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Assessment of diagnostic criteria for the identification of central sensitization in patients with osteoarthritis pain

Results from a Delphi survey

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Abstract

To assess diagnostic criteria and currently used tools for the identification of central sensitization (CS) in patients with joint pain due to osteoarthritis (OA).

Qualitative, cross-sectional and multicenter study based on a 2-round Delphi survey

Public and private medical centers attending patients with joint pain.

A total of 113 specialists in traumatology, physical medicine and rehabilitation, pain management, rheumatology, primary care physicians and geriatrics were enrolled in the study.

Participants completed an ad-hoc 26-item questionnaire available from a microsite in Internet.

The questionnaire was divided into 6 sections with general data on CS, impact of CS in patients with knee osteoarthritis (KOA), diagnostic criteria for CS, non-pharmacological and pharmacological treatment of CS and usefulness of the concept of CS in the integral management of patients with KOA. Consensus was defined as 75% agreement.

Diagnostic criteria included pain of disproportionate intensity to the radiological joint lesion (agreement 86.7%), poor response to usual analgesics (85.8%), progression of pain outside the site of the lesion (76.1%) and concurrent anxiety and depression (76.1%). Based on the opinion of the specialists, about 61% of patients with KOA present moderate-to-severe pain, 50% of them show poor response to conventional analgesics, and 40% poor clinical-radiological correlation. Patients with KOA and CS showed higher functional disability and impairment of quality of life than those without CS (88.5%) and have a poor prognosis of medical, rehabilitation and surgical treatment (86.7%). Early diagnosis and treatment of CS may preserve function and quality of life during all steps of the disease (90.3%).

The management of patients with osteoarthritis pain and CS requires the consideration of the intensity of pain related to the joint lesion, response to analgesics, progression of pain to other areas and concurrent anxiety and depression to establish an adequate therapeutic approach based on diagnostic criteria of CS.

Abbreviations: CNS = central nervous system, CS = central sensitization, CSI = central sensitization inventory, DN4 = Doleur neuropathique 4 questionnaire, KOA = knee osteoarthritis, OA = osteoarthritis.

Keywords: central sensitization, cross-sectional study, knee osteoarthrosis, osteoarthritis, pain, survey

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1. Introduction

Chronic pain is recognized as a major public health problem producing a significant disability, economic and social burden.[1] Moreover, chronic pain not only affects the patient as a sensory and emotional problem, but it also affects his/her family and social circle.[2] In a large scale survey to assess the impact of chronic pain in 15 European countries, pain of moderate to severe intensity occurred in 19% of adult Europeans, seriously affecting the quality of their social and working lives.[3] Very few were managed by pain specialists and nearly half received inadequate pain treatment. In a recent cross-sectional nationwide study carried out in Spain, the prevalence of chronic pain among the general population was 16.6%, and among these subjects more than 50% referred limitations in their daily activities, 30% felt sad and/or anxious and 47.2% indicated that their pain was affecting their family life.[4]

Knee osteoarthritis (KOA) is the most common form of arthritis affecting a substantial proportion of adults and 1 of the most frequent causes of musculoskeletal pain (15% prevalence of symptomatic KOA and 25% prevalence of radiographic KOA in cohort studies)[5,6] because it is the final stage of traumatic and degenerative diseases. According to the literature, its prevalence has doubled since mid-twentieth century[7] Pain symptoms in early stages of osteoarthritis (OA) that are nociceptive in nature may progress to a more persistent constant pain that likely reflects other additional processes. Tissue injury and/or inflammation, as may be seen in OA, lead to a decrease in the excitation threshold and an increase in responsiveness to suprathreshold stimuli of peripheral nociceptors (i.e., peripheral sensitization).[8] Noxious mechanical stimuli can then evoke exaggerated responses (primary hyperalgesia), and normally innocuous stimuli, such as movement of the joint through its normal range of motion, may evoke a pain response (allodynia). As a result of the nociceptor activity after tissue injury or inflammation, a number of changes occur in the central nervous system (CNS). These include changes to dorsal horn transmission neuron receptors, leading the transmission neurons to become increasingly responsive to peripheral input (central sensitization, [CS]), with reduction in the threshold for mechanically induced pain and an expansion of the receptive field of dorsal horn neurons (spatial summation).[9] Once established, CS is maintained by low-level noxious and even non-nociceptive input from the periphery. Such changes in the CNS are mainly responsible for the enhanced sensitivity to mechanical stimuli that develop outside the area of the injury (secondary hyperalgesia).

It has been suggested that the CNS becomes hypersensitized in patients with chronic OA pain and that the phenomenon of CS plays a crucial role in the pain complaints reported by these patients, as well as in the poor response to conventional pain relief treatment strategies.[10–12] There is evidence that CS is present in patients with KOA and may be associated with symptom severity.[13–15] Also, CS may be a determinant factor of patient's benefit from total knee replacement. Patients with high preoperative pain and low pain threshold have a higher risk of persistent pain after total knee replacement for OA, which is interpreted as reflecting CS.[16,17]

In clinical practice, the identification of CS is important to assist the phenotyping of patients for choosing treatments that produce analgesia by normalizing hyperexcitable central neural activity. However, although awareness is growing that CS may be of prime importance in the persistence and management of chronic OA pain, a clear set of diagnostic criteria for CS in the clinical scenario is currently lacking.[9,11] Therefore, the objective of this study was to reach consensus regarding diagnostic criteria and currently available tools for identifying CS in patients with OA pain and to obtain relevant data from the integral management of patients with KOA pain based on the opinion of specialists involved in the care of these patients.

