Aspects of pain, its assessment and evaluation from an acupuncture perspective

Irene Lund, Thomas Lundeberg

Abstract

Pain is a major clinical problem that causes great suffering for the individual and incurs costs for society. Accurate assessment and evaluation of perceived pain is necessary for diagnosis, for choice of treatment, and for the evaluation of treatment efficacy. The assessment of an individual's pain is a challenge since pain is a subjective, multidimensional experience, and assessment is based on the person's own self-report. The results are often varied, possibly due to inter-individual variation, but also in relation to gender and aetiology.

A gold standard for pain assessment is still lacking, but rating scales, questionnaires, and methods derived from psychophysical concepts, such as threshold assessments and perceptual matching, are used. In the evaluation of pain and associated variables, both systematic and individual variation should be taken into account, as should pain-associated symptoms.

Recommendations for pain treatment should be based on the patient's specific needs. Therefore, it is important to assess the level of perceived pain taking individual variation into account. The methods used should preferably have proved to be useful in randomised controlled trials, and analysis of pain assessment should consider its non-metric properties. In the future, the use of studies with a naturalistic protocol together with individual assessment of individual pain responses could increase the internal and external validity.

Keywords

Nociception, pain measurement.

Iréne Lund
post-doctoral researcher
registered physiotherapist
Karolinska Institutet
Stockholm, Sweden

Thomas Lundeberg
senior consultant
Danderyds Hospital
Stockholm, Sweden

Correspondence:
Irene Lund

irene.lund@ki.se

Introduction

The subjective experience of pain is not to be regarded as a single entity but rather a complex multivariate problem that has to be defined by its different components in diagnostic assessment, and in choice and evaluation of treatment. Given the variability and complexity of subjective pain, it is important to evaluate the individual as well as the group responses in order to understand the patient's pain and to optimise decisions about treatment.

As pain is a uniquely personal experience that is not necessarily proportional to the physiological process of nociception, reliance on patients' self report – pain intensity, unpleasantness, or interaction with thoughts and life – is essential. Methods of assessment, even though they are sophisticated and defined as objective, are most probably influenced by patients' motivation and psychological state; however, they are a valuable complement to the verbal report.[1-4]

Furthermore, pain levels as rated by patients may not agree with ratings made by a physician, another member of the medical team, or a parent, so using the these ratings can be problematic.[6;7] Since there is no gold standard in pain assessment, communication about the perceived pain may be optimised by using a measure that the patient prefers.

In clinical work, the phenomenon of pain is both considered and treated differently. Irrespective of the origin of the pain, it is important to attempt to capture the perceived pain, ie to assess and evaluate the perceived pain. In statistical analysis of pain data, there is some discussion whether the intervals of different pain scales like the visual analogue scale (VAS), are equidistant or not, since assumptions about the distribution of the data have major implications for the choice of method of analysis. The chosen method for analysis of pain may influence the quality and validity of the results, having possible implications on evidence based decisions and choice of recommendations of pain treatment.

The aim of this article is to describe some of the commonly used pain assessment methods and to introduce a newly developed statistical method in order to evaluate experimental and clinical pain from an acupuncture perspective. Also, we discuss the possible use of corticotropin releasing factor (CRF) in urine as a possible marker of symptoms associated with pain.

Pain in society

Pain is a major clinical problem.[7] The prevalence of chronic pain was recently reported to be approximately 54% and associated with female gender, older age, being on sick leave and early retirement.[8] Also, pain is associated with low self-rated health,[9] and is one of the most frequent causes of seeking healthcare.[10] Consequently pain, including its change and associated symptoms, is probably the most evaluated variable in clinical work.

Definition of pain

From a biological perspective, the feeling of pain is a somatic sensation, termed nociception. The meaning of nociception is a warning signal essential for survival but also intimately related to homeostasis.[11]

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[12] The pain sensation is described as multi-dimensional including sensory-discriminative (eg intensity), affective-motivational (eg unpleasantness), and cognitive-evaluative (eg thoughts, beliefs) dimensions.[13] All three dimensions are like to be activated more or less simultaneously,[14-16] and are all important to include in the assessment of the patient's pain. The sensory-discriminative dimension, ie pain intensity or pain severity, is probably the most commonly evaluated.[17]

The duration of a pain condition is often described in terms of acute or chronic, the latter often exceeding three months, without clear definitions and borders between the two phases. The chronic phase is associated with changes in plasticity in peripheral and central neural structures.[18;19] Therefore, chronic pain is a clinical entity by itself and should not be treated as being an acute condition.[20;21] A long term pain condition is also reported as associated with affective components like depression and anxiety.[22-24]

