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Subgroups based on thermal and pressure pain thresholds in women with chronic whiplash display differences in clinical presentation – an explorative study

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Purpose: To investigate the presence of subgroups in chronic whiplash-associated disorders (WAD) based on pain thresholds for pressure (PPT), cold (CPT), and heat (HPT) and to compare these subgroups with respect to symptomatology, disability, and health aspects.

Methods: Two groups of female subjects – patients with chronic WAD (n = 28) and healthy controls (CON; n = 29) – were investigated. Quantitative sensory testing (QST) for thermal thresholds and algometry for PPT at four sites in the body (over the trapezius and tibialis anterior bilaterally) were determined. Habitual pain intensities, psychological strain, disability, and health aspects were registered using a questionnaire.

Results: A cluster analysis based on PPT, CPT, and HPT identified two subgroups of chronic WAD: one sensitive subgroup (s-WAD; n = 21), and one less sensitive subgroup (ls-WAD; n = 6). S-WAD displayed widespread hyperalgesia, whereas ls-WAD had localized hyperalgesia in the neck area, with tendencies to supernormal values in remote areas of the body. Generally, s-WAD had a significantly worse situation than the CON with respect to symptomatology, disability, and health aspects. The ls-WAD group was intermediary between s-WAD and CON in these aspects.

Conclusion: Different explanations, eg, severity of the pain condition per se, etiological factors, and pre-trauma differences in pain sensitivity, may exist for the differences in pain thresholds between the two subgroups. Future research should investigate the role of pain thresholds in the chronic stage to determine the efficacy of treatment interventions.

Keywords: cold pain threshold, pain, pressure pain threshold, heat pain threshold, subgroup, whiplash, WAD

Introduction

In many Western countries, whiplash-associated disorders (WAD) with chronic pain, most commonly occurring after motor vehicle accidents, are a major problem; the average incidence varies between 0.8 and 4.2 per 1000 inhabitants.[1] The Quebec Task Force categorizes WAD into five grades of severity.[2] Although many recover completely after whiplash trauma, a substantial number of people have problems with persistent and eventually chronic pain symptoms. As many as 40%–50% of persons in traffic accidents with acute whiplash trauma develop and maintain pain symptoms 1 year after the trauma.[3,4] Studies of chronic WAD patients have reported increased disability, decreased participation, and decreased quality of life.[5–8] In addition, heterogeneities have been noted with chronic WAD with respect to psychological aspects,[8–10] coping

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strategies,[11,12] and pain intensity.[7] In the literature, there are several indications that subgroups also exist with respect to pain sensitivity in different chronic pain disorders, including chronic WAD.[13–16]

Psychophysical methods (ie, somatosensory testing for different modalities such as thermal [hot and cold] and pressure pain sensitivity and thresholds) have been used to investigate the clinical picture of chronic pain. Quantitative sensory testing (QST), an umbrella term for sensitive tools that investigate pain thresholds of mainly cutaneous thermal modalities, has been used to investigate pain sensitivity in different chronic pain conditions, including chronic WAD.[17–20] QST is often combined with algometry, which measures pressure pain threshold (PPT). PPT reflects the sensitivity of several tissues, including muscles.

Widespread cold and pressure pain hyperalgesia are present in chronic WAD at the group level; for a brief review, see Wallin et al.[21] In chronic WAD, heat pain hyperalgesia is generally found in the primary pain area,[22–24] but it is unclear whether hyperalgesia of heat is widespread.[21,22,25] In a recent study, we reported significant interrelationships in chronic WAD among pain-sensitivity measures, pain intensities, and psychological aspects.[21] Scrutinizing the data of that study, we noted that the within-group variations of PPT, cold pain threshold (CPT), and heat pain threshold (HPT) were relatively large, possibly indicating heterogeneity, ie, the presence of subgroups. If subgroups are present, the question arises whether these subgroups are associated with differences in pain intensity, psychological strain, disability, and health aspects. Due to the relatively small number of subjects in relation to the statistical requirements of the clustering technique, our study has to be considered explorative.

Our explorative study had two main aims: (1) to investigate the presence of subgroups in chronic WAD based on pressure and thermal pain thresholds and (2) to relate these subgroups to pain and psychological symptomatology and consequences such as aspects of participation, health-related, and generic quality of life.

Methods and participants

Participants

The two groups of subjects have been described in detail in our recent study,[21] so here we provide only a brief summary. All female patients at the Pain and Rehabilitation Centre at the University Hospital, Linköping, Sweden with the diagnosis of whiplash injury or status postwhiplash injury (ICD S13.4, T91.8), treated and discharged between 2007 and 2008, had their medical records scrutinized. The inclusion criteria for the subjects were women who were 20–55 years of age with chronic WAD (>3 months) grade II and III according to the Quebec classification, acquired through motor vehicle accident. All participants had to be able to read and write Swedish. Since chronic WAD is more prevalent in women than men, only women were included in this study. In future studies, we will investigate men. Those patients who fit the inclusion criteria were mailed a questionnaire and letter inviting them to participate in the study. The women who indicated interest (n = 30) were then contacted by telephone; two were excluded after the phone interview, as they did not fulfill the inclusion criteria. In total, 28 women with chronic pain after whiplash injury were included (mean age 40.1 years [standard deviation ± 7.1 years]; range 20–55 years); all with grade II, according to the Quebec classification. Exclusion criteria were diagnosed psychiatric illness, hypertension, inflammatory pain states, widespread pain (including fibromyalgia), cognitive malfunction, not being able to abstain from analgesics 1 day before examination, and a body mass index higher than 35. Thirteen patients were employed, four patients were on sick leave, three were students, and eight were unemployed.

Through local advertising, 29 healthy pain-free women (mean age 35.4 years [standard deviation ± 10.6 years], ranging from 21 to 54 years of age) were recruited as the control (CON) group. Inclusion criteria for the CON group were self-reported good health, no ongoing pain, and no evidence of the exclusion criteria set for the subject group. Twenty-three of the controls were employed, five were students, and one was unemployed.

This study was approved by the Regional Ethics Committee (Dnr M-113-08). All procedures followed the Helsinki protocol. All participants gave written consent and were informed that they could withdraw from participating at any time. All participants received €100 for participating.