2. Methods

2.1. Design and setting

A qualitative observational, non-randomized, multicenter, 2-round Delphi study ("The Scenarios Study", acronym for *Sensibilización Central en paciEntes coN dolor Articular: criteRIos diagnósticOS* [Central Sensitization in Patients with Joint Pain: Diagnostic Criteria]) was conducted in the framework of Spanish public and private medical centers attending patients with OA pain in routine daily practice. The primary objective of the study was to assess diagnostic criteria and methods used for the recognition of CS in patients with OA pain. Secondary objectives were as follows: a) to evaluate the homogeneity of the diagnosis of CS among different specialties, particularly Primary Care, Traumatology, Physical Medicine and Rehabilitation and Pain Units; and b) to determine the clinical applicability of the diagnostic tools for CS and its usefulness to improve referral care patterns in patients with KOA pain. The study protocol was approved by the Ethics Committee for Clinical Research of Hospital Clínico San Carlos, Madrid (Spain). We consider KOA as patients with radiological signs of OA according to the Kellgren-Lawrence classification.[18]

2.2. Study procedures

The consensus process incorporated a 2-round Delphi method which took place between January and April 2017. The Delphi method is recommended for use in the health care setting as a reliable means of determining consensus for a defined clinical problem.[19,20]

A multidisciplinary expert panel (scientific committee) was composed of 4 Spanish renowned professionals, 1 specialist in family and community medicine, 1 specialist in traumatology and orthopaedic surgery, 1 specialist in physical rehabilitation and 1 specialist in pain management, all of them with large experience in the care of patients with chronic OA pain. The study questionnaire was designed by the scientific committee based on their experience and a comprehensive search of the literature to identify previously conducted studies with high level of evidence and key primary studies focused on the role of CS in patients with OA pain. A first list of topics was developed that, after being reviewed for comments, were then modified and approved as the initial draft of the questionnaire.

The protocol and the study questionnaire were lodged in an Internet microsite to which participants accessed via a weblink included in the e-mail. A total of 500 participants classified as specialists in the management of patients with OA (primary care, traumatology and orthopaedic surgery physical rehabilitation and pain units) in Spain were invited to participate in the study through an electronic information leaflet with a full description of the objectives and characteristics of the survey, and those who accepted were provided with the microsite URL and the user's password. Participation in the study was, voluntary and

compensated. The inclusion period was planned to be finished at the time at which 240 participants have completed the questionnaire of the first Delphi round although the final amount of participants included in the study were 113 in the first round and 93 in the second round. This unexpected loss of respondents occurred for unknown reasons although it is assumed that could be due to an inadequate recruitment strategy and it can be considered as a bias of the study. It should be taken into consideration that the distribution of the study invitation was done through an emailing campaign only, in a short period of time and a considerable extension of items to be answered in the questionnaire.

The final document emerged from a 2-round Delphi consensus process and consisted of a 26-item questionnaire, divided into 6 sections, which included data of the participants (5 items); general data on CS (9 items); impact of CS in the patient with pain secondary to KOA (5 items), including impact on the course of the disease, non-pharmacological and pharmacological treatment, surgical treatment, and overall results of treatment (5 items); diagnostic criteria for CS (4 items), including data from the medical history, physical examination and complementary tests; treatment of CS (2 items), including pharmacological and non-pharmacological treatment; and usefulness of the concept of CS in the integral management of the patients with KOA (1 item). The study questionnaire is described in the supplementary material, http://links.lww.com/MD/F315. The level of agreement was rated according to a 5-point Likert scale, categorized as 0='strongly disagree', 1='somewhat agree', 2='agree but not determinant for the prognosis of treatment', 3='agree and determinant for the prognosis of treatment', and 4='strongly agree and very determinant for the prognosis of treatment'. Consensus was defined if more than 75% of researchers rated the item as 'agree and determinant for the prognosis of treatment' or 'strongly agree and very determinant for the prognosis of treatment'. According to a systematic review on the Delphi methodology studies, 75% was the value defined in most of the studies included in the review.[21]

2.3. Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables. Differences in the responses provided by primary care physicians and specialists were analyzed with the Fisher exact probability tests for categorical variables, and the Student *t* test or 1-way analysis of variance for continuous variables. Data were analyzed using the SAS statistical program (Statistical Analysis Systems, SAS Institute, Cary, NC) version 9.1.3 for Windows.