Pain mechanism

Depending on the aetiology, pain has been classified into different categories,[25;26] each with its own characteristics. Woolf recently proposed a categorisation of pain based on its mechanisms, into: nociceptive – transient pain in response to a noxious stimulus; inflammatory – spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation; neuropathic – spontaneous pain and hypersensitivity to pain in association with damage to or a lesion of the nervous system; functional – hypersensitivity to pain resulting from abnormal central processing of normal input.[27]

Biochemical markers of pain associated symptoms

In long term pain conditions, associated symptoms of physiological and psychological distress are reported,[22] as well as anxiety and depression.[23;24] From a physiological perspective, an aberrant function of the sympathetic nervous system,[28] the hypothalamic-pituitary-adrenal (HPA) axis,[29] or its negative feedback loop,[30;31] have been discussed as plausible causes of the stress related symptoms in pain conditions like fibromyalgia. Corticotropin releasing factor, CRF, synthesised in the hypothalamic paraventricular nuclei, is reported as one physiological mediator of different endocrine, autonomic, and behavioural responses to stress.[32-34] Elevated plasma and cerebrospinal fluid (CSF) concentrations of CRF have been found in patients with fibromyalgia,[22] and in patients with post-traumatic stress disorder.[35] Hyperactive CRF neurons have, therefore, been suggested to play a role in the nociceptive and psychological mechanisms in fibromyalgia.[22;29;31;36] The central autonomic control of stress is complex and not easily assessed by a single test, for which reason a variety of techniques have been tried.[28] CRF concentration is usually measured in CSF, which is a procedure that may be stressful by itself. To reduce the stress that is related to sampling procedures, but also to diminish the influence of diurnal variation, analysis of CRF concentration in 24-hour urinary samples could be an alternative.[37]

Endogenous pain modulation

Endogenous pain modulation systems, operating in the central nervous system (CNS), both inhibitory and facilitatory, have been described;[38-41] and a

number of different neurotransmitters like opioids, and monoamines have been suggested to play a key role.[42;43]

In order to activate the endogenous pain inhibitory mechanisms, different modes of sensory stimulation like acupuncture are used. The pain inhibitory control is attributed to activity induced by needle stimulation starting in the peripheral receptors and primary afferent nerves leading to an inhibition of propagation of pain impulses in the dorsal horn at the spinal cord level, first described by Melzack and Wall (1965) as the gate control theory.[44] The activity in afferent nerves also leads to inhibitory effects elicited from higher centres in the CNS.[41;45;46] The induced effects of sensory stimulation techniques such as acupuncture are often reported as an increase in pain thresholds and a decrease of rated pain.[47-49]

Acupuncture is increasingly used for alleviation of clinical pain. However, questions of evidence for acupuncture treatment efficacy are discussed in the medical community. In a recent report, the Swedish Council on Technology Assessment in Health Care concluded that there is evidence for the usefulness of acupuncture in different chronic pain states.[21]

Assessment of pain

Rating scale assessments

Pain is a personal and subjective experience, ie a complex perceptual phenomenon which is not necessarily proportional to the physiological process of nociception. Since pain is subjective, it can only be assessed indirectly based on the patient's self-report. The perception of pain is influenced by internal and external factors,[50-52] and is also reported differently.[53;54]

The variability in pain is also reported as being influenced by gender. Women as compared to men are more sensitive to experimental painful stimuli, perceiving clinical pain at higher severity and greater frequency, of longer duration and present in a greater number of body regions.[55-58] Taking all the above factors into account, evaluation of group effects may be difficult to interpret, whereas individual responses are important, ie what may be true for the individual is not valid for the group. Therefore, it is important to assess the level of perceived pain and its change, taking the individual variation into account, in order to optimise treatment regimes.[59]

For self-reported pain assessments, different types of uni-dimensional rating scales like the Visual Analogue Scale (VAS),[60] the Numeric Rating Scale (NRS),[61] the Verbal Rating Scale (VRS),[62] the Category Ratio (CR-10 scale),[63] or multi-dimensional instruments like the McGill Pain Questionnaire are used.[64] Pain is also a common sub variable in multi-dimensional instruments such as the Nottingham Health Profile.[65] The VAS and NRS are probably the most commonly used pain assessment instruments but there is so far no evidence for recommending one against the other.[66] In chronic pain clinical trials the NRS has, however, previously been recommended.[67] Due to the lack of gold standard, there is a need to study if the individual score captured on one pain scale is interchangeable with that of another pain scale. In our study, pain intensity assessments using VAS and VRS were found not to be interchangeable due to inconsistency of pain scores between the two scales, and the results showed systematic disagreement when comparing the two scales. This may also indicate that scales can have different interpretations.[68]

