

# Is Chronic Pain a Disease in Its Own Right? Discussions from a Pre-OMERACT 2014 Workshop on Chronic Pain

Ann M. Taylor, Kristine Phillips, Justin O. Taylor, Jasvinder A. Singh, Philip G. Conaghan, Ernest H. Choy, Peter S. Tugwell, Ulrike Kaiser, Vibeke Strand, Lee S. Simon, and Philip J. Mease

**ABSTRACT.** At the pain workshop held prior to the Outcome Measures in Rheumatology (OMERACT) 12 conference, chronic nonmalignant pain (CP) as a “disease” was discussed, in response to growing interest in this concept and in terms of the effect on the OMERACT Filter 2.0 framework. CP is often assessed as a unidimensional outcome measure; however, if CP is a disease, then outcome measures need to define the disease state and identify all its manifestations as well as its effects, as specified by Filter 2.0. The aim was to write a discussion piece, reflecting the workshop contributions and debate, as an important step in opening a dialogue around future OMERACT Filter 2.0 Framework developments. (J Rheumatol First Release July 1 2015; doi:10.3899/jrheum.141328)

## Key Indexing Terms:

CENTRAL SENSITIZATION  
BIOMEDICAL

BIOPSYCHOSOCIAL

RHEUMATOLOGIC CONDITIONS  
OMERACT

The Outcome Measures in Rheumatology (OMERACT) Filter 2.0<sup>1</sup> requires a definition of the area/domain of interest before selecting outcome measures for a disease, and currently sees chronic pain (CP) as a domain under Pathophysiologic Manifestations or as an element under Life Impact. Given that pain is now being considered a disease in its own right by some, it was decided at a pre-OMERACT

workshop to discuss how CP should be classified (see Table 1 for working definitions shared with participants).

A number of presentations were given at the workshop including one that proposed that CP should be reclassified because it can no longer be seen as just a symptom. Participants were then asked to informally vote (Figure 1), and this showed widespread opinions on what pain repre-

*From Cardiff University, Cardiff, UK; Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; Barry Chiropractic Clinic, Cardiff; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and UK National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK; SDG LLC, Cambridge, Massachusetts, USA; Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; Medicine Service, VA Medical Center, Birmingham; Department of Medicine at the School of Medicine, and Division of Epidemiology at the School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama; Department of Orthopedic Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; University Hospital Carl Gustav Carus, Dresden, Germany; Swedish Medical Center and University of Washington, Seattle, Washington; Division of Immunology/Rheumatology, Stanford University, Palo Alto, California, USA.*

*Authors were funded as follows: Dr. Conaghan, in part by Arthritis Research UK; Dr. Singh, by grants from the Agency for Health Quality and Research Center for Education and Research on Therapeutics U19 HS021110, US National Institute of Arthritis and Musculoskeletal and Skin Diseases P50 AR060772 and U34 AR062891, US National Institute on Aging U01 AG018947, US National Cancer Institute U10 CA149950; by resources and use of facilities at the VA Medical Center at Birmingham, Alabama; and by research contract CE-1304-6631 from the Patient Centered Outcomes Research Institute; Dr. Choy, from the Arthritis Research UK and National Institute for Social Care and Health Research; and Dr. Kaiser, by a grant from the German Ministry of Education and Research (BMBF 01GY1326).*

*Financial disclosures are as follows: Dr. Singh, research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron, and Allergan; on the executive of OMERACT, which receives arms-length funding from 36 companies; member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care*

*Committee; and member of the Veterans Affairs Rheumatology Field Advisory Committee. Dr. Choy, research grants, membership on advisory boards and speaker bureaus of Abbott Laboratories, Allergan, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceutical, GSK, Hospita, ISIS, Jazz Pharmaceuticals, MedImmune, Merrimack Pharmaceutical, MSD, Napp, Novimmune, Novartis, Pfizer, Pierre Fabre Medicament, Regeneron, Roche, Sanofi-Aventis, Schering Plough, Synovate, Tonix, and UCB. Lee Simon: Nicox, Fidelity, Extera, Wyeth, Asahi, Sammuded, Metabolex, SarCode, Anthera, Antares, Vical, Daiichi Sankyo, Rigel, Bayer, Solace, Puretechventures, Abbott, Omeros, Jazz, Takeda, Teva, Zydus, Alder, Cephalon, Purdue, EMDSerono, Altea, Talagen, Tigenix, Agenus, Forest, Genzyme, Horizon, Pozen, ILPharma, Analgesic Solutions, Creabilis, Kowa, Array, JRX Biopharm, Imprimis, Dara, Genco, Neos, Bayer Consumer, Sanofi, Lilly, Idera, Medac, Inotec, Osteoanalgesia, and Akron.*