3. Results

3.1. Participants

A total of 113 physicians participated in the study (58.4% men), with a mean standard deviation age of 44.9 (10.1) years, and 74.3% of them practicing in a public medical center. The most common specialty of participants was primary care in 38% of the cases (n=43) followed by traumatology in 23.9%, anesthesiology/pain management in 17.7%, and physical rehabilitation in 9.7% (total n=70). Sixty-five percent of participants had more than 10 years of professional practice. The geographical distribution of the participants was the following: Andalucía (22; 19.5%), Aragon (6; 5.3%), Asturias (2; 1.8%), Islas Baleares (4; 3.5%), Cantabria (2; 1.8%), Catalonia (10; 8.8%), Castilla León (8; 7.1%), Castilla La Mancha (4; 3.5%), Extremadura (4; 3.5%), Galicia (6; 5.3%), Islas Canarias (2; 1.8%), Madrid (24.8%), Melilla (1; 0.9%), Murcia (1; 0.9%), Navarra (2; 1.8%), Valencia (8; 7.1%) and Basque Country (3; 2.6%). Regarding the concept of CS, 61.9% of participants knew the electrophysiological findings, its clinical repercussion (hyperalgesia), and the basic neurobiology involved in the process. Also, a large majority of participants (75.2%) defined osteoarthritis of the knee as a clinical concept that involves painful knee and clinical history compatible with joint wear.

3.2. General data on CS

Results obtained in this section of the questionnaire are summarized in Table 1. Salient findings included the following: 53.1% of participants considered that pain secondary to KOA can be classified as chronic when lasted for more than 6 months, 31% that they had treated between 11 and 20 patients with chronic pain related to KOA in the last month; 52.2% stated that the most prevalent age range for pain secondary to KOA was between 55 and 74 years; women are affected in 63.7% of the cases; 39.8% considered that the intensity of pain is moderate, with a poor response to conventional analgesics in 54.6% of the cases and poor clinical-radiological correlation in 39.5%; and 53.5% selected the range of 74 to 84 years as the age with more severe and limiting pain symptoms.

In relation to the CS phenotype in patients with pain due to KOA, the most commonly selected items were history of inadequate response to multiple analgesics and conservative measures (98.2%), presence of depression and/or anxiety (89.4%), pain and disability levels not proportional to the degree of the joint lesion (87.6%), long-lasting disease (74.3%), and pain at rest (71.7%). There were significant differences between primary care and specialized care with respect to the proportion of patients without pain (16.3% vs 11.2%, $P=.01$) or mild pain (29.3% vs 23.3%, $P=.005$) with higher percentages in primary care, whereas patients with moderate pain were more frequent in specialized care (42.6% vs 34.9%, $P=.001$). Also, the age range of patients with KOA in which painful symptoms were more severe and limiting was 74–84 years in primary care (53.5% vs 32.9% $P=.01$) in contrast to 55 to 74 years in specialized care (61.4% vs 39.9% $P=.01$).

3.3. Impact of CS in the patient with pain secondary to knee OA

As shown in Table 2, consensus was achieved for all items regarding the impact of CS on different areas, including the course of the disease, results of non-pharmacological and pharmacological treatment, total knee replacement surgery and overall results of treatment (Fig. 1). Very high percentages of agreement were obtained, particularly for the statements that patients with pain secondary to KOA and CS as compared to those without CS were more prone to suffer from higher pain intensity (89.4%), higher functional impairment and loss of quality of life (88.5%), suffer from concomitant anxiety and/or depression (90.3%), poor prognosis of medical, surgical, and rehabilitation treatment (92%), and lower response to conventional analgesic drugs (90.3%). For the items ' . . . are prone to suffer a higher pain intensity than patients without CS' and ' . . . they have a higher

Table 1

Responses of 113 participants to central sensitization data in the patient with knee osteoarthritis.

Variable	Number (%)
When do you consider that the pain can be classified as chronic?	
> 1 mo	5 (4.4)
> 3 mo	48 (42.5)
> 6 mo	60 (53.1)
How many patients with chronic pain did you treat over the last month?	
0–10 patients	17 (15.0)
11–20 patients	35 (31.0)
21–30 patients	31 (27.4)
> 30 patients	30 (26.5)
What are the age ranges in which pain is more prevalent	
30–54 yr	0
55–74 yr	59 (52.2)
75–84 yr	53 (46.9)
> 85 yr	1 (0.9)
Which is the percentage according to gender?	
Men	41 (36.3)
Women	72 (63.7)
What would be the percentages regarding the intensity of the pain?	
No pain	15 (13.3)
Mild pain	29 (25.7)
Moderate pain	45 (39.8)
Severe pain	24 (21.2)
What is the age range with more severe and limiting painful symptoms?	
30–54 yr	1 (0.9)
55–74 yr	58 (51.3)
75–84 yr	46 (40.7)
> 85 yr	8 (7.1)
Characteristics of central sensitization phenotype	
Pain at rest	81 /1.7)
Long lasting disease	84 (74.3)
Inadequate response to multiple analgesics and conservative measures	111 (98.2)
Progressive increase of the painful area	73 (64.6)
Mirror pain in the contralateral knee	41 (36.3)
Appearance of multiple painful sites during treatment	58 (51.3)
Poor acceptance of the disease	71 (62.8)
Insomnia	67 (59.3)
Depression and/or anxiety	101 (89.4)
Pain and disability not proportional to the degree of the joint lesion	99 (87.6)
What percentage of patients attended in one week present at least one Characteristic of the previous question?	
< 10%	8 (7.1)
10%–30%	34 (30.1)
31%–50%	26 (23.0)
51%–70%	29 (25.7)
> 70%	16 (14.2)

risk for not responding adequately to knee arthroplasty and to suffer from chronic pain after replacement surgery', the level of agreement was higher in specialized care as compared to primary care ($P = .03$).