Methods

Procedure

The procedure has previously been described in detail.[21] The subjects answered a questionnaire and were then examined with respect to PPT, CPT, HPT, and perception thresholds for cold and warmth. The perception thresholds have been reported in our previous study[21] and were not used in the present study.

Questionnaire

The participants answered a postal questionnaire. There is an increasing awareness that different psychological

aspects interact with the perception and consequences of pain. Hence, several facets of anxiety, for example, were investigated in order to achieve a comprehensive picture. The questionnaire contained the following variables and instruments.

Background data

Age and pain duration were registered.

Pain intensity

Pain intensity was registered using a visual analog scale. The participants marked a 100 mm horizontal line between end points 0 (no pain) and 100 (worst imaginable pain). Pain-intensity measurements were obtained concerning background pain, ie, habitual pain immediately before the experiment.

Sleep quality

Visual analog-scale ratings were obtained concerning sleep quality the night before testing with the end points 0 (worst-possible sleep quality) and 100 (best-possible sleep quality) or complete satisfaction with the quality of sleep.[26]

Pain catastrophizing scale

The pain catastrophizing scale (PCS) measures three dimensions of catastrophizing: rumination, magnification, and helplessness.[27,28] For the total PCS, 52 was the maximum score. For the subscale rumination, 16 was the total maximum score; corresponding values for magnification and helplessness were 12 and 24, respectively. For all subscales as well as the total score, a high score represents the worse outcome.

Hospital anxiety and depression scale

The hospital anxiety and depression scale (HADS) is a short self-assessment questionnaire that measures anxiety and depression.[29–31] HADS comprises seven items in each of the depression and anxiety scales (HADS-A – anxiety and HADS-D – depression). Possible subscale scores range from 0 to 21, with the lower score indicating the least depression and anxiety possible.

Pain anxiety symptoms scale

The short version of the pain anxiety symptoms scale (PASS) was used.[32] The PASS-20 comprises 20 items of four five-item subscales. The total score is between 0 and 100, with the highest score indicating the highest anxiety possible. Subscales can also be obtained, but were not used in this study.

Anxiety sensitivity index

The anxiety sensitivity index (ASI) is a self-report questionnaire containing 16 items concerning the amount of fear experienced regarding bodily complaints or sensations that are commonly seen in combination with anxiety.[33–35] The total score varies between 0 and 64, with the highest score indicating the highest level of anxiety possible.

Fear-avoidance beliefs questionnaire

The fear-avoidance beliefs questionnaire (FABQ) is based on theories of fear and avoidance behavior.[36–38] Items of FABQ focus specifically on patients' beliefs about how physical activity and work affected their chronic pain. A total maximum score of 70 is possible. It is also possible to obtain two subscales, but these were not used in the present study.

The pain self-efficacy questionnaire

The pain self-efficacy questionnaire (PSEQ)[39,40] is based on Bandura's concept of self-efficacy, which emphasizes persisting in the face of obstacles and aversive experiences.[41,42] The PSEQ measures both the strength and generality of a patient's beliefs about his/her ability to accomplish a range of activities despite his/her pain. Scores on the PSEQ may range from 0 to 60, with higher scores indicating stronger self-efficacy beliefs.

General self-efficacy scale

The general self-efficacy scale contains ten items that measure outcomes of efficacy perceptions.[43] Total scores range between 10 and 40, with a higher value representing a better outcome.[44]

Pain disability index

The pain disability index (PDI) is a seven-item self-report instrument based on a 10-point scale that assesses perception of the specific impact of pain on disability that may preclude normal or desired performance of a wide range of functions, such as family and social activities, sex, work, life support (sleeping, breathing, and eating), and daily living activities. The PDI has shown good reliability and validity in several studies.[37,45]

Quality-of-life scale

The quality-of-life scale, Swedish version (QOLS-S) is composed of 16 items that together describe the quality-of-life concept: (1) material comforts; (2) health; (3) relationships with parents, siblings, and other relatives; (4) having and rearing children; (5) close relationships with spouse or significant

others; (6) close friends; (7) helping and encouraging others, participating in organizations, and volunteering; (8) participating in political organizations or public affairs; (9) learning; (10) understanding yourself; (11) work; (12) expressing yourself creatively; (13) socializing; (14) reading, listening to music, or watching entertainment; (15) participating in active recreation; and (16) independence, being able to do things for yourself.[46,47] A seven-point satisfaction scale is used. Subjects estimated their satisfaction with their current situation. A higher total score reflects higher satisfaction. The item scores are added to a total score, ranging from 16 to 112.[46,47]

SF36 health survey (Swedish version)

The SF36 health survey intends to represent multidimensional health concepts and measurements of the full range of health states, including levels of well-being and personal evaluations of health. The instrument has eight dimensions (reported using a standardized scale from 0 to 100): physical functioning (SF36-PF), role limitations due to physical functioning (SF36-RP), bodily pain (SF36-BP), general health (SF36-GH), vitality (SF36-VT), social functioning (SF36-SF), role limitations due to emotional problems (SF36-RE), and mental health (SF36-MH).[48]

QST and algometry

Pain thresholds

The experimental variables in this study comprised PPT, CPT, and HPT. All measurements were performed by one of the authors (MW). The order of testing was as follows: PPT, CPT, and HPT.

Pressure pain thresholds

A handheld electronic pressure algometer (Somedic, Hörby, Sweden) was used to assess PPT. The pressure was applied at a rate of 30 kPa/second using a 1 cm-diameter probe. All participants were instructed to press a button when they felt the first sensation of pain, not merely pressure. The maximum pressure was set at 600 kPa, at which point the application of pressure ceased. PPT of eight test sites was measured during the first session. The selected test sites were located at three points along the upper part of the trapezius muscle bilaterally and at one point over the belly of the tibialis anterior muscle bilaterally. The three points over the trapezius were marked on a line stretching from C7 to the acromion; this line was then divided in half and PP1, PP2, and PP3 were marked from the neck outwards, with PP1 being the most medial point. Approximately 5 minutes passed between measuring each point to allow enough time for recovery. Each PPT variable was determined as the mean of three trials. For analyses, a mean of PP1-3 was calculated for the trapezius. For the present study, the mean of both sides of trapezius and tibialis anterior were calculated.

