Topical Review

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Must we reduce pain intensity to treat chronic pain?

Mark D. Sullivan[a,*], Jane C. Ballantyne[b]

The idea that physicians have a duty to relieve human suffering dates back to antiquity. However, the notion that suffering can be quantified and monitored as a pain level is a much more recent development. A corollary to this quantitative approach to pain assessment is the notion that pain treatment should be "titrated to effect" on a measured pain intensity level. The titrate to effect principle was developed for treating acute and cancer pain, but was then extended to outpatient treatment of chronic noncancer pain. Because opioids have no strict ceiling dose and may produce rapid and marked reductions in pain intensity, they are uniquely suitable for titrating to effect. The idea that opioids should be used at whatever dose produces a satisfactory reduction in pain intensity, and especially the extension of this principle to chronic pain treatment, has led to dramatic increases in opioid prescribing in many developed countries.[12] Unfortunately, this increased use has been accompanied by increases in opioid abuse, overdose, and death without any significant easing of the population burden of chronic pain.[2,7,21,33,53] In this article, we will argue that focusing on pain intensity for the assessment and care of patients with chronic pain (1) establishes the wrong goal for care, (2) results in the selection of the wrong patients for the strongest analgesics, and (3) retards our understanding of chronic pain.

Let us consider our duty toward the following patient: Mr. Harris is a 41-year-old man who has had axial low back pain for 1 year. He has just moved into town and comes for his first appointment with you, his new primary care physician. A previous lumbar magnetic resonance imaging showed a disk bulge at L5–S1 and some degenerative changes at the other levels, but there is no evidence on physical examination for nerve root irritation. He rates his average pain intensity as 10/10. He takes oxycodone sustained-release 20 mg b.i.d, which used to provide him significant relief, but no longer does. He wants his opioids increased until they relieve his pain. He explains that this was the treatment goal that he agreed on with his previous physician, who had called it the titrate to effect principle. When you express doubt as to whether an opioid dose increase is the right treatment, he responds, "Don't you believe I am in pain? Don't you believe that I deserve relief? Do you just want me to suffer?" You are confused. You do believe Mr. Harris is in pain and deserves relief, but you doubt that escalating his opioid dose will provide him a lasting and overall benefit.

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Departments of [a] Psychiatry and Behavioral Sciences and, [b] Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA

**Corresponding author. Address: Psychiatry and Behavioral Sciences, University of Washington, Box 356560, Seattle, WA 98195, USA. Tel.: (206) 685-3184; fax: (206) 221-5414. E-mail address: sullimar@uw.edu (M. D. Sullivan).*

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1. Establishing the right to pain relief

When beginning his 1953 work "Management of Pain," John Bonica argued that pain is not just a symptom of disease, but worthy of attention on its own. The struggle to legitimize pain that is not clearly caused by disease or injury goes on to this day. One clinical domain in which the argument for a right to pain relief was successful, was palliative care. In the 1970s and 1980s, the argument was made that it is morally unacceptable for patients to die in pain, unless this is chosen by the patient. Various long-standing concerns, including the danger of "dying addicted" and fears of inappropriately hastening death, were discredited. The right to pain relief at the end of life is captured best in a 1989 article in the *New England Journal of Medicine* by Wanzer et al stating "The proper dose of pain medication is the dose that is sufficient to relieve pain and suffering… To allow a patient to experience unbearable pain or suffering is unethical medical practice."[69]

Around the same time, a similar argument was made that pain relief should be a standard and essential component of cancer care. International, national, and state-based initiatives sought to improve the care of patients with cancer pain and liberalize their access to opioids. The World Health Organization disseminated the step-ladder approach to cancer pain treatment.[7] Step 1 included nonopioid analgesics. Step 2 included these non-opioid analgesics plus weak opioid analgesics. Step 3 included these non-opioid and weak opioid analgesics plus strong opioid analgesics. Each step also included adjuvant therapies. The underlying principle of the stepladder approach was that analgesic doses should be escalated with the aim of reducing the pain level as much as possible.