3.4. Diagnostic criteria for CS

Regarding data collected from the patient's medical history, participants considered that the most important information to make a diagnosis of CS in a patients with chronic OA pain were pain of disproportionate intensity for the degree of radiological lesion of the joint, poor response to conventional analgesics, progression of pain outside the original localization of the lesion, concurrent anxiety and/or depression (Fig. 2). Differences according to the level of care (primary care vs specialized care) were not found. Regarding concurrent associated symptoms, no consensus was achieved, but in reference to comorbidities, consensus was reached for the presence of chronic lumbar pain (75% agreement), myofascial pain syndrome (77.2%), fibromyalgia (80.4%), chronic fatigue syndrome (77.2%), and post-surgical persistent pain (87%).

Useful tests during physical examination for the diagnosis of CS for which consensus was reached are shown in Table 3. Differences between primary care and specialized care were not found except for consensus on assessment of temporal summation to touch in the most affected area (75.5% agreement) reported by primary care physicians. Consensus regarding other complementary tests included the use of a visual analogue scale (81.5% agreement), drawings of the painful area (79.3%), Central Sensitization Inventory (CSI) (76.1%), quality of life scales (SF-12, EQ-5D) (77.2%), the Doleur Neuropathique 4 questionnaire (DN4) (75.2%), and the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (77.2%). Of note, that in the first Delphi round, agreement was achieved for only the DN4 questionnaire. In relation to the DN4 instruments, there was a significantly higher percentage of agreement in specialized care than in primary care (80% vs 67.4%, $P = .01$). The finding of discrepancy between pain intensity, the degree of disability and the degree of joint lesion in the diagnostic images as a good indicator of CS in patients with KOA reached 83.2% agreement.

3.5. Treatment of CS

As shown in Table 4, consensus was achieved in 7 items of pharmacological treatment and in the 3 of non-pharmacological therapy. According to the respondents, the analgesics that specifically may act on CS in patients with KOA include tapentadol (90.3% agreement), the dual reuptake inhibitors of noradrenaline and serotonin (duloxetine, venlafaxine, amitriptyline) (81,4% agreement) and alpha2delta calcium channel ligands (gabapentin, pregabalin) (80,4% agreement) as well as physiopathological approaches of pain mechanisms. The non-pharmacological therapy includes recommendations of physical exercise, management of stress and education strategies for the patients with chronic pain.

3.6. The concept of CS in the integral management of the patient with knee OA

In this section of the questionnaire, consensus was achieved in all items with very high percentages of agreement ranging between 85% and 95.6%, which indicated that all participants recognized that early diagnosis of treatment of CS is essential to facilitate conservative and surgical treatment, to reduce length of hospitalization, direct and indirect costs, and to preserve functionality and quality of life. Differences between primary and specialized care were not found.

4. Discussion

This survey study provides information of the opinion of a sample of primary care physicians and other specialists, in particular, specialists in traumatology, physical medicine and rehabilitation and pain management on different aspects of the

Table 2

Responses of 113 participants regarding the impact of central sensitization in the patient with pain secondary to knee osteoarthritis.

Variables	'Strongly disagree' *n* (%)	'Somewhat agree' and 'agree but not determinant for the prognosis of treatment' *n* (%)	'Agree or strongly agree and determinant or very determinant for the prognosis of treatment' *n* (%)
Impact on the course of the disease			
Analgesic control difficult to manage with poor response to conventional analgesics.	3 (2.7)	12 (10.6)	98 (86.7)
Prone to suffer higher pain intensity than patients without CS	4 (3.5)	8 (7.1)	101 (89.4)
Higher degree of functional limitation and loss of quality of life than patients without CS	4 (3.5)	9 (8.0)	100 (88.5)
Higher risk of not adequate response to TKR and to suffer from chronic pain after TKR	3 (2.7)	17 (15.0)	93 (82.3)
More prone to suffer from psychological comorbidities (anxiety/depression)	2 (1.8)	9 (8.0)	102 (90.3)
Poor prognosis regarding the results of medical, surgical, and rehabilitation treatment.	3 (2.7)	6 (5.3)	104 (92.0)
Impact on non-pharmacological treatment			
Lower response to non-pharmacological treatment (immobilization, rest, exercises), decreasing the impact of these measures on results of treatment.	3 (2.7)	23 (20.3)	87 (77.0)
Lower degree of attaining goals of rehabilitation	4 (3.5)	15 (13.3)	94 (83.2)
Impact on pharmacological treatment			
Great lack of knowledge about the pathophysiology mechanisms of pain due to knee OA and correct taxonomy and treatment (total responses 92)*	1 (1.1)	14 (15.2)	77 (83.7)
Patients with knee OA and CS respond to a lesser extent to conventional analgesics.	2 (1.8)	9 (8.0)	102 (90.3)
Most patients with pain due to knee OA are given analgesics whose mechanism of action is not adequate to counteract the mechanisms involved in the pathophysiology of pain	2 (1.8)	26 (23.0)	85 (75.2)
Impact on surgical treatment			
Important predictor of the functional recovery time after TKR (total responses 92)*	3 (3.3)	10 (9.2)	79 (85.9)
Important predictor of results of rehabilitation after TKR	4 (3.5)	21 (18.6)	88 (77.9)
It implies more pain and functional limitation early after TKR and, in general, a higher consumption of analgesics as compared to patients without CS	5 (4.4)	12 (10.6)	96 (85.0)
Impact on the general results of treatment			
The presence of CS may be an important prognostic factor for the success of treatment of patients with knee OA	4 (3.5)	11 (9.7)	98 (86.7)
A better knowledge of the mechanisms involved in the physiopathology of pain due to knee OA may improve the general prognosis of treatment	3 (2.7)	10 (8.8)	100 (88.5)
To date, there are no therapeutic guidelines or adequate treatment algorithms easily applicable to routine daily practice for the treatment of CS in patients with knee OA (total 92 responses*	4 (4.3)	10 (10.9)	78 (84.8)
Early recognition of the CS phenotype in patients with knee OA could improve treatment outcomes	3 (2.7)	13 (11.5)	97 (85.8)