*A.M. Taylor, PhD, Cardiff University; K. Phillips, MD, PhD, Department of Internal Medicine, University of Michigan; J.O. Taylor, BSc, Barry Chiropractic Clinic; P.G. Conaghan, MBBS, PhD; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit; P.S. Tugwell, MD, MSc, FRCPC, Department of Medicine, University of Ottawa; J.A. Singh, MBBS, MPH, Medicine Service, VA Medical Center, Department of Medicine at the School of Medicine, and Division of Epidemiology at the School of Public Health, University of Alabama at Birmingham, and Department of Orthopedic Surgery, Mayo Clinic College of Medicine; E.H. Choy, MD, FRCP, Cardiff University; U. Kaiser, Dr. rer. Nat. Dipl-Psych, University Hospital Carl Gustav Carus; P.J. Mease, MD, Swedish Medical Center and University of Washington; V. Strand, Division of Immunology/Rheumatology, Stanford University; L.S. Simon, SDG LLC.*

*Address correspondence to A.M. Taylor, Cardiff University, Heath Park Site, Cardiff CF14 4XN, UK. E-mail: Tayloram@cardiff.ac.uk*

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Table 1. Definitions.

Term	Definition	Source
Disease	A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms or that affects a specific location and is not simply a direct result of physical injury	The Oxford English Dictionary <sup>39</sup>
Symptom	A physical or mental feature regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient	The Oxford English Dictionary <sup>39</sup>
Syndrome	A group of symptoms which consistently occur together, or a condition characterized by a set of associated symptoms	The Oxford English Dictionary <sup>39</sup>
Disorder	An illness that disrupts normal physical or mental functions	The Oxford English Dictionary <sup>39</sup>
Condition	The state of somebody's health or how fit they are	The Oxford English Dictionary <sup>39</sup>
Longterm condition	Those conditions that cannot, at present, be cured, but can be controlled by medication and other therapies. The life of a person with a longterm condition is forever altered — there is no return to "normal"	Department of Health <sup>40</sup> , UK
Chronic pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage	International Association of Pain <sup>41</sup>

### Chronic pain is a separate...

1. Disease
2. Condition
3. Syndrome
4. Symptom complex
5. None of the above

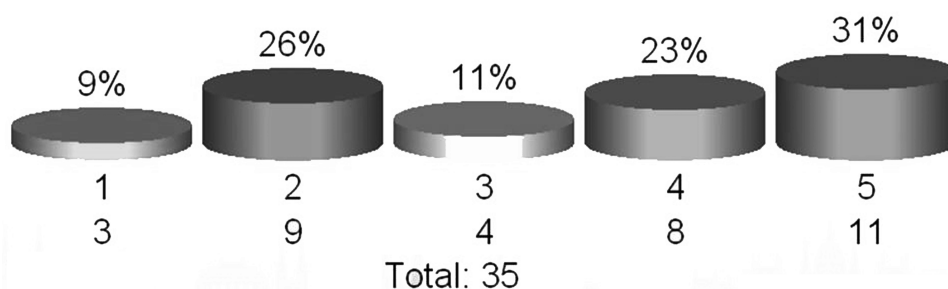


Figure 1. Results of an informal poll conducted at the pre-OMERACT workshop on participants' opinions of how to define chronic pain.

sented. Admittedly, this poll was difficult to interpret, participants could not respond to more than 1 statement, and there was no option to explain choices. However, it provided a stimulus for the discussions that followed.

This workshop, although sponsored by OMERACT, was not characteristic of OMERACT workshops: It was not informed by a prior, systematic, and methodologic approach normally taken; thus participants (healthcare professionals, scientists, and patient research partners) could air opinions, network, and lay foundations to inform the newly created pain subgroup regarding future OMERACT workshops and activity. If CP is considered a disease in its own right, this will have an effect on future OMERACT work streams in

terms of the Filter 2.0 framework. Therefore this exploratory article starts the process of reflecting on whether CP remains a symptom or should be considered a disease.