Thermal pain thresholds

Thermal sensory testing was performed using a modular sensory analyzer (Somedic, Hörby, Sweden); for a detailed description, see our previous work.[21] Thermal pain thresholds were measured on four sites: over the upper part of the trapezius muscle (bilaterally, approximately midway on a line between C7 and the acromion) and over the anterior tibialis muscle (bilaterally, approximately 7–10 cm below the patella). All tests were conducted according to a structured protocol and performed according to the Marstock method.[49] For the present study, the mean of both sides of trapezius and the tibialis anterior were calculated.

Statistics

Descriptive statistics were performed using SPSS Statistics version 20 (IBM, Armonk, NY). A cluster analysis (based on *k*-means algorithm) was used to identify subgroups of WAD patients. The cluster analysis was made using the PPT, CPT, and HPT variables of the trapezius (mean value of right- and left-hand sides) and the tibialis anterior (mean value of right- and left-hand sides) muscles; standardized variables were used. The Kruskal–Wallis test was performed to evaluate between group/subgroup differences and a post hoc test was used to evaluate possible significant differences between CON and the identified subgroups of WAD. According to earlier analysis,[21] one multivariate outlier was excluded from the WAD group (#14), and all analyses performed comprised 27 persons in the WAD group.

Due to the prerequisites of the *k*-mean cluster analysis with respect to the ratio between variables and subjects (>5–10) we have used a certain regression technique in order to confirm these statistical analyses. Also the risk for type I errors necessitates the use of multivariate techniques. Hence, orthogonal partial least squares or projection to latent structures (PLS)[50,51] was used for the multivariate regression analysis of group/subgroup membership (CON denoted 0 and subgroups of WAD denoted 1). The variables investigated in the present study, eg, different psychological variables, are intercorrelated (ie, presence of multicollinearity) and hence do not represent distinct aspects. In order to take advantage of the information of each variable, it is necessary to use multivariate techniques that handle such intercorrelations.

In fact, PLS can handle variable-to-subject ratios < 1 and takes advantage of highly intercorrelated regressors (x-variables). This analysis was done using, for instance, the psychological variables and pain-intensity variables as regressors. SIMCA-P (version 12; Umetrics AB) was used for the regression analyses. The PLS regressions aimed to confirm multivariately the group/subgroup differences. The variable influence on projection (VIP) indicates the relevance of each x-variable pooled over all dimensions and y-variables – the group of variables that best explain y. VIP ≥ 1.0 was considered significant. Coefficients (PLS scaled and centered regression coefficients) were used to note the direction of the relationship (positive or negative). R^2 describes the goodness of fit: the fraction of sum of squares of all the variables explained by a principal component.

Results

Identification and comparisons of subgroups based on pain thresholds

The cluster analysis of the WAD group, based on PPT, CPT, and HPT, identified two subgroups of WAD: one sensitive subgroup (s-WAD, n = 21) and one less sensitive subgroup (ls-WAD, n = 6) (Table 1). Significant differences were, as intended, found between the two subgroups for the PPT (except for PPT of trapezius), CPT, and HPT (Table 1). S-WAD was significantly more sensitive than CON according to PPT, CPT, and HPT. The less sensitive WAD subgroup (ls-WAD) presented values intermediary (nonsignificant differences versus CON except for PPT of trapezius) between s-WAD and CON (Table 1).

The sensitive subgroup (s-WAD) compared to CON with respect to symptoms and consequences

The s-WAD subgroup presented significantly higher pain intensities at different anatomical regions, spreading of pain (pain regions index [PRI]), and worse sleep quality. The s-WAD subgroup also reported significantly worse situations regarding psychological symptoms, ie, higher depression and anxiety measures, catastrophizing, fear avoidance, and self-efficacy than the CON group. Regarding the consequences of living with chronic pain, the s-WAD subgroup had significantly worse situations than the CON group with respect to disability (PDI), quality of life in general (QOLS), and health-related quality of life (SF36) (Table 1).

The reported differences were confirmed in a multivariate regression. In the significant ($R^2 = 0.83$) PLS regression (CON vs s-WAD) (the pain-intensity variables PRI_{10} and SF36-BP were excluded), the most important differences were for the following variables (in descending order of importance): SF36-RP (VIP = 1.29), SF36-VT (VIP = 1.27), PDI (VIP = 1.23), SF-36-SF (VIP = 1.21), SF36-PF (VIP = 1.21), FABQ (VIP = 1.20), SF36-GH (VIP = 1.15), PASS (VIP = 1.10), sleep quality (VIP = 1.07), and PCS total (VIP = 1.05).

The less sensitive subgroup (ls-WAD) compared to CON

The ls-WAD subgroup had higher pain intensities than the CON group, although they were not significant on all locations measured (Table 1). The ls-WAD subgroup also presented more spreading of pain (PRI_{10}). Concerning sleep and psychological variables, the ls-WAD subgroup showed worse situations than the CON group, although these differences were not significant except for pain anxiety (PASS), one subscale for catastrophizing, and fear avoidance (FABQ). The ls-WAD subgroup reported a significantly higher perceived disability (PDI) and worse situations for one of the subscales of SF-36 (SF36-RF) (Table 1).

In the multivariate context, differences existed between the ls-WAD subgroup and the CON (the pain-intensity variables PRI_{10} and SF36-BP excluded). Hence, the significant ($R^2 = 0.40$) PLS regression (CON vs ls-WAD) identified the most important differences for the following variables (in descending order of importance): SF36-PF (VIP = 1.73), FABQ (VIP = 1.59), PDI (VIP = 1.49), SF36-SF (VIP = 1.37), SF36-GH (VIP = 1.17), PASS (VIP = 1.12), and PCS-Magnification (VIP = 1.02).

Differences between the two subgroups of WAD

No significant differences were found between subgroups regarding pain variables, psychological variables, disability (PDI), and quality of life (Table 1). However, when scrutinizing Table 1, it is obvious that the mean values of ls-WAD indicate a more positive situation than the mean values for s-WAD. This observation was confirmed in a multivariate analysis.