CS = central sensitisation, OA = osteoarthritis, TKR = total knee replacement.

* No agreement was achieved in the first Delphi round.

phenomenon of CS in patients with chronic OA pain. Additionally, the study is in line with the lack of training on general knowledge of the pain mechanisms as well as the physiopathological aspects related to central sensitization among the pain healthcare professionals in Europe.[22]

In view of the lack of consensus in the literature regarding diagnostic criteria for CS, the results of this study allow to establish 4 characteristics as the most relevant diagnostic clinical signs (Table 5). These include the presence of pain which intensity is disproportionate to the degree of joint lesion found in the radioimaging studies, poor response to conventional analgesic medications, progression of pain beyond the affected joint, and concurrent complaints of anxiety and depression. Based on data recorded in the study, the participants considered that 61% of patients with KOA suffer from moderate to severe pain, with inadequate pain relief by conventional analgesics in 55% of them, and poor clinical-radiological correlation in 40%. These characteristic signs should alert clinicians to the likelihood of poor outcomes related to the presence of CS component in a patient with chronic OA pain. Data of reviews and clinical studies have shown that the presence of CS in OA is predictive of several adverse clinical outcomes, including more severe and unpredictable pain that is difficult to manage with conventional analgesics, other comorbidities, reduced quality of life and functional disability, and poor results after join replacement surgery.[11,23,24] These features contradict traditional notions that have considered pain in OA as only acute and nociceptive as well as being primarily related to inflammation and mechanical factors such as cartilage damage. The evidence of poor correlation between radiographic findings and clinical manifestations supports the notion that chronic OA pain is insufficiently explained by simple acute nociceptive pain mechanisms alone, indicating that a central CS mechanism is likely to be present in many patients with OA pain. Our study highlights the consensus obtained and the low general knowledge of the pathophysiology mechanisms of CS in patients with KOA perceived by the respondents. This is an important gap that may be explained by the still emerging nature of this condition, the poor linkage between research data and clinical tools and the lack of systematic recommendations for the diagnosis and management of CS in OA pain.

Our study also shows difficulties in achieving consensus regarding the usefulness of complementary tests and other tools for the assessment of CS in clinical practice. It is noteworthy that, in the first Delphi round, agreement was only achieved for the use

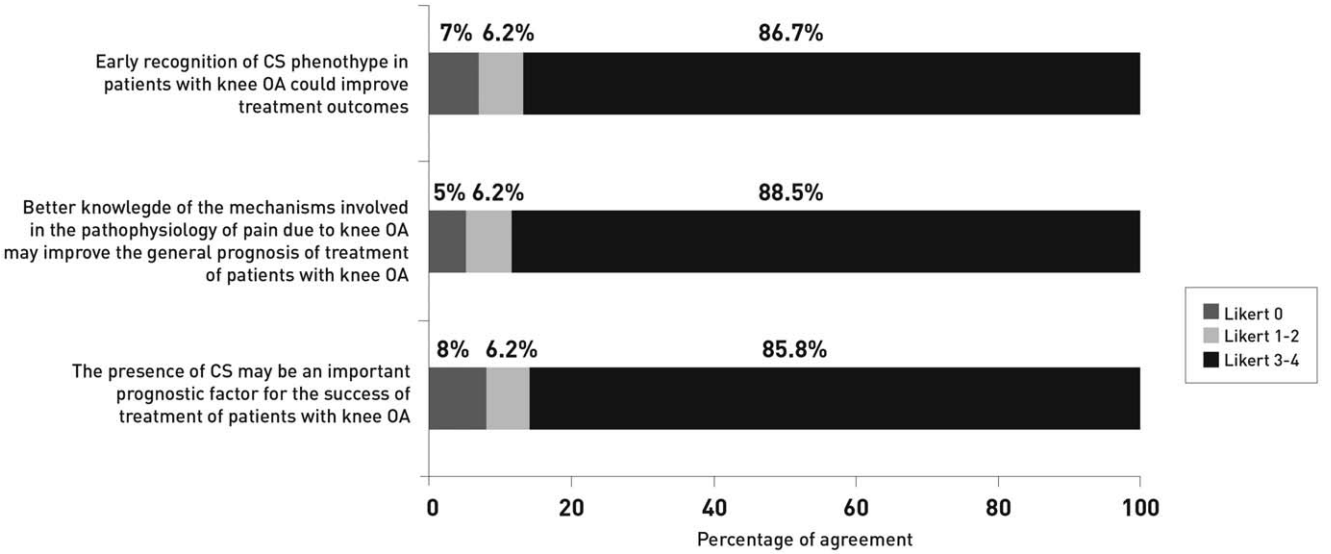

Figure 1. Impact of central sensitization (CS) of the overall results of treatment in patients with pain due to knee osteoarthritis (OA) (Likert score 0: 'strongly disagree'; 1-2: 'somewhat agree' and 'agree but not determinant for the prognosis of treatment; 3 to 4: 'agree or strongly agree and determinant or very determinant for the prognosis of treatment').