Threshold assessments

An alternative method for pain evaluation, derived from the psychophysical concept, is the use of threshold assessments.[69] The sensory threshold is defined as the least level of stimulation that can be detected by the subjects and the pain threshold as the least level of stimulation required producing the first perception of pain. Different modes of stimulation are applied for the threshold assessments,[70-72] commonly with ascending intensities of stimulation, the Method of Limits.[63;73;74] The assessed threshold levels are generally dependent on the status of the nervous system, and sociocultural and psychological factors.[16;50] In pain patients, the assessed electrical sensory threshold was found to be unaffected,[75] or decreased,[76] and the electrical pain thresholds were found to be lower in comparison with healthy individuals.[77] Further, the electrical pain thresholds were found to increase following successful treatment in patients with painful osteoarthritis,[76] indicating that a shift in pain thresholds could serve as a measure of a change in perceived pain (see Figure 1).

Lowered pain thresholds have been reported in patients with pain within, as well as outside, the painful area.[76;78-81] This may reflect greater pain sensitivity.[82] Threshold assessment is generally not

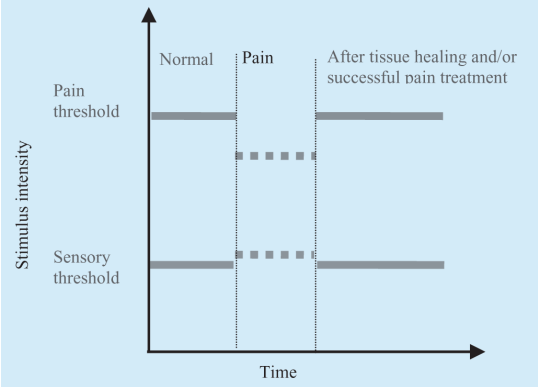

Figure 1 Possible threshold levels, sensory detection and pain, in health and pain. Figure reproduced from dissertation (Lund) with permission.

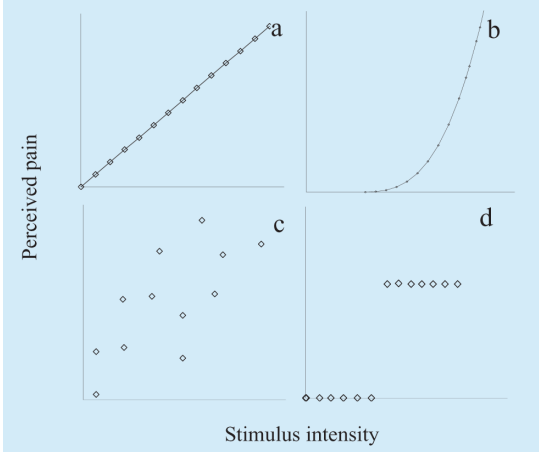

Figure 2a-d Possible models of perceived pain in response to increase of stimulus intensity presented as linear (a) or exponential (b) distributions producing data with known size and distance. Data of perceived pain presented as ordinal (c) or dichotomised into no pain/pain (d) without known size and distance. Figure reproduced with permission.

part of a clinical evaluation of pain and has mostly been restricted to neurodiagnostic and experimental procedures.[83;72] We have reported that threshold assessments are stable and reliable in repeated assessments.[84] We also found that the sensory thresholds had increased and the pain thresholds had decreased in pain patients as compared to healthy subjects. In another study, womens' pain thresholds were found to be lower than mens', and responses to TENS were indicated to be gender related – assessed as increased pain thresholds in women but not in men.[85]

Interestingly, the assessment of supra-threshold stimulation has been suggested as a prognostic tool for patients at risk of developing chronic pain.[86]

Matching strategies

Matching the perceived pain, ie a comparison of the intensity of clinical pain with pain derived from a different modality of stimulation, is an additional method for the assessment of pain from the psychophysical perspective,[63;72;87;88] and could serve as another strategy for pain assessment.

Properties of assessed pain

It has been suggested that pain data have linear or exponential distributions, or distributions without known size and distance, or just dichotomy into pain or no pain.[4;70;72] See Figure 2a-d for some examples of possible models of pain data.