2. Pain intensity as measure of treatment need

In the following decades, the idea that pain intensity is the best measure of the need for pain treatment has spread from palliative care and cancer pain to the treatment of chronic noncancer pain. In his presidential address before the American Pain Society in 1996, James Campbell introduced the idea of pain as the fifth vital sign. He stated, "if pain were assessed with the same zeal as other vital signs are, it would have a much better chance of being treated properly."[1] The American Pain Society advocated the assessment of "Pain, the fifth Vital Sign" along with a patient's traditional vital signs: pulse, blood pressure, temperature, and respiration. Other health care organizations followed suit. In 1998, the US Veterans Health Administration (VHA) enacted a national strategy to improve pain management.[16] This strategy required providers to assess the patient's pain intensity, as measured on a 0-to-10 Numeric Rating Scale (NRS), and record this in their electronic medical record. It was also noted that a pain score of 4 or higher should trigger a comprehensive pain assessment and prompt intervention.[15] By 2005, quantitative pain assessment was occurring in over 90% of the clinical encounters across the VHA. But multiple studies have questioned whether this has improved pain care in the VHA.[42,51,72]

In 2001, the body responsible for accrediting US health care organizations (The Joint Commission, previously known as Joint Commission for Accreditation of Healthcare Organizations [JCAHO]) followed the suggestion of a group of pain advocates and mandated national pain assessment and management standards.[36] Although JCAHO did not specifically require the use of the 0-to-10 NRS, this became the most common way the mandate was implemented. It is notable that in 2015 The Joint Commission is revising its pain treatment standard to include nonpharmacological treatments, but is not revising its pain assessment standard.[61]

3. Pain intensity is the wrong goal for chronic pain treatment

Does pain intensity measurement provide a good assessment of the burdens of chronic pain for a patient? The experience of chronic pain is not simply the perception of an aversive sensation of some specific intensity.[52] It can become a disruption in one's ability to live the life that one values. A National Institutes of Health task force on research standards for chronic low back pain has recently recommended that a minimal dataset to characterize the impact of chronic low back pain should include pain intensity, pain interference, and physical function.[17] It further recommended that patients be characterized in terms of depression, sleep disturbance, catastrophic and fear-avoidance cognitions, work disability, substance abuse, and treatments received. All these measures have personal and prognostic significance for patients with chronic low back pain.

In modern medicine, pain and suffering are often conflated: severe physical pain is equated with extreme suffering. But if pain is a means to a reward, it may be both intense and tolerable. Intense postoperative pain may be tolerable because it signifies healing; triathletes tolerate pain as a means to fitness or victory; and most women tolerate labor pain without medication as a means to childbirth.[3,25,40] But pain that has no meaning or known end may produce great suffering, not only because of its intensity but also because it poses a threat to one's integrity.[9] As stated by the contemporary philosopher Daniel Dennett: "Suffering is not a matter of being visited by some ineffable but intrinsically awful state, but of having one's life hopes, life plans, life projects blighted by circumstances imposed on one's desires, thwarting one's intentions—whatever they are."[14] A recent meta-analysis of laboratory pain and chronic pain studies found that pain intensity, impairment, affective distress, and passive coping were all strongly related to the appraisal of pain as a threat.[34]

Suffering and disability are more associated with the meaning of chronic pain than with its intensity. Over time, pain intensity becomes linked less with nociception and more with emotional and psychosocial factors.[47] A prospective functional magnetic resonance imaging study of patients with low back pain showed that as back pain evolves from acute/subacute to chronic, the associated brain activity shifts from regions involved in acute pain to emotion-related circuitry.[30] Depression and stress mediate the effect of pain on disability in wrist fracture patients.[55] In physical trauma patients, anxiety predicts pain better than pain predicts anxiety, and the role of anxiety in predicting functional deficits increases over time.[10] The impact of pain on the quality of life is more strongly associated with treatment preferences than is pain intensity.[23] Among persons with physical disabilities, pain and dysfunction are strongly predicted by catastrophizing, task persistence, and social support.[35]