of the DN4 questionnaire, with consensus for visual analog scale, drawing of the painful area, CSI, LANSS, and quality of life questionnaires being achieved on the second round. Different studies have shown the usefulness of DN4 for the assessment of neuropathic and chronic pain.[25–27] In our study, the percentage of agreement for the use of DN4 was significantly higher among

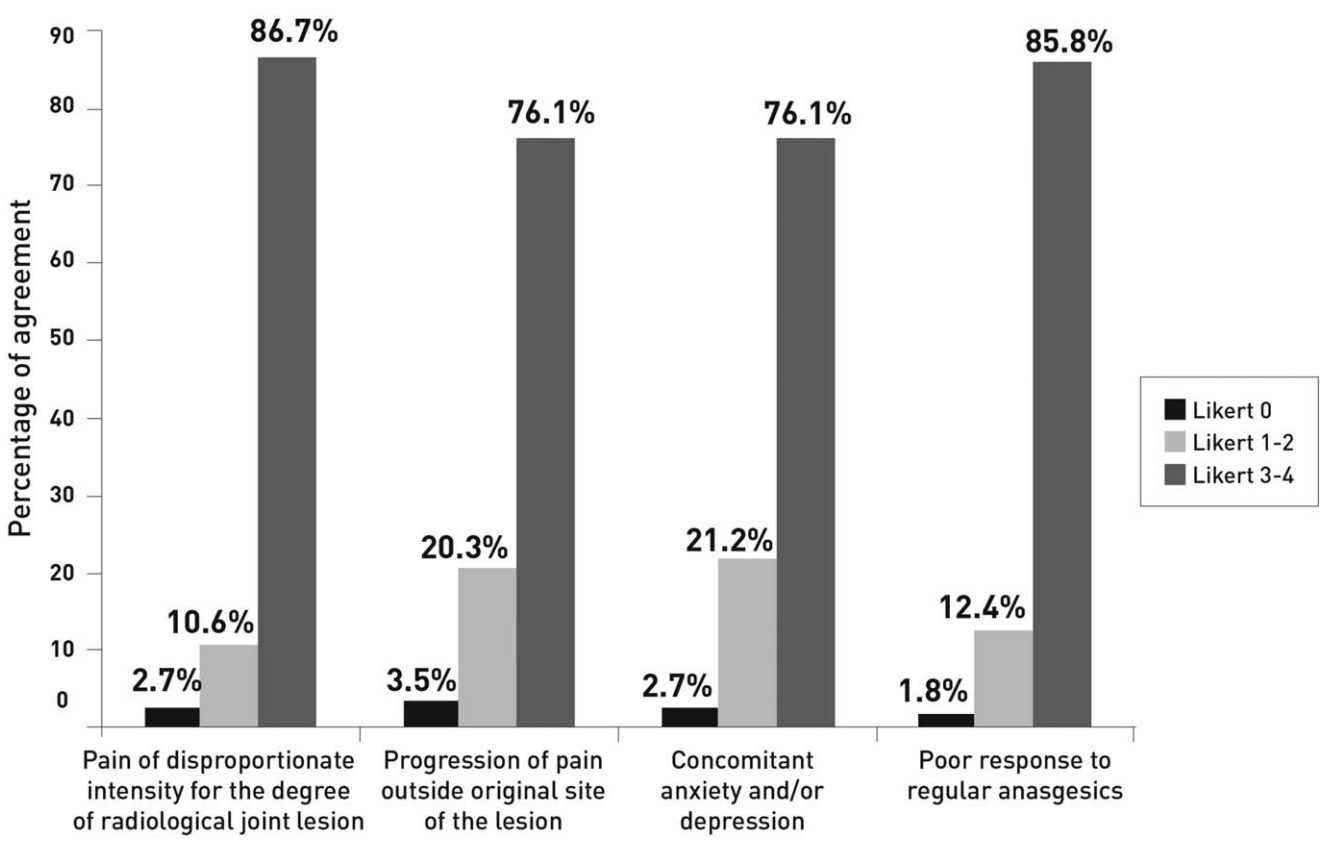

Figure 2. Signs from the patient's medical history in which consensus was achieved for the diagnosis of CS (Likert score 0: 'strongly disagree'; 1-2: 'somewhat agree' and 'agree but not determinant for the prognosis of treatment; 3-4: 'agree or strongly agree and determinant or very determinant for the prognosis of treatment').

Table 3

Useful tests performed during physical examination for the diagnosis of CS in which consensus was reached.

