had infiltrations, active physiotherapy, or CBT. Twenty-seven (37%) patients were randomized to infiltration therapy, 23

Table 1 Baseline (T1) patient data

		Treatment groups					
Basic patient data	All	Infiltration	Medication	Physiotherapy	No CBT	With CBT	*p* Value
No. (%)	73 (100)	27 (37)	23 (31.5)	23 (31.5)	33 (45)	40 (55)	
Age, y, median (range)	34 (18-64)						
Age, y, mean (SD)	40.5 (12.11)	38.3 (11.12)	43.1 (13.08)	40.3 (12.26)	39.1 (12.35)	41.6 (11.95)	NS
Sex, % women	62	67	61	57	67	58	NS
Age, y, mean (SD) women	36.5 (11.8)						
Age, y, mean (SD) men	46.7 (9.8)						
Interval to therapy, mo (median)	10	9	9	10	9	10	NS
Employment status, % employed	86	96	78	83	85	88	NS
Other influencing factors							
Marital status, n (%)	73 (100)	27 (100)	23 (100)	23 (100)	33 (100)	40 (100)	NS
Unmarried	23 (32)	8 (30)	8 (35)	7 (30)	12 (36)	11 (28)	NS
Married	35 (48)	16 (59)	10 (44)	9 (39)	14 (43)	21 (52)	NS
Divorced	12 (16)	3 (11)	4 (17)	5 (22)	5 (15)	7 (18)	NS
Widow	3 (4)	0 (0)	1 (4)	2 (9)	2 (6)	1 (2)	NS
Own fault (%)	6 (8)	2 (7)	1 (4)	3 (13)	3 (9)	3 (8)	NS
Lawyer, involved (%)	20 (27)	9 (33)	7 (30)	4 (17)	6 (18)	14 (35)	NS
Magnetic resonance degenerative findings, mean sumscore (SD)	1.04 (1.242)	0.88 (1.107)	1.27 (1.42)	1.0 (1.225)	0.79 (1.023)	1.28 (1.386)	NS

Abbreviations: CBT = cognitive-behavioral therapy; McGill = McGill pain questionnaire; VAS = Visual Analog Scale.

(31.5%) to physiotherapy, and 23 (31.5%) to medication. There were more women who were younger than men equally distributed among the treatment groups. Half of each treatment group, a total of 40 patients (55%), had in addition CBT (table 1: Baseline Patient Data). There was no difference between the treatment groups regarding the duration of symptoms after injury. Pain as the main symptom was located in the neck (88%), head (77%), shoulder (41%), back (22%), or elsewhere (49%).

Efficacy of therapy and course. ***Primary outcome measures.*** *Subjective outcome rating.* After the 8-week treatment period (T2), of the 73 patients, 47 (64%) were subjectively improved (48%) or free of symptoms (16%), with a preponderance of women (73% vs 50%, $p = 0.047$) (table 2). There was a high correlation of improvement in subjective outcome rating (unchanged, improved, resolved) with reduction of the pain scales ($p = 0.000$). The change in the mean VAS (100-point scale) was 33 points improvement between unchanged and improved and 24 points improvement between improved and resolved.

There was no difference among the 3 different treatment modalities, or between men and women. The most robust difference was achieved with the addition of CBT, which was associated with a higher rate of recovery (free of symptoms) (23% vs 9%) or improvement (53% vs 42%) ($p = 0.024$), compared with no CBT. CBT provided an absolute risk reduction of 23% with a number needed to treat of 4.3 and a 95% confidence interval of 2 to 56. There was a gender difference ($p = 0.01$) for CBT, which was effective only in women ($p = 0.004$ for women, $p = 0.69$ for men). In women, medication without CBT was the least (n = 8, 0%) and infiltration with CBT the most effective treatment combination (n = 11, 45%) regarding rate of symptoms resolution. Among men there was no single combined treatment that was most beneficial.

Six months later (T4), 41 patients (56% of 73) still felt improved (43%) or had recovered (13%). The differences for CBT or the favorable combination treatment were no longer significant, not even in women (table 3).

Among the 26 (36%) patients without any treatment efficacy after 2 months, 4 improved during the following 6 months without further treatment: 3 women in the medication and 1 man in the infiltration group. None of them had had CBT.

A gender-dependent efficacy was detected in several ways: depending on gender but not on treatment modality, 33 women (73%) and only 14 men (50%) improved with treatment (T2) ($p = 0.047$). The

Table 2 Treatment efficacy (primary and secondary outcome measures), short term (T2)