In the evaluation of pain data the importance of psychometric characteristics has been acknowledged.[90] Support for metric properties of pain data using VAS comes from work based on direct magnitude scaling methods by means of thermal stimulation in healthy subjects,[70;90] supporting the ideas of psychophysical laws. In the area of psychophysics, general sensations like pain are studied with the goal of describing how a continuum of a sensation is represented in the mind.[91] The properties of these relations have been suggested to follow a logarithmic model (the Weber-Fechner Law) while Stevens, in 1970, suggested that the direct reports of subjective intensity are related to the physical intensity of stimuli by a linear relationship between the logarithm of the stimulus amplitude and the logarithm of the sensory experience.[92]

The general applicability of the psychophysical functions, however, has been questioned by Lockhead, who suggested that the scales are dynamic and that the judgement of a stimulus is dependent not only on its intensity but also on its duration, change of intensity, and relation to its environment.[93]

Implications for statistical evaluation

In psychophysics, the linear and ratio models have been suggested as preferred, since they allow for a simpler calculation of sums and differences, but also for the possibility of evaluating magnitude of pain, thereby allowing comparisons between subjects.[53;70]

The possibility of making statistical calculations and predictions is also given as the rationale for using ratio scales or scales with at least semi-ratio properties.[70;94] However, the assumptions of these models can never be perfectly met when analysing pain data of a group of individuals.[94]

Since rated pain is a subjective variable, pain data may be regarded as qualitative with an ordered structure but without metric properties of distance and magnitude, ie ordinal.[95;96] These rank invariant properties imply that arithmetical operations are not appropriate since a numeric ordinal record has no arithmetical meaning but only indicates the ordered structure.[95;97] Therefore, a change of the perceived pain can be assessed by transitional scales with the labels such as much better, somewhat better, unchanged, somewhat worse and much worse.[98] The concepts of interval and ratio levels of data proposed by Stevens (1946)[99] belong to quantitative data with complete metric properties,[100] and are therefore not regarded as appropriate to use in ordered categorical data.

Appropriate statistical approaches for analysis of pain data have been discussed.[97;101-104] Non-parametric methods are recommended since no assumption about the data is required for order, or that the data could be dichotomised into no pain or pain.[104-106] The non-metric properties of ordinal data imply that the median, quartiles, and range are the measures for description and that change in pain assessments can be categorised as increased, (+), unchanged, (0), or decreased, (-), see Figure 3.

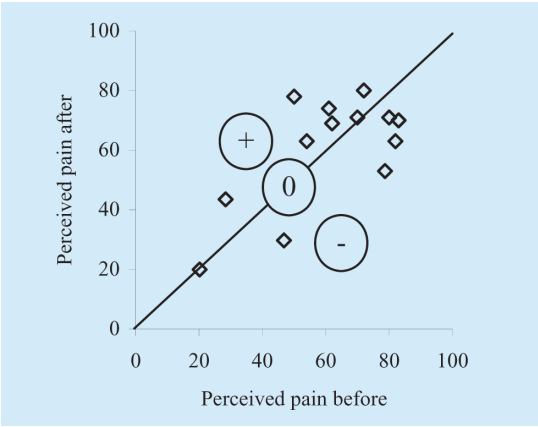

Figure 3 Paired data of rated pain before and after intervention shown as increased (+), unchanged (0) or decrease (-) in a scatter plot. Figure reproduced with permission.

According to the psychometric paradigm, some have recommended parametric methods with or without compensating for normality.[70;101;107] But we recommend caution in using such tests, especially when many patients (>16%) rank their pain at one of the extremes of the rating scale.[107] Furthermore, the use of parametric methods is restricted by the requirements of quantitative and normally distributed data or being transformed to better fit a normal distribution if these assumptions are not met.

As a result of statistical research, new methods taking into account the non-metric, ordered, categorical properties of data from scale assessments has been developed.[97] The methods for paired categorical data enable analyses of systematic and individual changes, but also for inter- and intra-observer agreement as well as comparisons between scales. The advantages of using statistical methods that do not require metric or other distributional properties of data are that the results are reliable and valid without restrictions and can also be used for small samples.

Implications

The personal experience of pain can only be judged by the person in pain. Therefore the evaluation of pain assessment and treatment effect should take the individual response into account.[108;109] However, present recommendations for treatment are based on studies evaluating the effects preferably on a group level. Using evaluating procedures from recent statistical research[97;110] it is possible to calculate individual as well as group effects.

Randomised controlled clinical trials (RCTs) have become the gold standard for evidence based medicine. Recommendations based solely on RCTs and evaluations of group effects may, therefore, circumvent the possibility of an effect on an individual level. RCTs commonly employ a placebo control group for the control of non-specific effects produced by therapy. The design of RCTs does not allow for evaluation of different types of non-specific effects.[111;112] Also, it is generally not possible to determine placebo response rates in RCTs, since a natural history group is often lacking. However, placebo control in studies using sensory stimulation is, by definition, impossible to conduct. Furthermore, in a recent study aimed at elucidating the placebo response rates in RCTs it was demonstrated that non-

specific treatment effects are more important than specific effects.[113] This highlights the importance of evaluating the non-specific treatment effects.

