# Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease

C. Patrick Carroll, MD,[1] Sophie Lanzkron, MD,[2] Carlton Haywood Jr., PhD,[2] Kasey Kiley, MPH,[1] Megan Pejsa, BS,[1] Gyasi Moscou-Jackson, PhD, MHS, RN,[3] Jennifer A. Haythornthwaite, PhD,[1] Claudia M. Campbell, PhD[1]

Chronic opioid therapy (COT) for chronic non-cancer pain is frequently debated, and its effectiveness is unproven in sickle cell disease (SCD). The authors conducted a descriptive study among 83 adult SCD patients and compared the severity of disease and pain symptoms among those who were prescribed COT ($n$=29) with those who were not using COT. All patients completed baseline laboratory pain assessment and questionnaires between January 2010 and June 2014. Thereafter, participants recorded daily pain, crises, function, and healthcare utilization for 90 days using electronic diaries. Analyses were conducted shortly after the final diary data collection period. Patients on COT did not differ on age, sex, or measures of disease severity. However, patients on COT exhibited greater levels of clinical pain (particularly non-crisis); central sensitization; and depression and increased diary measures of pain severity, function, and healthcare utilization on crisis and non-crisis diary days, as well as a greater proportion of days in crisis. Including depressive symptoms in multivariate models did not change the associations between COT and pain, interference, central sensitization, or utilization. Additionally, participants not on COT displayed the expected positive relationship between central sensitization and clinical pain, whereas those on COT demonstrated no such relationship, despite having both higher central sensitization and higher clinical pain. Overall, the results point out a high symptom burden in SCD patients on COT, including those on high-dose COT, and suggest that nociceptive processing in SCD patients on COT differs from those who are not.

(Am J Prev Med 2016;51(1S1):S69–S77) 

## Introduction

Sickle cell disease (SCD) is a group of autosomal recessive hematologic diseases, rare in the U.S., linked to the hemoglobin beta S allele.[1,2] In the U.S., the disease is heavily concentrated in people of African descent.[3,4] The clinical hallmark of SCD is the painful crisis, sometimes called a vaso-occlusive crisis (VOC). VOCs are characterized by severe pain, in variable locations, lacking any clear objective signs of etiology.[5] The pathophysiology of VOC is complex and still remarkably poorly understood, but involves interactions among activated endothelium, malformed "sickled" red blood cells, both chronic and acute inflammatory processes, and the nervous system.[6–17] Patients experiencing VOC are at increased risk for subsequent acute chest syndrome or stroke, both potentially life-threatening complications.[18]

The medical literature for some time used acute care visits for VOC as a proxy measure for the pain burden of SCD.[12,19,20] However, many adults with SCD have a high burden of chronic pain as well.[21] The mechanisms of chronic pain in SCD are likely varied, and both preclinical and human studies suggest that abnormal sensitization of the peripheral and central nervous system plays a role.[16,17,22–25] Some complications of SCD, such as avascular necrosis of bone, are independently painful, and accumulation of such complications contributes to the burden of chronic pain.[26,27]

Clinicians attempting to alleviate chronic pain in patients with SCD have limited evidence to guide management. Chronic opioid therapy (COT) is often used, although its long-term efficacy is not established in SCD. Even in common non-cancer pain conditions, rigorous long-term studies of COT are lacking.[28,29]

From the [1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and [3]Johns Hopkins University School of Nursing, Baltimore, Maryland

Address correspondence to: C. Patrick Carroll, MD, The Johns Hopkins Hospital, Meyer 3-139, 600 N. Wolfe Street, Baltimore MD 21287. E-mail: ccarrol1@jhmi.edu.

This article is part of the supplement issue titled Developing a Unified Approach for Sickle Cell Disease.