Item of the questionnaire	Percentage of agreement	
	Primary care N = 43	Specialized care N = 79
Assessment of these signs in the most affected joint area:	77.3	83.1
Pressure pain thresholds		
Touch sensitivity	84.3	77.2
Touch sensitivity (pinprick hyperalgesia)	78.6	78.6
Temporal summation to touch	75.5	No agreement
Dynamic mechanical allodynia triggered by touch	81.4	75.7
Deep somatic hyperalgesia to touch	78.6	77.4

CS = central sensitisation.

specialists as compared to primary care physicians, probably reflecting that they could be more familiarized with the use of this instrument and a better understanding of the overlapping characteristics of CS and NP. On the other hand, the CSI developed to identify and quantified key symptoms related to CS[28] showed an agreement of 76.1% on the second Delphi round.

The present survey provides also interesting data regarding the treatment approach that would be used by specialists in the management of patients with KOA pain and CS. Interestingly, it was recognized that adequate treatment of CS should involve reducing hyperexcitability of the ascending pain pathway, reestablishment of the normal function of the noradrenaline descending pathway and the fact that the mechanisms involved in the pathophysiology of CS pain and the intensity of pain should guide pharmacological therapy. The reuptake inhibitors of serotonin and noradrenaline, such as duloxetine, venlafaxine, and amitriptyline together with tapentadol and inhibitors of the alpha2-delta voltage-gated calcium channel, gabapentin and pregabalin, were considered adequate medications for OA pain. The benefits of centrally acting drugs have been also reported by others.[11,29,30] In relation to non-pharmacological therapy, consensus reached included the recommendation of exercise, education interventions for chronic pain, and management of stress. Increased physical activity is effective for managing pain in patients with OA and overweight[31] as well as for OA patients in general,[32] but positive effects of the processes involved in CS remains unclear.

The present results should be interpreted taking into account the observational and exploratory nature of the survey, the relative small number of participants, which limits the representativeness of the study sample and the use of a non-validated questionnaire. The questionnaire was written in Spanish and distributed to general practitioners and specialists interested in the care of patients with OA pain. It is important to emphasize the limited number of participants, which was lower than expected, and the loss of participants in the second round of the Delphi process, the reasons of which are unknown but probably

Table 4

Consensus achieved by 113 participants regarding pharmacological and non-pharmacological treatment of central sensitization the patient with pain secondary to knee osteoarthritis.

Variables	'Strongly disagree' n (%)	'Somewhat agree' and 'agree but not determinant for the prognosis of treatment' n (%)	'Agree or strongly agree and determinant or very determinant for the prognosis of treatment' n (%)
Pharmacological treatment that specifically may act on CS in patients with knee OA.			
Dual reuptake inhibitors of epinephrine and serotonin (duloxetine, venlafaxine, amitriptyline)	1 (0.9)	20 (17.7)	92 (81.4)
alpha2delta calcium channel ligands (gabapentin, pregabalin)	2 (1.8)	20 (17.7)	91 (80.5)
Tapentadol	0	11 (9.7)	102 (90.3)
The most important mechanism in the treatment of CS is to reestablish the normal function of the epinephrine descending inhibitory pathway (total responses 92)	1 (1.1)	17 (18.5)	74 (80.4)
The most important mechanism in the treatment of CS is to reduce hyperexcitability of the ascending pain pathway.	2 (1.8)	24 (21.2)	87 (77.0)
Pharmacological treatment should be guided by the mechanisms involved in the physiopathology of pain	0	17 (15.0)	96 (84.9)
Pharmacological treatment should be guided by the intensity of pain, both al rest and on movement.	2 (1.8)	24 (21.2)	87 (77.0)
Non-pharmacological treatment			
Exercise	2 (1.8)	17 (15.0)	94 (83.2)
Education of the patient with chronic pain	0	14 (12.4)	99 (87.6)
Management of stress	1 (0.9)	22 (19.5)	90 (79.6)

CS = central sensitisation, OA = osteoarthritis.

Table 5

Diagnostic criteria for the identification of central sensitization in patients with osteoarthritis pain.

Diagnostic criteria for the identification of central sensitization in patients with osteoarthritis pain
Disproportionate intensity to the radiological joint lesion.
Poor response to usual analgesics.
Progression of pain outside the site of the lesion.
Concurrent anxiety and depression.

influenced by the recruitment strategy. Also, specialists in pain management accounted for a reduced percentage of participants (17.7%) as compared to primary care physicians and traumatologists. Although 65% of participants had more than 10 years of professional experience, the distribution of participants by autonomous communities was irregular, with 24.8% concentrated in Madrid followed by 19.5% in Andalucia. The influence of these factors on the outcome of the study should not be underestimated. However, as far as we are aware, no previous survey studies addressing the problems of CS in patients with pain due to OA have been published in the literature. In this respect, there is little information addressing the treatment of CS, specifically in patients with OA.[33,34] In a systematic review of CS in patients with OA pain based on from 36 studies, the majority of which were case-control studies in KOA, evidence was inconclusive regarding both clinical identification and treatment of CS in OA.[35]

In summary, the consensus obtained on diagnosis criteria as well as the mentioned study results add valuable information regarding the diagnosis and the management of patients with CS and OA pain. Early assessment of the characteristic clinical signs of CS allows recognition of the CS component that may be present in some patients with chronic OA pain. Also, prompt recognition of the CS phenotype in patients with KOA may be an important factor to improve the outcome of treatment in these patients. The management of OA pain and CS requires an early diagnosis and treatment in order to reduce the impact of CS on the course of the disease, and especially on functionality and quality of life of patients. However, studies like the present survey analysis should have a wider range of population and the questionnaire should be updated with more pain specific level questions to determine the level of the pain experienced by the individuals. In clinical practice, disproportionate intensity to the radiological joint lesion, poor response to usual analgesics, progression of pain outside the site of the lesion, and concurrent anxiety and depression are suggestive diagnostic clues. Among non-pharmacological measures, exercise and educational interventions could be recommended, whereas duloxetine, venlafaxine, and amitriptyline together with gabapentin and pregabalin were considered adequate medications for the management of CS in patients with OA.