In a future study, a combination of RCT and naturalistic designs could be adopted.[114;115] Naturalistic studies, where the choice of, for instance, mode of stimulation and number of treatments is offered to patients, are less likely to misrepresent the relationship and influence of these factors upon the assessed outcome when incorporated into standard (randomised) biomedical designs. In this way, a further optimisation of the therapeutic effects would be likely. Furthermore, a naturalistic approach may mimic the practical use of an intervention in a clinical context more closely.

Conclusion

In conclusion, we have described and discussed the importance of evaluating both the systematic and the individual responses in different pain assessment methods and thereby emphasised not only the need to consider individual responses in the evaluation of pain and variables associated with pain, but also the need for individually designed treatment regimens. However, evaluation of assessed pain should take both systematic and individual variation into consideration. Our findings suggest that the assessment of pain intensity on the Visual Analogue Scale is not interchangeable with assessment on the Verbal Rating Scale and that threshold assessment may be an additional, valuable tool for clinical evaluation given gender separated analyses. Biochemical markers, such as urinary CRF-LI concentrations may be used for measurement of stress related symptoms in pain conditions.

Reference list

1. Kanda M, Matsuhashi M, Sawamoto N, Oga T, Mima T, Nagamine T, et al Cortical potentials related to assessment of pain intensity with visual analogues scale (VAS). *Clin Neurophysiol* 2002;113:1013-24.
2. Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. Pain 2002;95:1-5.
3. Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Chen AC. Psychophysical and EEG responses to repeated experimental muscle pain in humans: Pain intensity codes EEG activity. *Brain Res Bull* 2003;6:533-43.
4. Donaldson GW, Chapman CR, Nakamura Y, Bradshaw DH, Jacobson RC, Chapman CN. Pain and the defense response: structural equation modeling reveals a coordinated psychophysiological response to increasing painful stimulation. *Pain* 2003;102:97-108.
5. Berntson L, Svensson E. Pain assessment in children with juvenile chronic arthritis; a matter of scale and rater. *Acta Paediatr* 2001;90:1131-36.
6. Mantyselka P, Kumpusalo E, Ahonen R, Takala J. Patients' versus general practitioners' assessments of pain intensity in primary care patients with non-cancer pain. *Br J Gen Pract* 2001;51:995-7.
7. Harstall C, Ospina M. How prevalent is chronic pain? [newsletter] *Pain Clinical Updates* 2003;XI:1-4.
8. Gerdle B, Bjork J, Henriksson C, Bengtsson A. Prevalence of current and chronic pain and their influences upon work and healthcare-seeking: a Population study. *J Rheumatol* 2004;31:1399–406.
9. Mantyselka PT, Turunen JH, Ahonen RS, Kumpusalo EA. Chronic pain and poor self-rated health. *JAMA* 2003;290:2435-42.
10. Scudds RJ, Scudds RA, Simmonds MJ. 2001 Pain in the physical therapy (pt) curriculum: a faculty survey. *Physiother Theory Practice* 2001;17:239-56.
11. Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci* 2003;26:303-7.
12. Merskey H, Bogduk N. *Classification of Chronic Pain.* 2nd ed. Seattle: IASP Press: 1994. p. 209-14.
13. Melzack R, Casey KL. Sensory, motivational and central control determinants of pain: 4 new conceptual models. In: Kenshalo D, editor. *The skin senses.* Springfield, IL: Charles C. Thomas; 1968. p. 423-39.
14. Villanueva L, Bing Z, Bouhassira D, Le Bars D. Encoding of electrical, thermal, and mechanical noxious stimuli by subnucleus reticularis dorsalis neurons in the rat medulla. *J Neurophysiol* 1989;61:391-402.
15. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol* 1997;14:2-31.
16. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769-72.
17. von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. *Spine* 2000,25:3140-51.
18. Melzack R, Coderre TJ, Katz J, Vaccarino AL. Central neuroplasticity and pathological pain. *Ann N Y Acad Sci* 2001;933:157-74.
19. Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci* 2002;5 Suppl:1062-67.
20. Niv D, Devor M. Chronic pain as a disease in its own right. *Pain Practice* 2004;4:179-81.
21. Lundberg D, chair. *Methods for treating chronic, non-malignant pain*. Stockholm: The Swedish Council on Technology Assessment in Health Care; 2006. No 177, vol 1-2.
22. Riedel W, Schlapp U, Leck S, Netter P, Neeck G. Blunted ACTH and cortisol responses to systemic injection of corticotrophin-releasing hormone (CRH) in fibromyalgia: role of somatostatin and CRH-binding protein. *Ann N Y Acad Sci* 2002;966;483-90.
23. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. *Psychosom Med* 2004;66: 837-44.
24. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum* 2005;52:1577-84.