Cognitions such as catastrophizing and fear avoidance may also come to overshadow nociception over time. Moseley and Vlayen recently advanced "the imprecision hypothesis of chronic pain," which postulated that chronic pain may begin as an unconditioned response to nociception, but may persist as the conditioned and "imprecise" response to fear-avoidance behavior.[48,50] On this view, pain has ceased to be the origin of suffering and is merely a component of a vicious cycle of suffering and disability. Patients with fibromyalgia, for example, tend to overgeneralize movement-related fear.[49] If visual feedback is manipulated to overstate the amount of neck rotation, patients get neck pain with less rotation than seen in the absence of manipulated visual feedback.[29]

Acceptance of pain, however, has a beneficial effect on suffering and disability. McCracken and Vowles have shown that the 2 primary aspects of pain acceptance that are important are: (1) willingness to experience pain and (2) engagement in valued life activities despite the pain experience. Acceptance of pain is not well correlated with its intensity, ie, it is not simply those persons with less pain who are willing to accept pain.[46] Other studies have demonstrated that pain willingness and activity engagement predict pain interference and depression more strongly than pain intensity.[41,68] Pain intensity is only a part of the chronic pain experience, and may not be the most important part for patients' suffering and disability.

When pain progresses in a predictable fashion tied to nociception, as it does soon after an injury or at the end of life, the intensity rating is a useful tool for assessing the need for and success of treatment. But in the case of chronic pain, how should we interpret and respond to a pain rating? Long ago, Bill Fordyce advocated approaching pain ratings as a form of pain behavior.[45] A chronic pain rating is a personal communication about a complex and life-altering problem. In a recent Veterans Affairs study, the correlation between the pain intensity NRS scores obtained by clinical staff and those obtained by research staff at the same clinical visit were not strong ($r = 0.56$). The clinically obtained score was lower than the research-obtained score, especially in patients with diabetes, posttraumatic stress disorder (PTSD), major depression, or in patients of non-white race.[28] This suggests we should interpret pain rating in terms of the situation in which it is provided and the persons who are providing and receiving it.

A clinical and ethical policy focussing on pain intensity reduction by means of titrated opioid therapy may have contributed to the rapid escalation in prescription opioid use, abuse, and overdose seen in the US, Canada, Australia, and other countries.[20,26,27,60,65] We know from randomized trials that opioids reduce chronic pain on an average approximately 30% more than placebo after 12 weeks of treatment, but other medication and nonmedication treatments that are proven to work for chronic pain, produce smaller and slower changes in pain intensity ratings. For example, duloxetine and pregabalin are approved for the treatment of diabetic neuropathy and fibromyalgia, yet they reduce pain by no more than 1 point of 10, compared to placebo.[43,64,71] The most effective psychosocial treatments for chronic pain also show only modest reductions in pain intensity. Cognitive-behavioral therapy for fibromyalgia produces 0.5 points of 10 more pain reduction than controls.[4] Multidisciplinary pain rehabilitation programs reduce pain by 37% or 1 to 2 points of 10.[32] If patients and prescribers are titrating treatment to effect on pain intensity, they will tend to favor opioid over nonopioid chronic pain treatments.

Furthermore, it is not clear whether these proven nonopioid chronic pain treatments produce their benefit primarily by decreasing pain intensity. Although many patients understand chronic pain to be the cause of their many problems in living,

clinical treatments for chronic pain often improve sleep, mood, or functional status before they improve pain. A variety of research studies suggest that nonopioid chronic pain treatments affect pain intensity indirectly or secondarily. The effect of pregabalin on the 8 subscales of the SF-36 general health status measure is only partially mediated by pain reduction.[66] Other analyses demonstrate that pregabalin pain relief is preceded and predicted by sleep improvement.[67] In another study, improvements in *both* pain and depression after 2 weeks of venlafaxine treatment predicted the amount of improvement in pain at 6 weeks.[54] Multidisciplinary pain rehabilitation programs and cognitive-behavioral treatments of chronic pain often produce earlier and more marked reductions in pain-related disability than pain intensity.[37,44] Thus many of the chronic pain treatments that produce the most lasting and comprehensive benefit to patients, do not affect pain intensity ratings substantially or primarily. They address the suffering and disability aspects of chronic pain problems and thereby improve patients' lives. This suggests that pain intensity reduction may be the wrong goal for chronic pain treatment.