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References

[1] Dueñas M, Ojeda B, Salazar A, et al. A review of chronic pain impact on patients, their social environment and the health care system. J Pain Res 2016;9:457–1457.

[2] Closs SJ, Staples V, Reid I, et al. The impact of neuropathic pain on relationships. J Adv Nurs 2009;65:402–11.

[3] Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287–333.

[4] Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general Spanish population: identifying clinical subgroups through cluster analysis. Pain Med 2015;16:811–22.

[5] Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Current Opin Rheumato 2015;27:276–83.

[6] Turkiewicz A, Petersson IF, Björk J, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis Cartilage 2014;22:1826–32.

[7] Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. Proc Natl Acad Sci U S A 2017;114:9332–6.

[8] Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145–53.

[9] Woolf CJ. Central sensitization: implications for diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2–15.

[10] Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol 2007;26:465–73.

[11] Lluch E, Nijs J, Courtney CA, et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. Disabil Rehabil 2018;40:2836–45.

[12] Schäfer AGM, Joos LJ, Roggemann K, et al. Pain experiences of patients with musculoskeletal pain + central sensitization: A comparative Group Delphi Study. PLoS ONE 2017;12:e0182207.

[13] Arendt-Nielsen L, Simonsen O, Laursen MB, et al. Pain and sensitization after total knee replacement or nonsurgical treatment in patients with knee osteoarthritis: identifying potential predictors of outcome at 12 months. Eur J Pain 2018;22:1088–102.

[14] Fingleton C, Smart K, Moloney N, et al. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:1043–56.

[15] Skou ST, Graven-Nielsen T, Rasmussen S, et al. Facilitation of pain sensitization in knee osteoarthritis and persistent post-operative pain: a cross-sectional study. Eur J Pain 2014;18:1024–31.

[16] Wylde V, Sayers A, Odutola A, et al. Central sensitization as a determinant of patients' benefit from total hip and knee replacement. Eur J Pain 2017;21:357–65.

[17] Baert IA, Lluch E, Mulder T, et al. Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review. Osteoarthritis Cartilage 2016;24:213–23.

[18] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.

[19] Dalkey NC. The Delphi method: an experimental study of group opinion. Rand Corp Public RM-58888-PR. Santa Monica: Rand Corp; 1969.

[20] Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. J Clin Epidemiol 2003;56:1150–6.

[21] Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401–9.

[22] Briggs EV, Battelli D, Gordon D, et al. Current pain education within undergraduate medical studies across Europe: advancing the provision of pain education and learning (APPEAL) study. BMJ Open 2015;5: e006984.

[23] Akinci A, Al Shaker M, Chang MH, et al. Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component. Int J Clin Pract 2016;70:31–44.

[24] Arendt-Nielsen L. Pain sensitization in osteoarthritis. Clin Exp Rheumatol 2017;35(Suppl 107): S68-S-74.

[25] VanDenKerkhof EG, Stitt L, Clark AJ, et al. Sensitivity of the DN4 in screening for neuropathic pain syndromes. Clin J Pain 2018;34:30–6.

[26] Timmerman H, Steegers MAH, Huygen FJPM, et al. Investigating the validity of the DN4 in a consecutive population of patients with chronic pain. PLoS One 2017;12:e0187961.

[27] Madani SP, Fateh HR, Forogh B, et al. Validity and reliability of the Persian (Farsi) version of the DN4 (Douleur Neuropathique 4 Questions) questionnaire for differential diagnosis of neuropathic from non-neuropathic pains. Pain Pract 2014;14:427–36.
[28] Bennett EE, Walsh KM, Thompson NR, et al. Central Sensitization Inventory as a predictor of worse quality of life measures and increased length of stay following spinal fusion. World Neurosurg 2017;104:594–600.
[29] Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009; 146:253–60.
[30] Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. Age Ageing 2012;41:646–52.
[31] Brosseau L, Wells GA, Tugwell P, et al. Ottawa Panel evidence-based clinical practice guidelines for the management of osteoarthritis in adults who are obese or overweight. Phys Ther 2011;91:843–61.
[32] Pisters MF, Veenhof C, Schellevis FG, et al. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized controlled trial comparing two different physical therapy interventions. Osteoarthritis Cartilage 2010;18:1019–26.
[33] Lluch Girbés E, Nijs J, Torres-Cueco R, et al. Pain treatment for patients with osteoarthritis and central sensitization. Phys Ther 2013;93:842–51.
[34] López-Ruiz M, Losilla JM, Monfort J, et al. Central sensitization in knee osteoarthritis and fibromyalgia: Beyond depression and anxiety. PLoS One 2019;14:e0225836.
[35] Lluch E, Torres R, Nijs J, et al. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. Eur J Pain 2014;18:1367–75.