The significant PLS analysis ($R^2 = 0.23$) showed that the following five variables were significant and most important (in descending order of importance): SF36-RP (VIP = 1.87), pain intensity – neck (VIP = 1.67), SF36-VT (VIP = 1.66), pain intensity – shoulders (VIP = 1.65), and SF36-BP (VIP = 1.52). Other variables relatively important (with VIP > 1) were habitual pain intensity, sleep quality,

Table 1 Mean values (±standard deviation) of the different psychological, participation, and quality-of-life instruments in the two subgroups of WAD (s-WAD, sensitive; ls-WAD, less sensitive) and CON (whole group)

Groups/ variables	CON (n = 29)	ls-WAD (n = 6)	s-WAD (n = 21)	Statistics	Post hoc test		
				Kruskal–Wallis	CON vs ls-WAD	CON vs s-WAD	ls-WAD vs s-WAD
Pain thresholds							
PPT – trapezius	328 ± 114	201 ± 86	126 ± 44	<0.001	S	S	NS
PPT – tibialis anterior	451 ± 129	492 ± 136	254 ± 98	<0.001	NS	S	S
CPT – trapezius	14.6 ± 5.3	14.5 ± 4.2	24.4 ± 5.1	<0.001	NS	S	S
CPT – tibialis anterior	13.4 ± 5.0	10.0 ± 0.0	20.2 ± 5.4	<0.001	NS	S	S
HPT – trapezius	45.7 ± 2.2	46.2 ± 1.1	41.7 ± 2.5	<0.001	NS	S	S
HPT – tibialis anterior	45.8 ± 2.3	46.5 ± 1.1	44.6 ± 2.3	NS			
Habitual pain intensity (100)	0.0 ± 0.0	20.4 ± 12.8	34.2 ± 10.5	<0.001	S	S	NS
PRI_{10} (9)	1.3 ± 1.7	6.0 ± 3.7	6.6 ± 2.3	<0.001	S	S	NS
Pain intensity – neck (100)	4.2 ± 8.5	42.7 ± 26.6	70.2 ± 21.7	<0.001	S	S	NS
Pain intensity – shoulders (100)	5.7 ± 11.2	38.2 ± 26.2	68.4 ± 25.2	<0.001	NS	S	NS
Pain intensity – arms (100)	1.8 ± 5.1	28.7 ± 26.4	37.3 ± 30.3	<0.001	S	S	NS
Pain intensity – hands (100)	0.4 ± 2.0	27.8 ± 27.6	37.7 ± 33.6	<0.001	S	S	NS
Pain intensity – upper back (100)	3.5 ± 8.2	38.2 ± 25.5	51.7 ± 27.8	<0.001	S	S	NS
Pain intensity – lower back (100)	8.3 ± 16.6	34.0 ± 30.8	54.7 ± 28.8	<0.001	NS	S	NS
Pain intensity – hips (100)	4.2 ± 10.7	35.0 ± 27.6	34.1 ± 34.6	<0.001	S	S	NS
Pain intensity – knees (100)	7.7 ± 19.9	26.8 ± 31.9	15.4 ± 25.4	NS			
Pain intensity – feet (100)	1.0 ± 3.6	31.7 ± 33.9	28.3 ± 34.6	<0.001	S	S	NS
Pain duration	NA	52.2 ± 53.6	76.8 ± 47.4	NA			NS
Sleep quality (100)	83.7 ± 16.1	66.8 ± 29.8	43.7 ± 26.2	<0.001	NS	S	NS
Psychological variables							
HADS-D (21)	1.7 ± 2.1	4.7 ± 6.5	5.5 ± 3.0	<0.001	NS	S	NS
HADS-A (21)	3.2 ± 3.0	4.3 ± 4.3	6.8 ± 4.1	0.008	NS	S	NS
ASI (64)	9.5 ± 8.7	11.8 ± 7.5	18.8 ± 10.8	0.002	NS	S	NS
PASS total (100)	16.9 ± 13.2	35.3 ± 12.1	46.3 ± 16.0	<0.001	S	S	NS
PCS total (52)	6.2 ± 6.1	13.2 ± 10.4	19.8 ± 8.8	<0.001	NS	S	NS
PCS-Rum (16)	4.6 ± 3.6	8.7 ± 4.5	10.8 ± 3.9	<0.001	NS	S	NS
PCS-Magn (12)	2.9 ± 2.9	6.5 ± 2.9	6.0 ± 2.7	0.001	S	S	NS
PCS-Helpl (24)	6.6 ± 5.6	12.2 ± 3.6	15.7 ± 5.5	<0.001	NS	S	NS
FABQ (70)	8.5 ± 11.7	38.2 ± 14.9	50.9 ± 23.0	<0.001	S	S	NS
PSEQ (60)	49.3 ± 10.5	36.0 ± 14.6	32.8 ± 12.6	<0.001	NS	S	NS
GSES (40)	35.3 ± 8.7	33.0 ± 6.8	29.5 ± 5.6	0.022	NS	S	NS
Participation and QOL							
PDI (70)	9.5 ± 5.0	27.3 ± 17.8	34.2 ± 13.2	<0.001	S	S	NS
QOL (100)	91.7 ± 9.9	84.7 ± 13.0	76.1 ± 18.3	0.006	NS	S	NS
SF36-PF (100)	97.1 ± 4.1	75.0 ± 17.3	64.0 ± 19.9	<0.001	S	S	NS
SF36-RP (100)	94.8 ± 19.3	66.7 ± 40.8	22.6 ± 29.5	<0.001	NS	S	NS
SF36-BP (100)	86.9 ± 21.4	54.5 ± 27.6	32.9 ± 18.1	<0.001	NS	S	NS
SF36-GH (100)	87.1 ± 12.3	64.7 ± 25.0	55.3 ± 16.4	<0.001	NS	S	NS
SF36-VT (100)	73.6 ± 12.2	55.8 ± 31.4	30.0 ± 18.8	<0.001	NS	S	NS
SF36-SF (100)	96.6 ± 8.8	75.0 ± 20.9	57.7 ± 21.5	<0.001	NS	S	NS
SF36-RE (100)	94.3 ± 12.8	77.8 ± 34.4	69.8 ± 36.4	0.017	NS	S	NS
SF36-MH (100)	84.4 ± 10.4	77.3 ± 18.7	67.6 ± 20.4	0.004	NS	S	NS

Notes: The two subgroups of WAD are based on a cluster analysis. The variables above the dotted line (ie, PPT, CPT, and HPT) were used to identify subgroups in the WAD group; the possible ranges concerning the thresholds are PPT 0–600 kPa, CPT 10°C–32°C, and HPT 32°C–50°C. For each instrument, the maximum value is given in brackets. For abbreviations, please see the Methods section. To the right is given the result of the statistical evaluation (Kruskal Wallis test) and post hoc tests if applicable.
Abbreviations: WAD, whiplash-associated disorder; CON, control; PPT, pressure pain threshold; CPT, cold pain threshold; HPT, heat pain threshold; PRI, pain regions index; HADS-D, hospital anxiety and depression scale-depression; HADS-A, hospital anxiety and depression scale-anxiety ASI, anxiety sensitivity index; PASS, pain anxiety symptoms scale; PCS, pain catastrophizing scale; Rum, rumination; Magn, magnification; Helpl, helplessness; FABQ, fear-avoidance beliefs questionnaire; PSEQ, pain self-efficacy questionnaire; GSES, general self-efficacy scale; PDI, pain disability index; QOL, quality of life; PF, physical functioning; RP, role – physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role – emotional; MH, mental health; S, significant; NS, nonsignificant; NA, not applicable.