0749-3797/$36.00

http://dx.doi.org/10.1016/j.amepre.2016.02.012

Open-label follow-up and cross-sectional studies of long-term COT suggest modest effects. Many patients report continued severe pain, reduced function, high levels of distress, and a great deal of disability,[28–33] and many do not remain on COT.[30] Both COT and chronic pain are associated with the diagnosis of major depressive disorder as well, which may exacerbate the unpleasantness of noxious stimuli and contribute to poor outcomes.[34–36] Some painful conditions can worsen with COT.[37–39] Many multidisciplinary pain centers explicitly use opioid reduction or cessation as a technique in rehabilitation with documented improvements in pain severity and function.[40–45] This has remained unexplored in SCD but might be more complicated given the unique mixture of acute and chronic pain, as well as the greater risk of physiologic stress from opioid withdrawal.

Central sensitization (CS), nociceptive hyperexcitability that amplifies and maintains clinical pain, recently has been hypothesized to play a role in SCD pain.[17,22,23,25,46] The relationship between COT and CS remains poorly understood, though some work has suggested that opioids both induce CS[47–52] and can reverse it in certain circumstances.[53,54] It is unknown whether improvements in pain observed from opioid reduction are associated with normalization of CS processes.

This study is part of a larger project designed to define relevant mechanistic and clinical pain phenotypes in patients with SCD. Here, the authors report a descriptive study of 83 adult SCD patients, comparing severity of disease and pain symptoms among those who were prescribed COT ($n$=29) with those who were not using COT ($n$=54). All patients completed baseline laboratory pain assessment and questionnaires between January 2010 and June 2014. Thereafter, participants recorded daily pain, crises, function, and healthcare utilization for 90 days using electronic diaries. It was hypothesized that COT would be associated with greater daily pain, poorer functioning, and greater healthcare utilization. In addition to these primary aims, this study evaluated whether central sensitization, as measured using standardized laboratory techniques, moderated the expected association between COT group and clinical pain in SCD.

## Methods

Participants were recruited for participation from the Sickle Cell Center for Adults at Johns Hopkins Hospital or through posted advertisements. The study and its methods were approved by a Johns Hopkins IRB.

### Participants and Recruitment

Participants were adults (aged ≥18 years) with SCD (genotype confirmed by laboratory testing or study hematologist); adequate facility with the English language; and on a stable dose of nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids for 1 month prior to pain testing (if any). Participants were recruited from an adult SCD clinic with a stable census of approximately 541 active patients. At the time of submission, active patients in the clinic are 58.1% female, with a mean age of 36.0 (SD=11.8) years, and 63.2% of patients have the SS genotype.

Individuals with a significant cognitive impairment; severe or unstable psychiatric illness; active substance abuse; current infection; diagnosis of certain autoimmune disorders; HIV infection with neuropathy; or currently pregnant, lactating, or attempting to become pregnant within 6 months were excluded. Eighty-three participants (15.3% of the clinic) with SCD provided informed consent; enrolled in the parent study; and were included in these analyses.

### Study Procedures

Initial telephone screening ensured eligibility criteria were met. At the baseline visit, participants completed a standardized laboratory pain testing protocol and study instruments as well as self-report questionnaires for data not readily available via medical records, such as educational attainment. Participants attended the baseline visit when their pain was typical SCD pain, it was of no greater intensity on a verbal numerical rating scale than 5/10, and there had been no VOCs in at least the previous 3 weeks. At the conclusion of the baseline visit, participants were trained on the use of a daily electronic diary, which was used to capture daily pain data over the following 90 days. Quantitative sensory testing (QST) data were collected between January 2010 and June 2014, and analyses were conducted shortly after the final diary data collection period.

### Measures

Participants reported age, sex, and educational level, which was dichotomized as "some college or more" and "no college."

Self-reported least, worst, average, and current clinical pain severity for the week prior to testing was rated on an 11-point numerical rating scale, similar to that used for the Brief Pain Inventory (anchors, *no pain* = 0 and *pain as bad as it could be* = 10. Note that the high anchor was slightly unintentionally altered from that of the Brief Pain Inventory).