#### The Challenge

Several individuals and organizations have suggested that CP is a disease in its own right<sup>2,3,4</sup>; however, others disagree<sup>5,6</sup>. At the outset, it must be stressed that untangling all the strands of the "CP, a disease" debate is a complex and nuanced task; for this reason, neuropathy is not included because it is seen as part of an ongoing pathophysiologic process of damage, especially, for example, diabetic painful neuropathy, which is already regarded as a disease. Cancer

pain was also omitted because it is viewed as part of palliative care; pain in cancer is directly related to the ongoing presence of disease rather than a chronic condition without further input. The complexities under consideration, for example, include the fact that pathophysiological manifestations are different (central vs peripheral mechanisms); there are varying degrees of neurobiology that are not specific to a pain condition; some patients have very complex central pain changes and others appear not to; and finally, there are issues surrounding the grouping of all pain conditions into a disease model given the differing assessment needs and outcome measures. Following this and other such articles, OMERACT may need to reconceptualize CP in terms of the OMERACT Filter 2.0.

### What Does the Literature Describe?

A number of literature reviews have explored the issue of whether CP is a disease. All have used relatively recent neuroimaging research to either support or refute its disease status.

Cousins<sup>7</sup> and Siddall and Cousins<sup>3</sup> both contended that CP is a disease entity, proposing that it has recognizable signs and symptoms and its own specific cause. Both reviews provide comprehensive discussions regarding functional and structural central nervous system (CNS) changes associated with CP. However, CP can manifest in different ways, have different signs and symptoms, and may not have a specific cause. For instance, differences can be seen in how individuals describe their pain<sup>8</sup>, in how pain is modulated by the CNS<sup>9</sup>, and in how individuals can respond to treatment: all suggesting different pathophysiological processes.

Cousins<sup>7</sup> and Siddall and Cousins<sup>3</sup> list a number of psychosocial sequelae that lead to structural and functional changes in the brain: the “pain pathology.” These include mood disturbances, loss of self-belief in abilities, fear avoidance, and loss of social roles and relationships, as specific changes in physiological mechanisms. Siddall and Cousins<sup>3</sup> state, in support of CP as a disease, that these pathologies and signs and symptoms are dependent on, and unique to, the presence of pain. This proposition can be challenged; many of these are not pathological in a true sense, nor unique to chronic pain, in that the majority can be seen in people living with various chronic conditions unrelated to the presence of pain.

Tracey and Bushnell<sup>10</sup> reviewed the evidence from neuroimaging studies, presenting functional, anatomical, and neurochemical evidence that people with CP have altered brains compared to healthy controls. What they could not identify is whether these changes were the result of an adaptive response to the continuing nociceptive barrage, or a real disease-specific process, which would support the conclusion that neuroimaging research has established CP as a true disease state. It is not surprising that pain results in brain changes, given that it is a sensory and emotional

experience; other sensory and emotional experiences (meditation<sup>11</sup>, exercise<sup>12</sup>, pleasant touch<sup>13</sup>) are known to alter the brain. Therefore, caution is required when using altered CNS processes to define a disease state.

Tracey and Bushnell’s review<sup>10</sup>, in which support is given for CP as a disease, mentions that one motivation for their review was that CP treatment options are pharmacologically and behaviorally similar for many patients despite different etiologies, thereby suggesting that similar mechanisms generate the pain, in turn supporting the claim that CP is a disease. It is agreed that common interventions are used across diverse groups of people living with pain, but these interventions have only moderate success rates<sup>14</sup> in low back pain, for example, and are even more variable across a range of pain conditions; this may reflect different outcome measures used in the studies, however. Not one treatment option works for all cases of CP; instead, a wide range of treatment options is advocated and used to address the complex biopsychosocial aspects that can be present.

Cohen, *et al*<sup>5</sup> argue that CP is not a disease; they examine the evolutionary models used to explain CP and comment upon propositions in other reviews. They cite May<sup>15</sup>, who concluded that it was not clear whether structural changes in CP were due to pain, the consequences of pain, or both; and that other factors may have contributed to the findings. A number of studies have examined cortical structural changes accompanying chronic musculoskeletal pain<sup>16,17,18</sup>, and while different regions appear to be implicated in different CP states, there appears to be consistency in the involvement of the cingulate cortex, insula, and dorsolateral prefrontal cortex. Some researchers have controlled for other variables (anxiety and depression<sup>10</sup>, opioid use<sup>13</sup>, reduction in physical activity<sup>19</sup>, general drug consumption<sup>10</sup>) to account for structural loss but still found significant differences in CP patients versus controls.