SF36-SF, PCS total, PASS, pain intensity – low back, ASI, and PCS-helplessness. Hence, in the multivariate context, there were significant differences between the two subgroups of WAD.

Discussion

This explorative study produced three main findings:

- The identification of two subgroups of WAD based on PPT, CPT, and HPT: one sensitive subgroup (s-WAD, n = 21) and one less sensitive subgroup (ls-WAD, n = 6).
- Generally s-WAD had significantly worse situations than CON with respect to symptomatology, disability, and health aspects.
- In the multivariate context, the ls-WAD group was intermediary between s-WAD and CON in these aspects.

Identification of subgroups based on pain thresholds

Some authors on a general level state that chronic WAD is a hypersensitivity (central sensitization) pain condition.[52,53] The WAD classification according to the Quebec classification does not take into account factors such as central hypersensitivity. Nijs et al concluded that central sensitization is a characteristic of chronic WAD;[52] however, the present WAD group was heterogeneous with respect to pain sensitivity and two subgroups were identified. Hence, only relying on significant group differences between WAD patients and healthy controls will lead to simplistic conclusions about the characteristics of a clinical diagnosis and not reflect individual differences in pain processing within the patient group.[54] A primary care study reported that patients with WAD were similar to other patients with neck pain concerning pain, function, and recovery,[55] so both clinical conditions are reasonably heterogeneous, since the activated pain mechanisms are not the basis for the diagnoses.

For the ls-WAD subgroup, the pain-threshold variables of the trapezius were intermediary between CON and the s-WAD subgroup. When scrutinizing the thresholds in Table 1, there are differences in PPT in relation to the CON group in the primary pain area, but not for the other variables and anatomical areas. For the other threshold variables, the ls-WAD subgroup showed differences versus the s-WAD subgroup. These differences imply a more localized hyperalgesia for pressure in the ls-WAD subgroup. From Table 1, it can also be concluded that the mean values of the pain-threshold variables of ls-WAD were high in the normal interval in the lower limb. Why is this? One possibility is that the subjects belonging to the ls-WAD subgroup generally had low pain sensitivity before the trauma, which still was present in the lower limb. Prospective studies are needed to confirm such a suggestion concerning the causality. Such studies are very complicated and require a substantial number of subjects. An alternative way to investigate such a mechanism is to use a planned trauma, such as surgery, and collect data pretrauma, immediately after trauma, and at a long-term follow-up. Several such longitudinal surgical studies exist that have registered pain sensitivity,[56–59] but none of them has analyzed data from the perspective discussed here.

Subgrouping can have different aims. For acute WAD, it is most reasonable to relate to the prognosis. One way to do this is to use prospective studies. A strict systematic review of the risk factors for the transition from acute to chronic WAD[60] identified risk factors with strong evidence: acute pain intensity, acute headache, grades of severity according to the Quebec Task Force, and level of education. Significant risk factors with moderate evidence included catastrophizing and sex. Based on such results, patients with acute WAD can be subdivided into subgroups. The review did not include studies using QST and algometry variables.[60] To the best of our knowledge, there are only three prospective studies of acute WAD that address pain sensitivity. In a prospective study of trigeminal sensibility in WAD patients registered in the acute–subacute stage (mean 6 weeks) and at follow-up (after mean 71 months), three groups of subjects were identified: (1) normal on both occasions; (2) slight–moderate alterations initially with deterioration at follow-up; and (3) severe alterations initially as well as at follow-up.[61] In a study of WAD patients, pressure and thermal pain thresholds were followed prospectively from the acute stage (within 2 months of injury) and at 2, 3, and 6 months postinjury.[62] Those with moderate/severe symptoms at the 6-month follow-up had generalized hypersensitivity and high psychological distress in the acute stage. These results were essentially repeated in a later study,[63] which also reported decreased nociceptive flexion reflex thresholds only in those with moderate/severe symptoms at the 6-month follow-up. These data taken together certainly indicate the presence of subgroups and that lowered pain thresholds in the acute stage are indicative of a worse situation in the chronic stage.[61–63] Although pain thresholds were important factors, it cannot be ruled out that other variables more easily registered – such as pain intensity[60] and psychological strain[60,62,63] – have better power with respect to course and prognosis. This suggestion has to be investigated in future studies.

The most reasonable approach for the optimal selection of variables in the chronic stage has to be done in prospective efficacy studies of treatment or rehabilitation. A recent study reported that chronic pain patients with signs of hypersensitivity according to the QST were at high risk for misuse of prescription opioids.[15] Pain hypersensitivity was associated with less positive response when investigating the efficacy of a rehabilitation program in chronic WAD according to a preliminary randomized controlled trial.[16] In clinical practice, not all patients can be offered participation in rehabilitation programs, and various explicit or implicit biased selections occur.