	T1 (baseline)					T2 (after 2 months treatment)				
Subjective outcome rating, n (%)	Infiltration	Medication	Physiotherapy	No CBT	With CBT	Infiltration	Medication	Physiotherapy	No CBT	With CBT
Total (n)						27	23	23	33	40
Worse						0	0	0	0	0
Unchanged						10 (37)	9 (39)	7 (30)	16 (49)	10 (25)
Improved						9 (33)	12 (52)	14 (61)	14 (42)	21 (53)[a]
Resolved						8 (30)	2 (9)	2 (9)	3 (9)	9 (22)[a]
Ability to work, mean (SD)	61 (39)	64 (40)	65 (37)	63 (44)	64 (34)	71 (40)	68 (37)	71 (35)	67 (43)	72 (32)
Self rating, mean (SD)										
VAS	55 (20)	55 (22)	54 (21)	51 (22)	57 (19)	34 (28)	38 (25)	36 (21)	41 (26)	32 (24)
McGill total	12.4 (3.6)	11.2 (4.2)	11.5 (3.5)	11.9 (4.0)	11.6 (3.5)	8.9 (5.6)	9.4 (4.7)	9.1 (5.3)	9.6 (4.8)	8.7 (5.5)
HAQ	6.2 (4.8)	5.6 (4.5)	5.6 (4.5)	5.9 (4.1)	5.8 (4.9)	4.7 (4.7)	6.1 (6.6)	4.5 (3.8)	5.1 (4.0)	5.1 (6.0)
CFQ	38.7 (13.7)	35.7 (15.0)	34.0 (17.1)	36.2 (16.8)	36.3 (13.9)	37.3 (14.6)	32.6 (14.1)	33.4 (16.9)	36.1 (16.3)	33.3 (14.2)
Well-Being Scale (Zerssen)	25.4 (14.3)	21.6 (11.4)	14.9 (12.5)	22.8 (13.5)	19.3 (13.4)	20.4 (13.8)	20.5 (13.5)	17.5 (13.6)	23.1 (14.7)	16.5 (11.8)

Abbreviations: CBT = cognitive-behavioral therapy; CFQ = Cognitive Failure Questionnaire; HAQ = Health Assessment Questionnaire; McGill = McGill pain questionnaire; VAS = Visual Analog Scale.

Table 3 Treatment efficacy (primary and secondary outcome measures), long term (T4)

	T1 (baseline)					T4				
Subjective rating, n (%)	Infiltration	Medication	Physiotherapy	No CBT	With CBT	Infiltration	Medication	Physiotherapy	No CBT	With CBT
Total						27	23	23	33	40
Worse						2 (7)	1 (4)	0	2 (6)	1 (2)
Unchanged						12 (45)	8 (35)	9 (39)	14 (42)	15 (38)
Improved						7 (26)	12 (52)	12 (52)	14 (42)	17 (43)
Resolved						6 (22)	2 (9)	2 (9)	3 (10)	7 (17)
Ability to work, mean (SD)	61 (39)	64 (40)	65 (37)	63 (44)	64 (34)	76 (35)	76 (35)	80 (35)	76 (39)	77 (32)
VAS	55 (20.5)	55 (21.9)	52 (20.4)	51 (22.3)	57 (18.9)	38 (27)	38 (24)	42 (27)	40 (24)	39 (27)
McGill total	12.4 (3.6)	11.2 (4.2)	11.5 (3.5)	11.9 (4.0)	11.6 (3.5)	10.2 (4.6)	10.4 (4.9)	10.1 (5.2)	10.0 (4.6)	10.4 (5.1)
HAQ	6.2 (4.8)	5.6 (4.5)	5.6 (4.5)	5.9 (4.1)	5.8 (4.9)	6.3 (6.9)	5.8 (6.0)	6.1 (6.3)	5.7 (4.4)	6.4 (7.6)
CFQ	38.7 (13.7)	35.7 (15.0)	34.0 (17.1)	36.2 (16.8)	36.3 (13.9)	38.9 (17.9)	35.6 (18.8)	37.8 (18.8)	37.0 (17.1)	37.5 (16.5)
Well-Being Scale (Zerssen)	25.4 (14.3)	21.6 (11.4)	14.9 (12.5)	22.8 (13.5)	19.3 (13.4)	24.5 (15.5)	16.0 (10.8)	19.7 (15.5)	19.4 (14.3)	21.0 (14.6)

Abbreviations: CBT = cognitive-behavioral therapy; CFQ = Cognitive Failure Questionnaire; HAQ = Health Assessment Questionnaire; McGill = McGill pain questionnaire; VAS = Visual Analog Scale.

gender-dependent difference persisted over the following 6 months without therapy (T4); however, it was no longer significant. There was no influence on treatment efficacy related to degenerative changes in cervical spine MRI (degeneration sum score), level of education, employment status, marital status, liability, or involvement of a lawyer.

Pain ratings. Pain intensity after 2 months of treatment was improved with all treatments (VAS: $p = 0.01$, $p = 0.003$, and $p = 0.000$, and McGill total: $p = 0.004$, $p = 0.122$, and $p = 0.014$ for infiltration, medication, and physiotherapy). There were no significant differences among the 3 treatment modalities at any timepoint. There was neither a difference between patients with and without CBT or between the treatment groups.

VAS was higher in unemployed ($p = 0.019$) and divorced ($p = 0.045$) patients at T4, whereas at T2 and T3 there was no difference vs baseline.

MRI degeneration sumscore of the cervical spine, gender, and liability had no influence on pain ratings during the study.

Employment. Working ability improved overall ($p = 0.023$) in the infiltration ($p = 0.016$) and physiotherapy ($p = 0.035$) groups but not in the medication group. CBT had a favorable influence overall ($p = 0.003$). Ability to work was lower at T2 ($p = 0.02$) if a lawyer was involved.