### Chronic Pain, a Disease?

Previous reviews have included rigorous debate concerning CP as a disease. Neuroimaging research has certainly provided rich detail regarding changes that occur as a result of pain, leading the debate supporting the idea that CP may indeed be a disease. Given that patients with CP are a large heterogeneous group, perhaps what qualifies chronic pain as a disease is a set of underlying mechanisms (central sensitization) or a particular type of pain (neuropathic).

Central sensitization can develop as a result of nociceptive inputs causing a reversible increase in the excitability and synaptic efficacy of neurons in the central nociceptive pathways<sup>20</sup>. It manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctuate or pressure hyperalgesia, enhanced temporal summation, and after-sensations<sup>20</sup>. Central sensitization and brain changes have been identified through neuroimaging studies<sup>10</sup>, and it has been proposed that CP is associated with cortical remodeling,

specifically, primary somatosensory cortex (S1) functional reorganization<sup>21</sup>. However, it appears that pain itself does not result in S1 reorganization<sup>22</sup>; neuropathic pain appears to lead to cortical reorganization and associated changes in somatosensory cortex activity and anatomy, where non-neuropathic pain does not<sup>22</sup>. Unfortunately, there are no absolute diagnostic criteria for identifying the presence of central sensitization in patients; Woolf contends that pain hypersensitivity by itself is not sufficient to make an irrefutable diagnosis of central sensitization<sup>20</sup>. However, studies have putatively identified that central sensitization has contributed to patients' pain phenotype (see Woolf<sup>20</sup>).

### Central Sensitization and Common Rheumatologic Conditions

In osteoarthritis (OA), Woolf has suggested that the degree of central sensitization correlates with clinical pain reports but not with radiographic findings<sup>20</sup>. While this is supported by some<sup>23,24</sup>, others disagree and suggest a strong correlation<sup>25,26</sup> between self-reported pain and radiographic changes. Central sensitization has been offered as an explanation for these differences, as described below.

In patients with hip OA accompanied by referred pain, hyperalgesia detected by quantitative sensory testing (QST) in the referred pain areas correlates with central pain modulation regions in the brain, including the anterior cingulate cortex<sup>27</sup>. In those with knee OA, patients vary in local and diffuse sensitization by QST — those reporting severe pain being more sensitive to local pressure stimulation than healthy controls<sup>28</sup>. Central sensitization was especially apparent among knee OA patients who reported high levels of clinical pain in the absence of moderate-to-severe radiographic evidence of pathologic changes<sup>29</sup>. Results were significant even after adjusting for differences on psychosocial measures, as well as age, sex, and race.

In rheumatoid arthritis (RA), self-reports of pain have been shown not to correlate with clinical, observable findings<sup>30</sup>. In some patients, symptoms persist even when RA flares have apparently subsided<sup>30</sup>. It has been suggested that pain processing in the CNS is impaired, and the continuous barrage of nociceptive activity in RA can lead to peripheral and subsequently persistent central sensitization<sup>31,32</sup>. Peripheral sensitization does not account for enhanced responses to sensory stimuli seen in non-inflamed regions adjacent to and even remote from the inflamed joint<sup>31</sup>. A number of studies have reported hyperalgesia or allodynia in patients with RA, signs of central sensitization<sup>33,34,35</sup> compared with healthy controls, and increased pain sensitivity appears to be related to longer disease duration<sup>35</sup>.

### Functional Pain Disorders

There are conditions in which pain appears not to be driven by noxious stimuli, inflammation, or direct damage to the nervous system; they present with pain hypersensitivity but

no clear etiological factors, which may reflect a primary dysfunction of the nervous system<sup>20</sup>. In a review of functional disorders<sup>36</sup>, various mechanisms were proposed to explain the cause of conditions such as irritable bowel syndrome, fibromyalgia, temporomandibular joint disorder, and interstitial cystitis, including enhanced pain perception, altered brain activation, dysregulations in immunologic and neuroendocrine function, and genetic factors. It does appear that heightened sensitivity of the CNS and an increased propensity to develop central sensitization are common features<sup>20</sup>.