One conceivable step before prospective studies is to use a cross-sectional approach in large patient groups of WAD. WAD patients have been sub grouped based on, for example, spreading of pain, pain intensity, and other prevalent symptoms.[7–12] One interpretation of these studies is that the present focus of the research groups determined their choice of variables used for the subgrouping. In the present study, subgroups were identified based on pain thresholds for pressure and thermal stimuli, which were multivariately associated with differences in clinical symptomatology, disability, and health aspects (Table 1). As in other studies, the choice of variables was predetermined based on our observation that great variability existed in pain thresholds.[21] One unprejudiced way to determine the important variables is to locate the variables associated with the greatest statistical variability in the data set, and then use these variables as a starting point for the subgrouping and finally investigate the importance of the subgroups for outcomes of treatment interventions. This requires a reasonably comprehensive data set. To obtain a relatively good coverage of important variables, the International Classification of Functioning, Disability and Health[64] can be applied. In the present study, it was not possible to achieve stable and valid results, due to a low number of WAD patients and because the cohort represents a selection of patients with a severe clinical picture. However, a preliminary analysis (data not shown) based on the variables displayed in Table 1 using principal component analysis indicate that pain intensity, anxiety aspects, and several of the subscales of SF36 are associated with greater variability than pain thresholds of pain and thermal stimuli. On the other hand, the advantage in using pain thresholds is that it is possible to semiobjectively characterize the state of the pain system, such as for hyperalgesia and hypersensitivity. That possibility does not exist using only subjective reports in a questionnaire.

Differences between groups with respect to symptoms and consequences

The ls-WAD subgroup was an intermediary group with respect to habitual pain characteristics, such as intensities and spreading of pain, sleep, psychological strain, participation aspects, and quality of life (Table 1). Therefore, the consequences are less for this subgroup than for the s-WAD subgroup; however, the ls-WAD subgroup is obviously not a healthy group when compared to the CON group according to the multivariate analysis.

Why do the two identified subgroups differ in their clinical presentations? The reasons for this are uncertain. It may reflect that the pain condition per se – including neurobiological alterations, as indicated by PPT, CPT, and HPT, symptomatology, and consequences – are less severe in the ls-WAD subgroup than in the s-WAD subgroup. Another relatively closely related alternative is the two subgroups express different conditions/prerequisites, so the processes that have evolved are very different; the nonsignificant difference in pain duration might support this line of argument (Table 1). A third alternative is that the ls-WAD and s-WAD subgroups reflect different types of etiology, with different predilections to develop alterations in central nociceptive systems and pain processing. Etiologies suggested are injuries to the upper cervical ligaments[65,66] and facet joints,[67,68] persistent musculoskeletal inflammation,[69,70] and psychocultural factors.[71]

Strengths and limitations

The major strength of this study is that one researcher performed all the measurements and judged inclusion criteria according to the patients' medical records, thereby avoiding measurement bias. Another strength is that the study used a wide array of pain measurements and a broad psychological perspective, with valid and reliable psychometric instruments entered into the analysis.

The patients in this study were recruited from a clinical department that specializes in managing severe chronic pain conditions. This reasonably means a selected sample of patients with severe pain and long pain duration. Hence, it is difficult to generalize the results to a broader spectrum of chronic WAD patients. Therefore, this study calls for further studies that include primary health-care patients with generally less pain severity.

Another limitation is the relatively small sample of patients. Our previous study using the same sample had sufficient power.[21] A problem with power does arise when any subgrouping is used, so there is a need for further studies to

confirm the results of this explorative study. However, by using powerful multivariate statistical methods such as PLS regression, we were able to overcome some of this limitation (cf Statistics).

QST and algometry require a cooperative subject and carefully standardized methods, including standardization of the stimulus parameters as well as the testing environment, instructions, and evaluation methods. In this study, a cross-sectional design was used, which means that the QST and algometry measures give only a momentary picture of the pain-sensitivity situation of each patient. Reliability studies of QST have mainly been done on healthy subjects, and there is a risk that patients with chronic pain may be associated with lower reliability.[54] However, QST measures have been shown to be relatively stable over time in patients with chronic low-back pain,[72] a consistency that may indicate that even a single QST measure accurately reflects the patient's pain sensitivity over a long period.

In the present study, we did not control for the menstrual cycle phase. Animal studies indicate that this is important,[73] but human studies have produced ambiguous results.[74–79]

Rehabilitation perspective

The existence of subgroups based on semiobjective measures such as pain thresholds are interesting from a rehabilitation perspective, which the preliminary randomized controlled study of Jull and colleagues indicates.[16] If future studies can confirm the validity of pain thresholds with respect to efficacy of rehabilitation, then assessing pain thresholds might be an important part of clinical assessments. Based on the differences in clinical pictures and a pattern of altered pain thresholds in the two identified subgroups of WAD, it can be speculated whether the patients need different treatment and rehabilitation perspectives. The ls-WAD subgroup might benefit from analgesic treatment only, whereas the s-WAD subgroup (with its relative complexity) might benefit from multimodal rehabilitation intervention (eg, synchronized interventions from different disciplines, such as medical, psychological, and physiotherapeutic). This issue calls for further studies. A first step towards understanding the optimal treatments could be to collect longitudinal data received by the two subgroups of chronic WAD.

Conclusion

The s-WAD subgroup displayed widespread hyperalgesia, whereas the ls-WAD subgroup had localized hyperalgesia in the neck area, with high values in the normal interval in the remote areas of the body. Generally, the s-WAD subgroup had significantly worse situations than the CON group with respect to symptomatology, disability, and health aspects; the ls-WAD subgroup was intermediary in these aspects. Different explanations – eg, severity of the pain condition per se, etiological factors, and pretrauma differences in pain sensitivity – may exist for the differences in pain thresholds. The role of pain thresholds in the chronic stage for determination of efficacy-of-treatment interventions needs further investigation.

Disclosure

The authors have no conflict of interest to declare.