Medical records provided SCD genotype; lifetime complications (acute chest syndrome and avascular necrosis of bone); and baseline hemoglobin count (Hb) from the most recent hematology visit (up to 1 year prior to testing). Genotype was unknown in one participant in the COT group owing to unclear notations in the medical record without available confirmatory testing. Baseline Hb was determined by recording the most recent four non-crisis Hb values within the past year, discarding the highest and lowest, and averaging the middle two observations. For participants whose Hb data were not available using these methods ($n$=10), baseline Hb was determined by extending the time period to include a time when the patient was more active in clinic when there were more data available (up to 3 years). For the remainder ($n$=4), a smaller number of observations were used provided they were not widely divergent and clearly not during crisis. This left two participants with missing baseline Hb data, one in each group.

Participants on COT were defined as those who were prescribed long-acting, daily opioids for chronic pain, which was obtained from chart review and clinic prescription databases. Opioids included sustained-release morphine preparations (50%); sustained-release oxycodone preparations (23%); methadone (17%); and transdermal fentanyl (10%). Prescribed doses were obtained by multiplying tablet strength by number of dispensed tablets and divided by the prescription interval, except for transdermal fentanyl, for which the total daily fentanyl dose was calculated by the patch strength. Each opioid dose was then converted to oral morphine equivalents using standard conversion tables. Duration of COT was not assessed, partly because of inadequate information regarding inception (such as patients whose COT was started at other institutions) and finding that in some cases, participants may have been using as-needed medication around the clock prior to inception. There was no systematic assessment for multiple prescribers; however, patients in the Sickle Cell Center for Adults sign opioid treatment contracts that prohibit multiple prescribers and are regularly assessed using the Maryland Prescription Drug Monitoring Program for receiving prescriptions from multiple providers. If this behavior is discovered, typically patients are required to produce evidence that the other prescribing relationships are terminated, or no longer receive opioids from the Sickle Cell Center for Adults.

Depressive symptoms were quantified using the 20-item version of the Center for Epidemiologic Studies Depression scale. Items are rated on 5-point scales from 0 (*rarely or less than one day*) to 4 (*most of the time, 5–7 days*) and the summary score indicates greater depressive symptom severity.[55,56]

The Current Opioid Misuse Measure was used to evaluate the existence of aberrant opioid use. It is a widely used, 17-item questionnaire, with high internal reliability, specifically designed with pain patients in mind that includes items assessing risk, emergent healthcare utilization, and mood disturbance.[57–59] A summary score is created and a clinical cut off score of $\geq 9$ identifies individuals for whom opioid medications may be problematic. Because the authors did not want to confound risk with mood and healthcare utilization, a Current Opioid Misuse Measure risk behavior subset score was calculated (Items 3, 4, 6, 8, 9, 10, 11, 14, 15, and 16).

A broad battery of QST measures were collected on the participants. These included heat and pressure pain thresholds as well as heat pain tolerance. Temporal summation, a measure of CS, was measured for heat and mechanical (punctate) stimuli. Heat pain stimuli for thermal temporal summation were tailored based on the previously measured heat pain threshold. Hot water immersion was used to measure conditioned pain modulation and hot water tolerance. Aftersensations were measured by obtaining pain rating 15 seconds following the final pulse in each thermal temporal summation series and 30 seconds and 1 minute following completion of the final hot water immersion. QST variables were Z-scored to combine measures with different scales into comparable indices, with heat pain threshold and tolerance, pressure pain threshold, water temperature, and conditioned pain modulation reversed to make their directionality consistent (i.e., higher scores correspond to enhanced sensitivity). A QST index was created by averaging Z-scores for heat pain threshold and tolerance, pressure pain thresholds, conditioned pain modulation, hand withdrawal time and intensity, and water temperature. A CS index was created by averaging Z-scores for thermal and mechanical temporal summation, and after sensations to temporal summation and hot water.[60–62]

A pain rating was obtained 15 seconds following the final pulse in each thermal temporal summation series and 30 seconds and 1 minute following completion of the final hot water immersion.