Defining the underlying pathophysiology of CP remains elusive; several reports now show evidence for peripheral nerve abnormalities in patients with fibromyalgia that could contribute to their chronic pain<sup>37,38</sup>. Discussing peripheral sensitization as a disease entity is outside the realm of this article, but further exploration is recommended.

Other unifying factors include functional disorders that overlap within the same individual, common pathophysiological disturbances, responsiveness to similar treatment interventions<sup>36</sup>, and a possible hereditary component<sup>20</sup>. Woolf<sup>20</sup> concludes that CP hypersensitivity in the absence of inflammation or nerve damage results in apparently phenotypically different syndromes depending on the tissue/organ affected.

### DISCUSSION

There is still a great deal of uncertainty about whether CP is a disease. In the United Kingdom, CP is considered a longterm (chronic) condition (LTC); however, CP is not recognized as such globally. This conceptualization appears to succinctly reflect our present level of understanding around CP and would appear to be an acceptable middle ground until further research offers greater insight (Table 1)<sup>39,40,41</sup>.

If CP is a symptom, what is it a symptom of? Traditionally, acute pain has been seen as a symptom of an underlying disease or an event such as trauma or surgery; treatment of the disease or cause would improve or eradicate the pain. In people diagnosed with a primary disease such as OA or RA, it may be relatively straightforward in that CP in the affected joint(s) is a symptom of the disease. However, as described, central sensitization and neuropathic changes can occur.

It appears that the medical paradigm in which the person presenting with pain is ultimately assessed and managed is important. For a rheumatologist presented with someone complaining of CP, a more biomedical model approach may initially be used in aiding a diagnosis. The focus is on biological factors responsible for the pain and less on psychological, environmental, and social influences. Once a diagnosis is reached, pain becomes a symptom of the disease diagnosed, with the assumption that if the disease is managed, the symptom of pain will improve or disappear.

Conversely, patients are referred to pain specialists by other medical specialists who have either diagnosed but are unable to treat them, or have failed to diagnose. In these instances, the biomedical model is no longer useful. Pain specialists would

be expected to explore the biopsychosocial issues associated with CP, including pain-related disability and distress. Some argue that because it is managed from a biopsychosocial perspective, CP is a disease. However, being a disease and using a biopsychosocial model are not synonymous; and given its complexity, CP may not be well served by a disease model. Figure 2 illustrates the issues with trying to fit CP as a disease into the biomedical model approach to RA.

Current research is focused on producing diagnostic criteria and biomarkers with good sensitivity and specificity for identifying neuropathic pain, as well as development of new therapies<sup>42,43</sup>. If these were available, central sensitization could be the diagnosis of a disease of the CNS. Similarly, given that cortical reorganization can be seen in important pain regions in neuropathic pain but not nociceptive pain, is neuropathic pain the disease?

CP has historically been regarded as a symptom although the International Association of Pain has defined over 500 CP syndromes<sup>41</sup>. Given the burden of CP<sup>44</sup>, we need to consider how to define and manage it, and a good start may be to identify how we conceptualize it. There has been a groundswell of opinion, based upon emerging neuroimaging evidence, that CP needs to be reclassified; Table 2 summarizes the debate presented here. If we accept, for instance, that CP is an LTC or disease, then the philosophy of care may change from a biomedical model that views CP as a symptom to that of a biopsychosocial one that views CP as a disease or LTC. The implications for further refinement of the OMERACT Filter 2.0 is that the biopsychosocial aspects of pain as an LTC/disease must be included in measurement outcomes; measuring pain-related distress and disability, physical functioning and participation, for instance, and not just measuring physical pain.

The authors propose that CP is definitely an LTC or chronic condition and would like to see continued debate

around central sensitization and neuropathic pain. However, a similar exploratory report is required to examine whether peripheral sensitization should be seen as a disease and to address other factors such as work undertaken in genetic factors (not included here) to inform future OMERACT work streams and research activity (see Table 3 for future OMERACT CP activity).