References

1. Sterner Y, Gerdle B. Acute and chronic whiplash disorders – a review. *J Rehabil Med.* 2004;36(5):193–209; quiz 210.
2. Spitzer WO, Skovron ML, Salmi LR, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine (Phila Pa 1976).* 1995; 20(Suppl 8):1S–73S.
3. Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Spine (Phila Pa 1976).* 2008; 33(Suppl 4):S83–S92.
4. Kamper SJ, Rebbeck TJ, Maher CG, McAuley JH, Sterling M. Course and prognostic factors of whiplash: a systematic review and meta-analysis. *Pain.* 2008;138(3):617–629.
5. Scholten-Peeters GG, Verhagen AP, Bekkering GE, et al. Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies. *Pain.* 2003;104(1–2):303–322.
6. Nederhand MJ, Hermens HJ, Izerman MJ, Turk DC, Zilvold G. Chronic neck pain disability due to an acute whiplash injury. *Pain.* 2003;102(1–2):63–71.
7. Borsbo B, Peolsson M, Gerdle B. The complex interplay between pain intensity, depression, anxiety and catastrophising with respect to quality of life and disability. *Disabil Rehabil.* 2009;31(19):1605–1613.
8. Borsbo B, Peolsson M, Gerdle B. Catastrophizing, depression, and pain: correlation with and influence on quality of life and health – a study of chronic whiplash-associated disorders. *J Rehabil Med.* 2008;40(7):562–569.
9. Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *J Manipulative Physiol Ther.* 2009; 32(Suppl 2):S97–S107.
10. Kall LB. Psychological determinants of quality of life in patients with whiplash associated disorders – a prospective study. *Disabil Rehabil.* 2009;31(3):227–236.
11. Peolsson M, Gerdle B. Coping in patients with chronic whiplash-associated disorder – a descriptive study. *J Rehabil Med.* 2004;36(1): 28–35.
12. Soderlund A, Denison E. Classification of patients with whiplash associated disorders (WAD): reliable and valid subgroups based on the Multidimensional Pain Inventory (MPI-S). *Eur J Pain.* 2006;10(2): 113–119.
13. Hurtig IM, Raak RI, Kendall SA, Gerdle B, Wahren LK. Quantitative sensory testing in fibromyalgia patients and in healthy subjects: identification of subgroups. *Clin J Pain.* 2001;17(4):316–322.

14. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and fibromyalgia syndrome. *Pain.* 2009;147(1–3):72–83.
15. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain.* 2011;12(9):953–963.
16. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypresensitivity influence outcomes of physical rehabilitation for chronic whiplash? A preliminary RCT. *Pain.* 2007;129(1–2):28–34.
17. Chien A, Eliav E, Sterling M. Hypoesthesia occurs in acute whiplash irrespective of pain and disability levels and the presence of sensory hypersensitivity. *Clin J Pain.* 2008;24(9):759–766.
18. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: an investigation using quantitative sensory testing. *Clin J Pain.* 2008;24(7):595–603.
19. Chien A, Eliav E, Sterling M. Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash – further evidence of a neuropathic condition. *Man Ther.* 2009;14(2):138–146.
20. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden A, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. *Clin J Pain.* 2001;17(4):306–315.
21. Wallin M, Liedberg G, Borsbo B, Gerdle B. Thermal detection and pain thresholds but not pressure pain thresholds are correlated with psychological factors in women with chronic whiplash-associated pain. *Clin J Pain.* 2012;28(3):211–221.
22. Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. *Clin J Pain.* 2005;21(2):175–181.
23. Raak R, Wallin M. Thermal thresholds and catastrophizing in individuals with chronic pain after whiplash injury. *Biol Res Nurs.* 2006;8(2):138–146.
24. Wallin M, Raak R. Quality of life in subgroups of individuals with whiplash-associated disorders. *Eur J Pain.* 2008;12(7):842–849.
25. Sterling M, Hodkinson E, Pettiford C, Souvlis T, Curatolo M. Psychologic factors are related to some sensory pain thresholds but not nociceptive flexion reflex threshold in chronic whiplash. *Clin J Pain.* 2008;24(2):124–130.
26. Schlesinger I, Hering-Hanit R, Dagan Y. Sleep disturbances after whiplash injury: objective and subjective findings. *Headache.* 2001; 41(6):586–589.
27. Sullivan M, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess.* 1995;7(4):524–532.
28. Miro J, Nieto R, Huguet A. The Catalan version of the Pain Catastrophizing Scale: a useful instrument to assess catastrophic thinking in whiplash patients. *J Pain.* 2008;9(5):397–406.
29. Angst F, Verra ML, Lehmann S, Aeschlimann A. Responsiveness of five condition-specific and generic outcome assessment instruments for chronic pain. *BMC Med Res Methodol.* 2008;8:26.
30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361–370.
31. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale: an updated literature review. *J Psychosom Res.* 2002;52(2):69–77.
32. McCracken LM, Zayfert C, Gross RT. The Pain Anxiety Symptoms Scale: development and validation of a scale to measure fear of pain. *Pain.* 1992;50(1):67–73.
33. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther.* 1986;24(1):1–8.
34. Zvolensky MJ, Goodie JL, McNeil DW, Sperry JA, Sorrell JT. Anxiety sensitivity in the prediction of pain-related fear and anxiety in a heterogeneous chronic pain population. *Behav Res Ther.* 2001;39(6):683–696.
35. Vujanovic AA, Arrindell WA, Bernstein A, Norton PJ, Zvolensky MJ. Sixteen-item Anxiety Sensitivity Index: confirmatory factor analytic evidence, internal consistency, and construct validity in a young adult sample from The Netherlands. *Assessment.* 2007;14(2):129–143.
36. Waddell GA, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic back pain and disability. *Pain.* 1993;52(2):157–168.
37. Denison E, Asenlof P, Lindberg P. Self-efficacy, fear avoidance, and pain intensity as predictors of disability in subacute and chronic musculoskeletal pain patients in primary health care. *Pain.* 2004;111(3): 245–252.
38. Sandborgh M, Lindberg P, Denison E. Pain belief screening instrument: development and preliminary validation of a screening instrument for disabling persistent pain. *J Rehabil Med.* 2007;39(6):461–466.
39. Asghari A, Nicholas MK. An investigation of pain self-efficacy beliefs in Iranian chronic pain patients: a preliminary validation of a translated English-language scale. *Pain Med.* 2009;10(4):619–632.
40. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. *Eur J Pain.* 2007;11(2):153–163.
41. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev.* 1977;84(2):191–215.
42. Nicholas MK, Wilson PH, Goyen J. Comparison of cognitive-behavioral group treatment and an alternative non-psychological treatment for chronic low back pain. *Pain.* 1992;48(3):339–347.
43. Conner M, Norman P. Body weight and shape control: examining component behaviours. *Appetite.* 1996;27(2):135–150.
44. Skaret E, Kvale G, Raadal M. General self-efficacy, dental anxiety and multiple fears among 20-year olds in Norway. *Scand J Psychol.* 2003;44(4):331–337.
45. Chibnall JT, Tait RC. The Pain Disability Index: factor structure and normative data. *Arch Phys Med Rehabil.* 1994;75(10):1082–1086.
46. Burckhardt CS, Archenhotz B, Bjelle A. Measuring the quality of life of women with rheumatoid arthritis or systemic lupus erythematosus: a Swedish version of the Quality of Life Scale (QOLS). *Scand J Rheumatol.* 1992;21(4):190–195.
47. Liedberg G, Burckhardt C, Henriksson C. Validity and reliability testing of the Quality of Life Scale, Swedish version in women with fibromyalgia – statistical analyses. *Scand J Caring Sci.* 2005;19(1):64–70.
48. Sullivan M, Karlsson J, Ware J. The Swedish 36 Health Survey – I. Evaluation of data quality, scaling assumption, reliability and construct validity across general populations in Sweden. *Soc Sci Med.* 1995;41(10):1349–1358.
49. Fruhstorfer H, Lindblom U, Schmidt W. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry.* 1976;39(11):1071–1075.
50. Eriksson LJE, Kettaneh-Wold N, Wold S. *Introduction to Multi- and Magavariate data Analysis Projection Methods (PCA and PLS)*. Umeå: Umetrics; 1999.
51. Norden B, Broberg P, Lindberg C, Plymoth A. Analysis and understanding of high-dimensionality data by means of multivariate data analysis. *Chem Biodivers.* 2005;2(11):1487–1494.
52. Nijs J, Van Houdenhove B, Oostendorp R. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther.* 2010;15(2): 135–141.
53. Woolf C. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011;152(Suppl 3):S2–S15.
54. Curatolo M. Diagnosis of altered central pain processing. *Spine (Phila Pa 1976).* 2011;36(Suppl 25):S200–S204.
55. Verhagen AP, Lewis M, Schellingerhout JM, et al. Do whiplash patients differ from other patients with non-specific neck pain regarding pain, function or prognosis? *Man Ther.* 2011;16(5):456–462.
56. Baad-Hansen L, Arima T, Arendt-Nielsen L, Neumann-Jensen B, Svensson P. Quantitative sensory tests before and 1(1/2) years after orthognathic surgery: a cross-sectional study. *J Oral Rehabil.* 2010;37(5):313–321.
57. Martinez V, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg.* 2007;105(3):815–821.