25. Lundeberg T, Ekholm J. Pain from periphery to brain. *Disabil Rehabil* 2002;24:402-6.
26. Wincent A, Liden Y, Arner S. Pain questionnaires in the analysis of long lasting (chronic) pain conditions. *Eur J Pain* 2003;7:311-21.
27. Woolf CJ; American College of Physicians; American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004;140:441-51.
28. Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. *Curr Rheumatol Rep* 2000;2:116-23.
29. Neeck G, Pathogenic mechanisms of fibromyalgia, *Ageing Res Rev* 2002;1:243-55.
30. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann N Y Acad Sci* 1998;840:684-97.
31. Neeck G, Riedel W. Hormonal perturbations in fibromyalgia syndrome. *Ann N Y Acad Sci* 1999;876:325-38.
32. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotrophin-releasing factor in depression and anxiety disorders. *J Endocrinol* 1999;160:1-12.
33. Baraniuk JN, Maibach H, Whalen G, Clauw DJ. Covariates of corticotropin-releasing hormone (CRH) concentrations in cerebrospinal fluid (CSF) from healthy humans. *BMC Neurosci* 2004;5(1):58.
34. Barden N. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. *J Psychiatry Neurosci* 2004;29:185-93.
35. Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry* 1997; 154:624-9.
36. Crofford LJ. Neuroendocrine abnormalities in fibromyalgia and related disorders. *Am J Med Sci* 1998;315:359-66.
37. Lund I, Lundeberg T, Carleson J, Sonnerfors H, Uhrlin B, Svensson E. Corticotropin releasing factor in urine—a possible biochemical marker of fibromyalgia. Responses to massage and guided relaxation. *Neurosci Lett* 2006a; 403:166-71
38. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci* 1984;7:309-38.
39. Rainville P. Brain mechanisms of pain affect and pain modulation. Curr Opin Neurobiol 2002;12:195-204.
40. Le Bars D. The whole body receptive field of dorsal horn multireceptive neurones. *Brain Res Brain Res Rev* 2002; 40:29-44.
41. Han JS. Acupuncture and endorphins. *Neurosci Lett* 2004; 361:258-61.
42. Millan MJ. Descending control of pain. *Prog Neurobiol 2002;66:355-474.*
43. Bodnar RJ, Klein GE. Endogenous opiates and behavior: 2004. *Peptides* 2005;26:2629-711.
44. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971-9.
45. Andersson S, Lundeberg T. Acupuncture—from empiricism to science: functional background to acupuncture effects in pain and disease. *Med Hypotheses* 1995;45:271-81.
46. Barlas P, Lundeberg T. Transcutaneous electrical nerve stimulation and acupuncture. In: McMahon SB, Koltzenburg M (red.).Wall and Melzack's *Textbook of pain* 5th ed.. Philadelphia: Elsevier Churchill Livingstone; 2006. p. 583-91
47. Widerstrom EG, Aslund PG, Gustafsson LE, Mannheimer C, Carlsson SG, Andersson SA. Relations between experimentally induced tooth pain threshold changes, psychometrics and clinical pain relief following TENS. A retrospective study in patients with long-lasting pain. *Pain* 1992;51:281-7.
48. Chesterton LS, Barlas P, Foster NE, Lundeberg T, Wright CC, Baxter GD. Sensory stimulation (TENS): effects of parameter manipulation on mechanical pain thresholds in healthy human subjects. *Pain* 2002;99:253-62.
49. He D, Veiersted KB, Hostmark AT, Medbo JI. Effect of acupuncture treatment on chronic neck and shoulder pain in sedentary female workers: a 6-month and 3-year follow-up study. *Pain* 2004;109:299-307
50. Turk DC. The role of psychological factors in chronic pain. *Acta Anaesthesiol Scand* 1999;43:885-8.
51. Rollman GB, Lautenbacher S, Jones KS: Sex and gender differences in responses to experimentally induced pain in humans. In Fillingim RB (ed): *Sex, gender and pain. Progress in Pain Research and Management,* Vol. 17. Seattle: IASP Press; 2000. p. 165-90.
52. Ploghaus A, Becerra L, Borras C, Borsook D. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. *Trends Cogn Sci* 2003;7:197-200.
53. de C Williams AC, Davies HT, Chadury Y. Simple pain rating scales hide complex idiosyncratic meanings. *Pain* 2000;85:457-63.
54. Rosier EM, Iadarola MJ, Coghill RC. Reproducibility of pain measurement and pain perception. *Pain* 2002;98: 205-16.
55. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. *Pain Forum* 1995;4: 209-21.
56. Unruh A. Gender variations in clinical pain experience. Pain 1996;65:123-67.
57. Berkley KJ. Sex differences in pain. *Behav Brain Sci* 1997; 20:371-80.
58. Wise EA, Price DD, Myers CD, Heft MW, Robinson ME. Gender role expectations of pain: relationship to experimental pain perception. *Pain* 2002;96:335-42.
59. Philadelphia Panel. Evidence-Based Clinical Practice Guidelines on Selected Rehabilitation Interventions: Overview and Methodology. *Phys Ther* 2001;81:1629-40.
60. Bond MR, Pilowsky I. Subjective assessment of pain and its relationship to the administration of analgesics in patients with advanced cancer. *J Psychosom Res* 1966;10:203-8.
61. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain measurement. *Pain* 1981;10:241-8.
62. Keele KD. The pain chart. *Lancet* 1948;2:6-8.
63. Borg G. Psychophysical scaling: An overview. In: Boivie J, Hansson P, Lindblom U, editors. *Touch, temperature, and pain in health and disease: Mechanisms and assessments.* Seattle: IASP Press; 1993. p. 27-39.
64. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;1:277-99.
65. Wiklund I, Dimenas E. The Swedish version of the Nottingham Health Profile. A questionnaire for the measurement of health-related quality of life. *Lakartidningen* 1990;87:1575-6 (In Swedish).