Daily electronic diaries recorded whether the participant was in crisis and least, worst, and average pain severity rated on a 0–100 scale. Functional measures were also queried using the same 0–100 scale, including pain-related interference, physical activity, and fatigue for non-crisis and crisis days. Healthcare utilization questions were also included, specifically whether a call to their provider or medical visit occurred, pain relief from their medications, and satisfaction with medications all on non-crisis and crisis days. Mean scores were calculated for each measure by participant, separately for crisis and non-crisis days. Diary data were included for participants who had $\geq 25\%$ of days with measures involved in the study recorded; there was no prompting for data entry ($n$=77, COT; $n$=25, non-COT, $p$=52; median completion ratio for evening diaries, 78.2%). Measures were recorded in the morning and evening, with the measures of interest for this study (e.g., pain, fatigue) being recorded in evening diaries addressing the prior 12 hours. Clinical pain during the diary follow-up period was summarized by averaging the reported lowest, highest, and average daily pain ratings across both crisis and non-crisis days, then computing the mean of all three ratings, thus producing a single index of non-crisis clinical pain summarized over time. All three ratings were included to account for variability in pain during a day. For all pain-related analyses, the unit of analysis was the individual participant.

## Data Analysis

Participants on COT were compared with non-COT participants on demographics, clinical measures, QST findings, and diary measures in bivariate analyses using ANOVA or chi-square tests as appropriate. Depressive symptoms were included as a covariate in multivariable regression models to test whether COT predicted measures of pain, function, and healthcare utilization. A Spearman rank-order (nonparametric) correlation coefficient was calculated to examine the relationship between non-crisis clinical pain and opioid dose in patients on COT, as well as the relationship between pain and CS. The potential moderating effect of CS on the relationship between COT and non-crisis clinical pain was tested using Hayes's PROCESS macro.[63] This macro uses an ordinary least squares or logistic regression–based path analytic framework to analyze models. Model 1, testing simple moderation, was used in the current analyses, which included depression as a covariate. Additionally, a cluster analysis used pain, pain-related interference, and healthcare use to classify each SCD patient based on the pattern of diary reports. A K-means cluster analysis was performed using the variables identified (pain, pain-related interference, and healthcare use) from the daily diaries. This split participants into two groups based on responses to these items. This was conducted to examine and confirm the greater symptom burden of the COT group, as the authors hypothesized that a larger percentage of patients from the COT group would fall into the more severe cluster. All analyses were performed in SPSS, version 23. Analyses used all complete observations available for each analysis. In the COT group, data from two participants were missing for the CS index, and one from the non-CS QST index. One participant did none of the QST measures, another was missing all temporal summation and hot water measures.

**Table 1.** Bivariate Comparisons of Participants With SCD With and Without Chronic Opioid Therapy

| Characteristic | No chronic opioids ($n$=54) | Chronic opioid therapy ($n$=29) |
|---|---|---|
| Demographics | | |
| Age | 38.0 (12.4) | 40.6 (11.7) |
| Female | 66.0% (35) | 75.9% (22) |
| ≥Some college | 77.8% (42) | 64.3% (18) |
| Disease severity | | |
| SS genotype | 61.1% (33) | 67.9% (19) |
| Baseline Hb | 9.37 (1.8) | 8.9 (2.2) |
| Acute chest syndrome | 42.6% (23) | 32.1% (9) |
| Avascular necrosis | 29.6% (16) | 35.7% (10) |
| Pain severity (BPI) | **1.3 (1.6)** | **3.6 (1.5)*** ** |
| Depression (CES-D) | **12.0 (8.1)** | **20.2 (13.9)** ** |
| Risk of medication misuse | | |
| Current opioid misuse measure | **6.2 (4.1)** | **13.1 (7.6)*** ** |
| COMM risk behavior subset | **2.3 (2.9)** | **7.4 (5.6)*** ** |

*Note:* Boldface indicates statistical significance (*$p<0.05$; **$p<0.01$; ***$p<0.001$). Values are reported as M (SD) or percent ($n$).
BPI, Brief Pain Inventory; CES-D, Center for Epidemiologic Studies Depression scale; COMM, Current Opioid Misuse Measure; Hb, hemoglobin; SCD, sickle cell disease.

## Results

Patients taking COT did not differ on age or sex (Table 1). Interestingly, none of the included disease severity measures (more severe genotype, acute chest syndrome, avascular necrosis of bone, or baseline Hb) were associated with greater baseline pain (all $p$-values ≥0.19), although the COT group did report greater baseline pain severity (3.6 vs 1.3, $p<0.001$), as well as ratings of depressive symptoms and, not surprisingly, risk for medication misuse.