58. Juhl GI, Jensen TS, Norholt SE, Svensson P. Central sensitization phenomena after third molar surgery: a quantitative sensory testing study. *Eur J Pain.* 2008;12(1):116–127.
59. Mikkelsen T, Werner MU, Lassen B, Kehlet H. Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. *Anesth Analg.* 2004;99(1):146–151.
60. Walton DM, Pretty J, MacDermid JC, Teasell RW. Risk factors for persistent problems following whiplash injury: results of a systematic review and meta-analysis. *J Orthop Sports Phys Ther.* 2009;39(5):334–350.
61. Sterner Y, Toolanen T, Knibestöl M, Gerdle B, Hildingsson T. Prospective study of trigeminal sensibility after whiplash trauma. *J Spinal Disord.* 2001;14(6):479–486.
62. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain.* 2003;104(3):509–517.
63. Sterling M. Differential development of sensory hypersensitivity and measure of spinal cord hyperexcitability following whiplash injury. *Pain.* 2010;150(3):501–506.
64. WHO. International classification of functioning, disability and health (ICF). Geneva: World Health Organization; 2001.
65. Johansson BH. Whiplash injuries can be visible by functional magnetic resonance imaging. *Pain Res Manag.* 2006;11(3):197–199.
66. Maak TG, Tominaga Y, Panjabi MM, Ivancic PC. Alar, transverse, and apical ligament strain due to head-turned rear impact. *Spine.* 2006;31(6):632–638.
67. Barnsley L, Lord SM, Wallis BJ, Bogduk N. The prevalence of chronic cervical zygapophysial joint pain after whiplash. *Spine (Phila Pa 1976).* 1995;20(1):20–25; discussion 26.
68. Lord SM, Barnsley L, Wallis BJ, Bogduk N. Chronic cervical zygapophysial joint pain after whiplash. A placebo-controlled prevalence study. *Spine (Phila Pa 1976).* 1996;21(15):1737–1744; discussion 1744–1735.
69. Gerdle B, Lemming D, Kristiansen J, Larsson B, Peolsson M, Rosendal L. Biochemical alterations in the trapezius muscle of patients with chronic whiplash associated disorders (WAD) – a microdialysis study. *Eur J Pain.* 2008;12(1):82–93.
70. Linnman C, Appel L, Fredrikson M, et al. Elevated [11C]-D-deprenyl uptake in chronic whiplash associated disorder suggests persistent musculoskeletal inflammation. *PLoS One.* 2011;6(4):e19182.
71. Obelieniene D, Schrader H, Bovim G, Miseviciene I, Sand T. Pain after whiplash – a prospective controlled inception cohort study. *J Neurol Neurosurg Psychiatry.* 1999;66(3):279–283.
72. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenwolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. *Pain Med.* 2011;12(12):1720–1726.
73. Terner J, Lomas L, Picker M. Influence of estrous cycle and gonadal hormone depletion on nociception and opioid antinociception in female rats of four strains. *J Pain.* 2005;6(6):372–383.
74. Klatzkin RR, Mechlin B, Girdler SS. Menstrual cycle phase does not influence gender differences in experimental pain sensitivity. *Eur J Pain.* 2010;14(1):77–82.
75. Vignolo V, Vedolin GM, de Araujo Cdos R, Rodrigues Conti PC. Influence of the menstrual cycle on the pressure pain threshold of masticatory muscles in patients with masticatory myofascial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008;105(3):308–315.
76. Tousignant-Laflamme Y, Marchand S. Excitatory and inhibitory pain mechanisms during the menstrual cycle in healthy women. *Pain.* 2009;146(1–2):47–55.
77. Ring C, Veldhuijzen van Zanten JJ, Kavussanu M. Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. *Biol Psychol.* 2009;81(3):189–191.
78. Kowalczyk WJ, Sullivan MA, Evans SM, Bisaga AM, Vosburg SK, Comer SD. Sex differences and hormonal influences on response to mechanical pressure pain in humans. *J Pain.* 2010;11(4):330–342.
79. Teepker M, Peters M, Vedder H, Schepelmann K, Lautenbacher S. Menstrual variation in experimental pain: correlation with gonadal hormones. *Neuropsychobiology.* 2010;61(3):131–140.