4. Pain intensity results in selection of the wrong patients for treatment with the strongest analgesics

Patients who report chronic pain of very high intensity (eg, 10/10) may actually be the patients who will benefit least from the most potent analgesics.[7,8,22] The higher the pain intensity reported for chronic musculoskeletal conditions, the larger the role played by depression and anxiety.[5] These psychiatric problems have been interpreted as the consequence of severe chronic pain, but anxiety disorders, in particular, often precede the onset of chronic pain.[38] Both physical and psychological trauma contribute to the course and severity of chronic pain.[59] Current and past depressive and anxiety disorders have been associated with pain of greater intensity.[13] Patients, such as Mr. Harris, who report 10/10 chronic pain, are often overwhelmed, with psychiatric comorbidities that can worsen with opioid treatment, such as PTSD, major depressive disorder or substance use disorders.[62] Prescribing opioids for patients with the highest chronic pain intensity ratings may select those who are least likely to benefit and most likely to be harmed by opioids. Reports of pain intensity need to be interpreted in light of other measures, such as function, quality of life, satisfaction with care, and progress in life, before they are translated into treatment recommendations. By themselves, even the highest chronic pain intensity ratings may not be a sufficient reason to treat with the strongest opioid analgesics.

Although all treatment guidelines concerning opioid treatment of chronic pain recommend caution in use of long-term opioid therapy in patients with substance abuse and mental health disorders,[11] multiple studies of clinical practice show that these patients are in fact, the most likely to be treated with opioids, at higher doses, for longer periods of time, and with concurrent sedative hypnotic medications.[19,39,58,70] These patients have higher rates of opioid adverse events including overdose, abuse, and emergency department visits.[6,63] We have termed this pairing of high-risk patients with high-risk opioid regimens "adverse selection" to highlight the contrast with the "careful selection" recommended in treatment guidelines. In practice it is often the highest risk patients who are are selected for opioid therapy because they report the highest pain intensity levels.[18,31,39]

Axial low back pain is extremely common. Mr. Harris, like many other patients, was given opioids because he reported severe 10/10 pain. But has opioid treatment reduced his suffering and disability? His pain has not actually improved, he has been put at risk of opioid dependence, he has been deactivated instead of activated, and he has likely entered the vicious cycle in which no dose of opioid will ever be enough. His life has been consumed with an unrealistic search for an unattainable goal. We contend that we would see better results if treatment were aimed at the pain diagnosis and prognosis, but not at the pain intensity rating. A 10/10 pain score may be telling us about a need for skill development and psychological therapy and not simply a need for medication.

5. A focus on pain intensity retards our understanding of chronic pain

Most clinicians now accept that the intensity of chronic pain cannot be predicted reliably based on the severity or extent of tissue damage. We accept that chronic pain's intensity and course are not primarily determined by nociception. We recognize that most chronic pains are not progressive, but follow an unpredictable course determined by history, resources, and context. Yet most pain clinicians still think of chronic pain as a persistent sensation of specific intensity. To treat patients like Mr. Harris with chronic pain, for which the cause cannot be identified, many clinicians aim for what seems to be the root of the problem, ie, the chronic pain itself. By attempting to reduce his chronic pain, we seek to restore his life. But opioid treatment focused on reducing pain intensity often increases both disability and suffering.[24,56,57] Chronic pain often does not just cause disability and suffering, but is caused by them in a vicious cycle of infirmity and misery.