## REFERENCES

1. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
2. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med* 2011;12:996-1004.
3. Siddall PJ, Cousins MJ. Persistent pain as a disease entity: implications for clinical management. *Anesth Analg* 2004;99:510-20.
4. Niv D, Devor M. Chronic pain as a disease in its own right. *Pain Pract* 2004;4:179-81.
5. Cohen M, Quintner J, Buchanan D. Is chronic pain a disease? *Pain Med* 2013;14:1284-8.
6. Pearce JM. Chronic regional pain and chronic pain syndromes. *Spinal Cord* 2005;43:263-8.
7. Cousins MJ. Persistent pain: a disease entity. *J Pain Symptom Manage* 2007;33:S1-3.
8. Jensen MP, Johnson LE, Gertz KJ, Galer BS, Gammaitoni AR. The words patients use to describe chronic pain: implications for measuring pain quality. *Pain* 2013;154:2722-8.
9. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010;120:3779-87.
10. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? *J Pain* 2009;10:1113-20.
11. Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, et al. Meditation experience is associated with increased cortical thickness. *Neuroreport* 2005;16:1893-7.
12. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA* 2011;108:3017-22.
13. Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, Browning

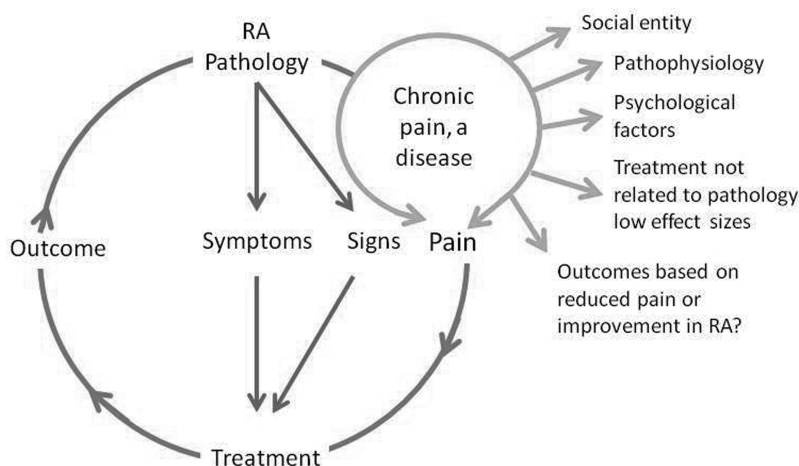


Figure 2. Illustrating the problems with trying to fit chronic pain as a disease into the biomedical model approach to rheumatoid arthritis (RA; used as an example).

Table 2. Synopsis of the debate for and against the concept of chronic pain as a disease.

Factors	For Chronic Pain as a Disease	Against Chronic Pain as a Disease
Healthcare resources	Recognition may lead to increase in resources, education, and priority	CP seen as an LTC is gaining support in terms of increasing resources, education and priority; it does not require a disease definition to fulfill this support
The field of medical specialization	EFIC and individual pain medicine specialists and researchers propose CP as a disease	Other specialists and researchers, e.g., rheumatologists and neurologists may see pain more as a symptom of the presenting disease
Neuroimaging research	Structural and functional changes used to support pain as a disease; CP is a disease of the CNS	Structural and functional changes are proposed not to be purely due to pain but to the consequences of pain and its management
Signs and symptoms	CP is uniquely represented by physiological, psychological, and social signs and symptoms	Signs and symptoms of CP are not unique, they can accompany any LTC
Brain alterations	Results from a “real” disease-specific process	Results from an adaptive response to continuing nociceptive barrage
Management	CP treatment options are pharmacologically and behaviorally similar, suggesting similar mechanisms generating the pain	CP treatment options have only moderate success and there is a wide range of treatment options that can have some effect in one group and not in another (nociceptive pain vs neuropathic pain management, for instance)
CP as a symptom	If CP is a symptom, what is it a symptom of? It does not serve as a warning as in acute pain	CP is a symptom of a chronic disease such as OA, RA, etc.
Paradigm	Managed using the biopsychosocial model, CP is perceived to be a disease	Managed using a biomedical model, CP is perceived to be a symptom.

CP: chronic pain; LTC: longterm or chronic condition; EFIC: European Pain Federation; CNS: central nervous system.