Participants on COT had greater scores on the CS index, which were also observed in the multivariate analysis controlling for depressive symptoms, but no group differences were observed on the QST index (Table 2). In bivariate analyses of the daily diary records, participants on COT reported greater average daily pain on both crisis and non-crisis days. Though participants on COT were no more likely to report at least one crisis during the diary period (12.5% vs 13.0%, $p>0.05$), they spent a greater proportion of their time in crisis and reported greater average pain during crisis (Table 2). Group differences in pain severity were most striking on non-crisis days (34.5 vs 10.3, $p<0.001$) and all of these group differences remained in the analyses controlling for depressive symptoms.

To further explore the relationship between clinical pain and chronic opioid use, total daily morphine equivalents for those participants on COT were correlated with non-crisis clinical pain, indicating a marginally significant opioid dose–pain relationship ($r$=0.41, $p$=0.051, Figure 1). Visual inspection of scatterplots of CS versus non-crisis pain suggested a differential relationship between those on COT and not. Further analysis revealed that CS was only correlated with non-crisis clinical pain in patients not taking COT ($r$=0.44, $p$=0.002 vs $r=-0.05$, $p>0.05$), which was evaluated further in the moderation analysis.

Participants on COT reported higher pain-related interference and greater fatigue on non-crisis days as compared with participants not on COT; this relationship remained significant when depressive symptoms were included in the multivariable models (Table 2). A similar pattern emerged for function on crisis days during the diary recording period, such that participants on COT reported greater pain-related interference and fatigue on crisis days compared with participants not taking COT. However, neither of these effects remained significant once baseline depressive symptoms were entered into the model. The effect of COT was not observed on reports of physical activity on either non-crisis or crisis days.

Participants on COT reported making more calls to providers, experiencing greater pain relief from medications, and greater satisfaction with their pain medication on non-crisis days as compared with participants not using COT (Table 2). These effects of COT remained significant when depressive symptoms were controlled in the multivariable models. The pattern on crisis days was slightly different, such that calls to providers and medical visits were higher in the COT group, even when depressive symptoms were controlled in the multivariable models. On crisis days, no differences were observed between groups on pain relief or satisfaction.

Greater CS was significantly associated with greater non-crisis clinical pain (β=16.2, $p$=0.0006). Being on

**Table 2.** Comparisons of QST, Pain, and Clinical Outcomes Between Participants With and Without Chronic Opioid Therapy, Controlled for Depression

| | | | Controlling for depression | |
|---|---|---|---|---|
| **Outcome** | **No chronic opioids M (SD)** | **Chronic opioid therapy M (SD)** | **β** | ***F*** |
| CS index$^{-2}$ | **−0.10 (0.4)** | **0.34 (0.8)**** | **0.33** | **6.0**** |
| QST index$^{-1}$ | 0.08 (0.5) | 0.02 (0.6) | −0.09 | 0.4 |
| Non-crisis pain | **10.3 (14.1)** | **34.5 (15.7)***** | **0.50** | **21.9***** |
| Proportion of days in VOC | **11.9% (16.4)** | **29.0% (26.3)**** | **0.30** | **7.3*** |
| Crisis pain | **41.0 (21.0)** | **60.6 (11.4)***** | **0.40** | **8.9**** |
| Non-crisis days | | | | |
| Pain-related interference | **7.4 (12.2)** | **24.9 (19.6)***** | **0.35** | **9.2**** |
| Physical activity | 44.3 (18.3) | 50.6 (15.3) | 0.15 | 0.7 |
| Fatigue | **27.0 (19.4)** | **49.7 (19.7)***** | **0.35** | **11.5**** |
| Days with provider calls | **1.3% (0.03)** | **3.2% (0.04)**** | **0.33** | **5.2**** |
| Days with medical visits | 0.2% (0.03) | 3.6% (4.3) | 0.16 | 1.5 |
| Pain relief with medications | **21.7 (25.8)** | **59.0 (20.1)***** | **0.61** | **18.4***** |
| Medication satisfaction | **40.6 (37.5)** | **61.1 (19.2)*** | **0.32** | **3.7**** |
| Crisis days | | | | |
| Pain-related interference | **37.7 (25.8)** | **56.7 (21.5)**** | 0.28 | 3.7 |
| Physical activity | 35.3 (22.8) | 45.5 (25.8) | 0.16 | 0.5 |
| Fatigue | **53.0 (23.1)** | **66.1 (21.3)*** | 0.14 | 3.6 |
| Days with calls to providers | **2.3% (0.05)** | **7.8% (0.2)**** | **0.31** | **3.5*** |
| Days with medical visits | **0.03% (0.06)** | **9.5% (0.2)**** | **0.29** | **3.2*** |
| Pain relief with medications | 51.9 (23.2) | 48.4 (19.6) | 0.05 | 1.3 |
| Medication satisfaction | 57.9 (22.7) | 46.7 (22.7) | −0.14 | 2.0 |