6. Conclusions

Striving to eliminate or minimize chronic pain through opioid therapy has led to the iatrogenic injury of patients and the general population. We propose that the root problem may be neither the high risks nor the low efficacy of long-term opioid therapy, but rather an improper focus on reducing pain intensity. Our duty to patients with chronic pain is not to reduce pain intensity, but to improve their quality of life. It is surely not humane to provide aggressive opioid pain management aimed at reducing pain intensity if it consigns a patient to serious and potentially life-long opioid adverse effects. The idea that opioids titrated to pain intensity can reliably reduce chronic pain and improve quality of life not only exposes patients to harm but also to unrealistic and potentially damaging expectations for those in pain, and for clinicians. What matters ultimately is not whether the patient's pain intensity has reduced, but whether the patient's life has improved.

Conflict of interest statement

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References

[1] American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. Glenview: American Pain Society, 1999.
[2] Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain 2008;24:469–78.

[3] Benedetti F, Thoen W, Blanchard C, Vighetti S, Arduino C. Pain as a reward: changing the meaning of pain from negative to positive co-activates opioid and cannabinoid systems. PAIN 2013;154:361–7.
[4] Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. Cochrane Database Syst Rev 2013;9:CD009796.
[5] Blozik E, Laptinskaya D, Herrmann-Lingen C, Schaefer H, Kochen MM, Himmel W, Scherer M. Depression and anxiety as major determinants of neck pain: a cross-sectional study in general practice. BMC Musculoskelet Disord 2009;10:13.
[6] Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 2010;170:1425–32.
[7] Cancer pain relief, World Health Organization. Expert Committee on Cancer Pain Relief and Active Supportive Care. Geneva: World Health Organization, 1986.
[8] Carr DB. Acute Pain Managment: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. Rockville: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, 1992. AHCPR Pub No 92-0032.
[9] Cassell E. The Nature of Suffering and the Goals of Medicine. New York: Oxford University Press, 2004.
[10] Castillo RC, Wegener ST, Heins SE, Haythornthwaite JA, Mackenzie EJ, Bosse MJ, Group LS. Longitudinal relationships between anxiety, depression, and pain: results from a two-year cohort study of lower extremity trauma patients. PAIN 2013;154:2860–6.
[11] Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10:113–30.
[12] Daubresse M, Chang HY, Yu Y, Viswanathan S, Shah ND, Stafford RS, Kruszewski SP, Alexander GC. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Med Care 2013;51:870–8.
[13] de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, Spinhoven P, Penninx BW, van der Feltz-Cornelis CM. The association of depression and anxiety with pain: a study from NESDA. PLoS One 2014;9:e106907.
[14] Dennett D. Consciousness Explained. New York: Little Brown Publishing, 1991.
[15] Department of Veterans Affairs Geriatrics and Extended Care Strategic Healthcare Group NPMCC. Pain: The 5th Vital Sign. Veterans Health Administration, Washington DC. 2000.
[16] Department of Veterans Affairs Veterans Health Administration. Pain Management: VHA Directive 2009-053. Veterans Health Administration, Washington DC. 2009.
[17] Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino J, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Von Korff M, Weiner DK. Focus article: report of the NIH Task Force on Research Standards for Chronic Low Back Pain. Eur Spine J 2014;23:2028–45.
[18] Dobscha SK, Morasco BJ, Duckart JP, Macey T, Deyo RA. Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clin J Pain 2013;29:102–8.
[19] Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. Clin J Pain 2010;26:1–8.
[20] Ekholm O, Kurita GP, Hojsted J, Juel K, Sjogren P. Chronic pain, opioid prescriptions, and mortality in Denmark: a population-based cohort study. PAIN 2014;155:2486–90.
[21] Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain. An epidemiological study. PAIN 2006;125:172–9.
[22] Foley KM. The treatment of pain in the patient with cancer. CA Cancer J Clin 1986;36:194–215.