Secondary outcome measures. Comparing results of the Well-Being Scale, only a short-term effect was found, with a difference between patients with and without CBT at T2 ($p = 0.036$) but no longer at T4.

Activities of daily living using HAQ showed worse results in men, at T2 ($p = 0.044$), and in unemployed patients at T4 ($p = 0.035$).

There were no differences in the Cognitive Failures Questionnaire and the Health Assessment Questionnaire between the different treatment groups, with or without CBT, at any time.

DISCUSSION This prospective, nonblinded, non-industry-sponsored study used randomized treatment allocation for evaluating different treatment strategies in patients with late whiplash syndrome. Intensive therapy led to improvement in two-thirds, and the effect of treatment persisted more than 6 months in half the patients.

There was no significant difference in the efficacy of the 3 treatment modalities used, which all showed a highly significant improvement of pain after 2 months. However, infiltration had a higher rate of recovery. During the 6 months follow-up, 6 patients showed symptom recurrence, most of them from the infiltration group, which therefore seems to have mainly a short-term efficacy. There was a high correlation between improvement of pain intensity scales and improvement of subjective outcome rating. The 30% improvement in the pain intensity numerical rating scale corresponding to a 1-point improvement in a 3-point subjective rating scale is in excellent agreement with the results of a previous study.[22]

Additional CBT had a significant effect on outcome independent of the concomitant therapies at least in the short term, but only in women. In parallel to symptom alleviation, there was also a significant improvement of overall working ability and again, especially in the CBT-treated patients. Looking for an optimal combined treatment regimen, in women, the highest rate of symptoms resolution was obtained with infiltration combined with CBT. In men, there was no recognizable optimal combination. Overall, there was a striking gender difference, with women not only prevailing in the whole study group (62%) but also showing a higher rate of improvement overall (73% vs 50%) and especially in response to the addition of CBT. In most studies, women prevail among whiplash sufferers, with a preponderance of 2:1 or more,[1,23] but not necessarily in those with late whiplash syndrome. The reasons for this observation are multiple, with women having different anatomic preconditions (less protective muscle mass, narrower spinal canal, increased segmental spinal mobility)[24] and probably being more pain prone.[25] Indeed, gender differences in perceiving and experiencing pain are well-acknowledged, for which the complex interrelationship between different genetic and psychosocial factors seems to be responsible.[26] This fact can also be taken as an argument against degenerative changes playing a relevant role, since women in our study were younger than men and degenerative cervical spine changes on MRI had neither influence on outcome in general nor on the course of pain scales. However, this might be an age-dependent phenomenon since in male patients, who were older and generally showed poorer treatment response than women, scores of well-being and daily activities were generally worse and tended to correlate with degenerative spine changes. One has to be extremely cautious in the interpretation of associations between some subscores and some subgroups due to small sample sizes. However, the role of an involved lawyer, which is difficult to assess in its real dimension, was interesting: it had a negative influence on working ability and on affective and evaluative McGill subscores. The role of lawyers in this study is certainly underestimated, as we became aware that several patients did not participate in the study on their lawyer's advice.[27] Further social factors, as expected, also played a role in this study, such as higher pain scales in unemployed and divorced patients. We cannot exclude

that all treatment modalities mainly had their effect (beneficial or not) under the "social" aspect of caregiving: 1) the weakest effect of CBT was found in the physiotherapy group, which had the highest response rate among the 3 treatments (apart from CBT); 2) the treatment effect of CBT did not persist in either subgroup. The positive results immediately after therapy, which did not persist beyond the end of therapy, may be interpreted as a result of a caregiver effect. Interestingly, results indicate that only women respond better to CBT, which could lead back to the fact that the treating psychologist was a man.

This study has several limitations regarding patient selection as well as generalization of the results. It was a small sample study. We recognize several reasons for this poor recruitment performance: first, the randomization process was the most difficult feature for patients to agree to, and the most frequent reason to decline participation. Dissatisfaction with the allocated treatment group was also the main reason for dropouts. Secondly, the intensity of the treatment during the 2-month period caused absence from employment. Furthermore, patient evaluation during follow-up was not strictly blinded even though the evaluating physician was not involved in the treatment. However, this should not influence the main outcome measures based on self-assessment.

The results of this study favor a multidisciplinary approach in the treatment of patients with late whiplash, with special emphasis on psychological support and guidance, which is a well-recognized important strategy.[28,29]

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Pietro Ballinari.

DISCLOSURE

Dr. Pato, Dr. Di Stefano, Dr. Fravi, and Dr. Arnold report no disclosures. Dr. Curatolo serves as an Associate Editor of *Anesthesia & Analgesia*; estimates that 30% of his clinical effort in the University Hospital where he practices is spent performing local anesthetic injections; and receives research support from Mundipharma Laboratories GmbH, the Swiss National Science Foundation (SNF), European Federation of IASP Chapters, and Foundation for Research in Anesthesia and Intensive Care, Berne, Switzerland. Dr. Radanov receives research support from the SNF. Dr. Sturzenegger reports no disclosures.

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