*Note:* Pain intensity, pain interference, fatigue, and physical activity all were rated by participants on a 1–100 scale. Boldface indicates statistical significance (*$p<0.05$; **$p<0.01$; ***$p<0.001$). Superscripts of the form $^{-x}$ indicate $x$ missing observations from the COT group in the analysis.
CS, central sensitization; QST, quantitative sensory testing; VOC, vaso-occlusive crisis.

COT (dichotomous group variable) was significantly associated with non-crisis clinical pain as well (β=19.5, $p<0.0001$). A significant interaction emerged between CS and COT (β=−18.2, $p=0.006$), despite controlling for the effects of depression on non-crisis clinical pain (β=0.4, $p=0.005$). This interaction is represented graphically in Figure 2, which depicts the simple slope of COT for low (−1 SD) and high (+1 SD) CS. Simple slopes were tested across the two COT groups and only the slope for non-COT users revealed a significant association between CS and non-crisis clinical pain (β=16.2, $p=0.0006$ vs β=−2.0, $p=0.7$). The authors probed the interaction with the Johnson–Neyman technique[64] to determine the regions of significance of the conditional effect. This depicts the range of values within the moderator where the interaction is significant. Figure 3 plots the conditional effect of COT on non-crisis clinical pain across values of CS. The region of significance lies where the CI does not include 0. Thus, COT is associated with non-crisis clinical pain when CS is <0.55. Those with CS scores <0.55 accounted for 83.1% ($n=64$) of the entire sample, 90.4% in the non-COT group and 68% in the COT group ($p=0.02$).

Two clusters (using the aforementioned K-means cluster analysis) were formed based on pain (41.9 vs 7.4); pain-related interference (32.8 vs 3.6); and health-care use (0.01 vs 0.03), classifying participants on diary reports. Three times as many participants in the COT group were included in the greater symptom burden cluster ($n=18$ vs $n=6$).

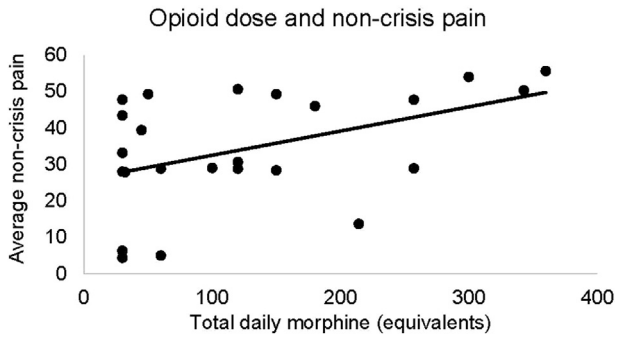


**Figure 1.** Scatterplot of clinical non-crisis pain by morphine equivalents.

## Discussion

These findings indicate that those on COT report an overall greater symptom burden. Specifically, they experience greater clinical pain (both crisis and non-crisis), higher CS, more crises, poorer functional outcomes, and higher healthcare utilization than those not on COT, independent of any depressive symptom effects. Surprisingly, however, disease severity measures do not differ between those not and those on COT. The relationship between CS and pain severity is complex and differs depending on COT status. The moderation analysis reveals that in participants not on COT, greater CS is associated with greater non-crisis clinical pain; however, in participants on COT, no relationship is observed between CS and non-crisis clinical pain.