[23] Fraenkel L, Falzer P, Fried T, Kohler M, Peters E, Kerns R, Leventhal H. Measuring pain impact versus pain severity using a numeric rating scale. J Gen Intern Med 2012;27:555–60.
[24] Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM, Disability Risk Identification Study Cohort. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. Spine (Phila Pa 1976) 2008;33:199–204.
[25] Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. PAIN 2013;154:2317–23.
[26] Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. Addiction 2014;109:1482–8.
[27] Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-dose opioid prescribing in Canada. Can Fam Physician 2014;60:826–32.
[28] Goulet JL, Brandt C, Crystal S, Fiellin DA, Gibert C, Gordon AJ, Kerns RD, Maisto S, Justice AC. Agreement between electronic medical record-based and self-administered pain numeric rating scale: clinical and research implications. Med Care 2013;51:245–50.
[29] Harvie DS, Broecker M, Smith RT, Meulders A, Madden VJ, Moseley GL. Bogus visual feedback alters onset of movement-evoked pain in people with neck pain. Psychol Sci 2015;26:385–92.
[30] Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136(Pt 9):2751–68.
[31] Henry SG, Wilsey BL, Melnikow J, Iosif AM. Dose escalation during the first year of long-term opioid therapy for chronic pain. Pain Med 2015;16:733–44.
[32] Hoffman JM, Pagulayan KF, Zawaideh N, Dikmen S, Temkin N, Bell KR. Understanding pain after traumatic brain injury: impact on community participation. Am J Phys Med Rehabil 2007;86:962–9.
[33] IOM (Institute of Medicine). Relieving Pain in America. A Blueprint for Transforming Prevention, Care, Education, and Research. Washington: The National Academies Press, 2011. Available at: http://www.nap.edu. Accessed 10 September 2015.
[34] Jackson T, Wang Y, Fan H. Associations between pain appraisals and pain outcomes: meta-analyses of laboratory pain and chronic pain literatures. J Pain 2014;15:586–601.
[35] Jensen MP, Moore MR, Bockow TB, Ehde DM, Engel JM. Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: a systematic review. Arch Phys Med Rehabil 2011;92:146–60.
[36] Joint Commission on Accreditation of Healthcare Organizations Pain management standards. Available at: www.jcaho.org/standard/. Accessed January 1, 2001.
[37] Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, van Tulder MW. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev 2014;9:CD000963.
[38] Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. Gen Hosp Psychiatry 2012;34:46–52.
[39] Kobus AM, Smith DH, Morasco BJ, Johnson ES, Yang X, Petrik AF, Deyo RA. Correlates of higher-dose opioid medication use for low back pain in primary care. J Pain 2012;13:1131–8.
[40] Kozhimannil KB, Johnson PJ, Attanasio LB, Gjerdingen DK, McGovern PM. Use of nonmedical methods of labor induction and pain management among U.S. women. Birth 2013;40:227–36.
[41] Kratz AL, Hirsh AT, Ehde DM, Jensen MP. Acceptance of pain in neurological disorders: associations with functioning and psychosocial well-being. Rehabil Psychol 2013;58:1–9.
[42] Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. J Gen Intern Med 2007;22:1453–8.
[43] Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1:CD007115.
[44] Lynch-Jordan AM, Sil S, Peugh J, Cunningham N, Kashikar-Zuck S, Goldschneider KR. Differential changes in functional disability and pain intensity over the course of psychological treatment for children with chronic pain. PAIN 2014;155:1955–61.
[45] Main C, Keefe F, Jensen M, Vlaeyen J, Vowles K, WE F. Fordyce's behavioral methods for chronic pain and illness: republished with invited commentaries. International Association for the Study of Pain. Philadelphia: Wolters Kluwer Health, 2015.
[46] McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: model, process, and progress. Am Psychol 2014;69:178–87.
[47] Mehling WE, Ebell MH, Avins AL, Hecht FM. Clinical decision rule for primary care patient with acute low back pain at risk of developing chronic pain. Spine J 2015;15:1577–86.
[48] Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JW, Moseley GL. Contingency learning deficits and generalization in chronic unilateral hand pain patients. J Pain 2014;15:1046–56.
[49] Meulders A, Jans A, Vlaeyen JW. Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. PAIN 2015;156:108–22.