66. McQuay H. Consensus on outcome measures for chronic pain trials. *Pain* 2005;113:1-2.
67. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9-19.
68. Lund I, Lundeberg T, Sandberg L, Budh CN, Kowalski J, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. *BMC Med Res Methodol* 2005;5:31.
69. Hardy JD, Wolff HG, Goodell H. Studies on pain. A new method for measuring pain threshold; observation on spatial summation of pain. *J Clin Invest* 1940;19;649-57.
70. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45-56.
71. Riley JL 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain* 1998:74; 181-7.
72. Gracely RH. Studies of pain in normal man. In: Wall PD, Melzack R, editors. *Textbook of Pain.* 4th ed. London: Churchill Livingstone; 1999. p. 385-407.
73. Gracely RH. Psychophysical assessment of human pain. In: Bonica JJ et al., eds. *Advances in pain research and therapy,* Vol 3. New York: Raven Press; 1979. p. 805-24.
74. Ohrbach R, Crow H, Kamer A. Examiner expectancy effects in the measurement of pressure pain thresholds. *Pain* 1998;74:163-70.
75. Ashkinazi IYa, Vershinina EA. Pain sensitivity in chronic psychoemotional stress in humans. *Neurosci Behav Physiol* 1999;29:333-7.
76. Wilder-Smith CH, Hill L, Spargo K, Kalla A. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAID's: a randomised study comparing analgesia, antinociception and gastrointestinal effects. *Pain* 2001;91:23-31.
77. Alstergren P, Forstrom J. Acute oral pain intensity and pain threshold assessed by intensity matching to pain induced by electrical stimuli. *J Orofac Pain* 2003;17:151-9.
78. Malow RM, Grimm L, Olson RE. Differences in pain perception between myofascial pain dysfunction patients and normal subjects: a signal detection analysis. *J Psychosom Res* 1980;24:303-9.
79. Sandrini G, Martignoni E, Micieli G, Alfonsi E, Sances G, Nappi G. Pain reflexes in the clinical assessment of migraine syndromes. *Func Neurol* 1986;1:423-9.
80. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain* 1996;64:415-23.
81. Moller AR, Pinkerton T. Temporal integration of pain from electrical stimulation of the skin. *Neurol Res* 1997;19: 481-8.
82. Edwards RR, Sarlani E, Wesselmann U, Fillingim RB. Quantitative assessment of experimental pain perception: multiple domains of clinical relevance. *Pain* 2005;114:315–9.
83. Dotson RM. Clinical neurophysiology laboratory tests to assess the nociceptive system in humans. *J Clin Neurophysiol* 1997;14:32-45.
84. Lund I, Lundeberg T, Kowalski J, Sandberg L, Budh CN, Svensson E. Evaluation of variations in sensory and pain threshold assessments by electrocutaneous stimulation. *Physiother Theory Pract* 2005;21:81-92.
85. Lund I, Lundeberg T, Kowalski J, Svensson E. Gender differences in electrical pain threshold responses to transcutaneous electrical nerve stimulation (TENS). *Neurosci Lett* 2005;375:75-80.
86. Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. *Neurology* 2005;65:437-43.
87. Price DD. Psychophysical measurement of normal and abnormal pain processing. In: Boivie J, Hansson P, Lindblom U, editors. *Touch, temperature, and pain in health and disease: Mechanisms and assessments*. Seattle: IASP Press; 1993. p. 3-25.
88. Lundeberg T, Lund I, Dahlin L, Borg E, Gustafsson C, Sandin L et al. Reliability and responsiveness of three different pain assessments. *J Rehabil Med* 2001;33(6): 279-83.
89. Turk DC, Melzack R (Eds). Trends and future directions in human pain assessment, pp 707-715. In: *Handbook of pain assessment.* 2nd edition. The Guilford Press, New York, London 2001.
90. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994;56:217-26.
91. Ottoson D. *Physiology of the Nervous System*. Oxford: Oxford University Press; 1989.
92. Stevens SS. Neural events and the psychophysical law. *Science* 1970;170:1043-50.
93. Lockhead GR. Psychophyscial scaling: Judgements of attributes or objects? *Behav Brain Sci* 1992;15:543-601.
94. Borg G, Borg E. A new generation of scaling methods: Level-anchored ratio scaling. *Psychologica* 2001;28:15-45.
95. Merbitz C, Morris J, Grip JC. Ordinal scales and foundations of misinference. *Arch Phys Med Rehabil* 1989;70:308-12.
96. Hand DJ. Statistics and the theory of measurement. *J R Statist Soc A* 1996;159:445-92.
97. Svensson E. *Analysis of systematic and random differences between paired ordinal categorical data* (dissertation). Stockholm: Almqvist & Wiksell International; 1993.
98. Kramer MS, Feinstein A. Clinical biostatistics LIV The biostatistics of concordance. *Clin Pharmacol Ther* 1981;29:111-23.
99. Stevens SS. On the theory of scales of measurement. *Science* 1946;103:677-80.
100. Siegel S, Castellan NJ. *Nonparametric Statistics for the Behavioral Sciences.* 2nd ed. Singapore: McGraw-Hill; 1988.
101. Maxwell C. Sensitivity and accuracy of the visual analogue scale: a psycho-physical classroom experiment. *Br J Clin Pharmac* 1978;6:15-24.
102. Philip BK. Parametric statistics for evaluation of the visual analogue scale. *Anesth Analg* 1990;71:710.
103. Akhtar-Danesh N. A review of statistical methods for analysing pain measurements. *Eur J Pain* 2001;5:457-63.
104. Svensson E. Guidelines to statistical evaluation of data from rating scales and questionnaires. *J Rehab Med* 2001;33:47-8.