Table 3. Future OMERACT CP activity

Activity	Description
Further debate	Build on the discussions outlined in this article examining other factors not currently addressed and refine Figure 2, framing the issues informed by more in-depth concept development
Research	Collaborate and conduct research to define domains and assess and develop outcome measures for CP as an LTC Evaluate outcome measures for CP across disease states and identify core domains that are relevant across these states and those that are unique to specific conditions Evaluate outcome measures used to assess pain across disease states and disciplines in the context of the OMERACT Filter 2.0, including ability to distinguish between “peripheral” and “centralized” pain
Collaborators	Integrate patient partners in the research process to better define the multidimensional aspects of pain (domains) and the ability of extant instruments to reflect patient-relevant aspects Integrate activities with key participants and organizations with similar agendas

- A, et al. The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* 1999;10:453-9.
14. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147:492-504.
  15. May A. Structural brain imaging: a window into chronic pain. *Neuroscientist* 2011;17:209-20.
  16. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004;24:10410-5.
  17. Gerstner G, Ichesco E, Quintero A, Schmidt-Wilcke T. Changes in regional gray and white matter volume in patients with myofascial-type temporomandibular disorders: a voxel-based morphometry study. *J Orofac Pain* 2011;25:99-106.
  18. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci* 2007;27:4004-7.
  19. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J Neurosci* 2009;29:13746-50.
  20. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2-15.
  21. Moseley GL, Flor H. Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabil Neural Repair* 2012;26:646-52.

22. Gustin SM, Peck CC, Cheney LB, Macey PM, Murray GM, Henderson LA. Pain and plasticity: is chronic pain always associated with somatosensory cortex activity and reorganization? *J Neurosci* 2012;32:14874-84.
23. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008;9:116-27.
24. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol* 2000;27:1513-7.
25. Laxafoss E, Jacobsen S, Gosvig KK, Sonne-Holm S. Case definitions of knee osteoarthritis in 4,151 unselected subjects: relevance for epidemiological studies: the Copenhagen Osteoarthritis Study. *Skeletal Radiol* 2010;39:859-66.
26. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* 2009;339:b2844.
27. Gwilym SE, Keltner JR, Warnaby CE, Carr AJ, Chizh B, Chessell I, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum* 2009;61:1226-34.
28. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. *Pain* 2010;149:573-81.
29. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 2013;65:363-72.
30. Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. *Pain* 1997;71:179-86.
31. Schaible HG, Grubb BD. Afferent and spinal mechanisms of joint pain. *Pain* 1993;55:5-54.
32. Konttinen YT, Kempainen P, Segerberg M, Hukkanen M, Rees R, Santavirta S, et al. Peripheral and spinal neural mechanisms in arthritis, with particular reference to treatment of inflammation and pain. *Arthritis Rheum* 1994;37:965-82.
33. Shenker NG, Haigh RC, Mapp PI, Harris N, Blake DR. Contralateral hyperalgesia and allodynia following intradermal capsaicin injection in man. *Rheumatology* 2008;47:1417-21.
34. Edwards RR, Wasan AD, Bingham CO, Bathon J, Haythornthwaite JA, Smith MT, et al. Enhanced reactivity to pain in patients with rheumatoid arthritis. *Arthritis Res Ther* 2009;11:R61.
35. Leffler AS, Kosek E, Lerdal T, Nordmark B, Hansson P. Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. *Eur J Pain* 2002;6:161-76.
36. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? *Neurogastroenterol Motil* 2012;24:895-913.
37. Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. *Brain* 2013;136:1857-67.
38. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 2013;154:2310-6.
39. Oxford English Dictionary, 3rd edition. Oxford: Clarendon Press; 2010.
40. UK Department of Health. Improving health and well-being of people with long term conditions. London: Department of Health; 2010. [Internet. Accessed May 26, 2015.] Available from: [www.yearofcare.co.uk/sites/default/files/pdfs/dh\\_improving%20the%20h%26wb%20of%20people%20with%20LTCs.pdf](http://www.yearofcare.co.uk/sites/default/files/pdfs/dh_improving%20the%20h%26wb%20of%20people%20with%20LTCs.pdf)
41. Merskey H, Bogduk N. Pain terms: classification of chronic pain. Second edition. Seattle: International Association for the Study of Pain; 1994.
42. Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia. Part 1: the need, reality, challenges, and solutions. *Discov Med* 2011;11:197-207.
43. Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia. Part 2: how, where, and what to look for using functional imaging. *Discov Med* 2011;11:209-19.
44. Häuser W, Wolfe F, Henningsen P, Schmutzer G, Brähler E, Hinze A. Untying chronic pain: prevalence and societal burden of chronic pain stages in the general population - a cross-sectional survey. *BMC Public Health* 2014;14:352.