[50] Moseley GL, Vlaeyen JW. Beyond nociception: the imprecision hypothesis of chronic pain. PAIN 2015;156:35–8.
[51] Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring pain as the 5th vital sign does not improve quality of pain management. J Gen Intern Med 2006;21:607–12.
[52] Ojala T, Hakkinen A, Karppinen J, Sipila K, Suutama T, Piirainen A. Chronic pain affects the whole person–a phenomenological study. Disabil Rehabil 2015;37:363–71.
[53] Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med 2010;363: 1981–5.
[54] Rej S, Dew MA, Karp JF. Treating concurrent chronic low back pain and depression with low-dose venlafaxine: an initial identification of "easy-to-use" clinical predictors of early response. Pain Med 2014;15:1154–62.
[55] Ross C, Juraskova I, Lee H, Parkitny L, Stanton TR, Moseley LG, McAuley JH. Psychological distress mediates the relationship between pain and disability in hand or wrist fractures. J Pain 2015.
[56] Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD, Residency Research Network of Texas Investigators. Change in opioid dose and change in depression in a longitudinal primary care patient cohort. PAIN 2015;156:348–55.
[57] Scherrer JF, Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, Bucholz KK, Lawler EV, Lustman PJ. Prescription opioid analgesics increase the risk of depression. J Gen Intern Med 2014;29:491–9.
[58] Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, Neylan TC. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA 2012;307: 940–7.
[59] Stratton KJ, Clark SL, Hawn SE, Amstadter AB, Cifu DX, Walker WC. Longitudinal interactions of pain and posttraumatic stress disorder symptoms in U.S. Military service members following blast exposure. J Pain 2014;15:1023–32.
[60] Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. PAIN 2013;154(suppl 1):S94–100.
[61] The Joint Commission Perspectives, Vol. 34. Joint Commission Resources, 2014. p. 11.
[62] Trevino CM, deRoon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? J Pain 2013;14:424–30.
[63] Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J Gen Intern Med 2015.
[64] Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. Cochrane Database Syst Rev 2013;10:CD010782.
[65] Veal FC, Bereznicki LR, Thompson AJ, Peterson GM. Use of Opioid Analgesics in Older Australians. Pain Med 2015.
[66] Vinik A, Emir B, Cheung R, Whalen E. Relationship between pain relief and improvements in patient function/quality of life in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia treated with pregabalin. Clin Ther 2013;35:612–23.
[67] Vinik A, Emir B, Parsons B, Cheung R. Prediction of pregabalin-mediated pain response by severity of sleep disturbance in patients with painful diabetic neuropathy and post-herpetic neuralgia. Pain Med 2014;15:661–70.
[68] Vowles KE, Sowden G, Ashworth J. A comprehensive examination of the model underlying acceptance and commitment therapy for chronic pain. Behav Ther 2014;45:390–401.
[69] Wanzer SH, Federman DD, Adelstein SJ, Cassel CK, Cassem EH, Cranford RE, Hook EW, Lo B, Moertel CG, Safar P, Stone A, van Eys J. The physician's responsibility toward hopelessly ill patients. A second look. N Engl J Med 1989;320:844–9.
[70] Weisner CM, Campbell CI, Ray GT, Saunders K, Merrill JO, Banta-Green C, Sullivan MD, Silverberg MJ, Mertens JR, Boudreau D, Von Korff M. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. PAIN 2009;145:287–93.
[71] Zhang SS, Wu Z, Zhang LC, Zhang Z, Chen RP, Huang YH, Chen H. Efficacy and safety of pregabalin for treating painful diabetic peripheral neuropathy: a meta-analysis. Acta Anaesthesiol Scand 2015;59:147–59.
[72] Zubkoff L, Lorenz KA, Lanto AB, Sherbourne CD, Goebel JR, Glassman PA, Shugarman LR, Meredith LS, Asch SM. Does screening for pain correspond to high quality care for veterans? J Gen Intern Med 2010;25: 900–5.