105. Huskisson EC. Measurement of pain. *J Rheumatol* 1982;9:768-9.
106. Altman DG. *Practical statistics for medical research.* London: Chapman & Hall; 1991.
107. Dexter F, Chestnut DH. Analysis of statistical tests to compare visual analog scale measurements among groups. *Anesthesiology* 1995;82:896-902.
108. Dionne RA, Bartoshuk L, Mogil J, Witter J. Individual responder analyses for pain: does one pain scale fit all? *Trends Pharmacol Sci* 2005;26:125-30.
109. Asenlof P, Denison E, Lindberg P. Individually tailored treatment targeting activity, motor behavior, and cognition reduces pain-related disability: a randomized controlled trial in patients with musculoskeletal pain. *J Pain* 2005;6:588-603.
110. Svensson E. Ordinal invariant measures for individual and group changes in ordered categorical data. *Stat Med* 1998;17:2923-36.
111. Thomas M, Eriksson SV, Lundeberg T. A comparative study of diazepam and acupuncture in patients with osteoarthritis pain: a placebo controlled study. *Am J Chin Med* 1991;19:95-100.
112. Hui KK, Liu J, Marina O, Napadow V, Haselgrove C, Kwong KK, Kennedy DN, Makris N. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. *Neuroimage* 2005;27:479-96.
113. Walach H, Sadaghiani C, Dehm C, Bierman D. The therapeutic effect of clinical trials: understanding placebo response rates in clinical trials—a secondary analysis. *BMC Med Res Methodol* 2005;5:26.
114. Thomas M, Lundeberg T. Importance of modes of acupuncture in the treatment of chronic nociceptive low back pain. *Acta Anaesthesiol Scand* 1994;8:63-9.
115. Leichsenring F. Randomized controlled versus naturalistic studies: a new research agenda. *Bull Menninger Clin* 2004;68:137-51.