Opioids are a mainstay for patients with SCD, and clinical use of COT for chronic non-cancer pain has expanded rapidly, perhaps beyond the evidence supporting its widespread use.[65] These findings suggest a harsher disease course, which may be the very reason these patients were originally prescribed COT. Although the authors are unable to glean whether any improvement in these variables has been witnessed since initiating COT from the study data, it does not appear that they have received substantial benefit from COT.

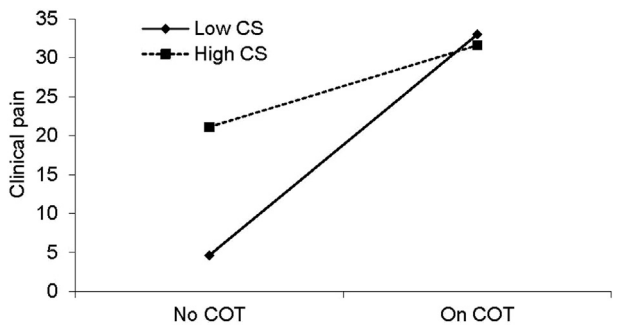


**Figure 2.** Interaction of COT and central sensitization predicting clinical non-crisis pain.
COT, chronic opioid therapy; CS, central sensitization.

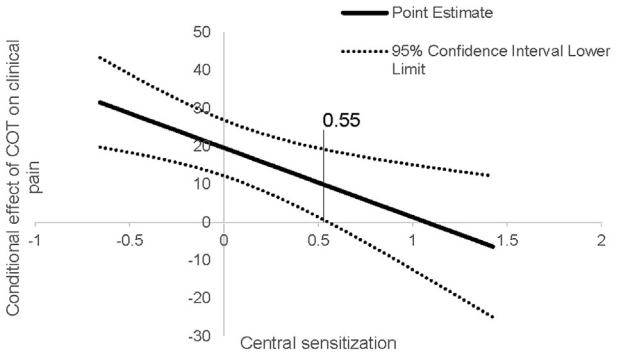


**Figure 3.** Conditional effect of COT on clinical pain across values of central sensitization.
*Note:* The region of significance lies where the CI does not include 0. Thus, COT is associated with clinical pain when CS is less than 0.55.
COT, chronic opioid therapy; CS, central sensitization.

An ongoing difficulty with respect to COT and CS is that opioids have both anti- and pro-nociceptive effects.[66–70] Though short-term studies have generally documented improvements in pain severity with opioid therapy, longer-term studies and clinical experience with refractory chronic pain suggest that opioids can have harmful effects and certain patients may have reduced pain off of COT.[28,40,42] Thus, although using opioids may produce reductions in pain in the short term, longer-term sensitizing effects may increase pain severity overall. If the clinical response to worsened pain is to increase opioid dosing, a vicious cycle may develop. Further complicating the clinical picture, opioid reduction itself is difficult, unpleasant, and likely to result in a hyperalgesic state due to opioid withdrawal effects.[71,72]

In this study, the positive relationship between CS and clinical pain, particularly non-crisis pain, among patients not on COT was expected. CS is associated with the development and maintenance of chronic pain and with chronic pain severity.[60,73] Measures of CS have been found to be elevated in animal studies of SCD, and in humans, and likely represent a fundamental mechanism of the pain experience of SCD as in other chronic pain conditions.[16,22,25] Although COT was associated with increased pain and CS overall, the moderation analysis highlights that patients on COT showed no relationship between CS and non-crisis clinical pain. The mechanisms underlying this puzzling lack of an association are unclear. The findings suggest that level of CS does not matter for those on COT—their pain is high regardless of CS. However, for the group not on COT, those with low CS report substantially lower levels of non-crisis clinical pain. One possible explanation for this finding is that

COT reduces clinical pain irrespective of the underlying level of central sensitization—a therapeutic effect. A second hypothesis is that COT increases CS in a qualitative (i.e., dose-independent) manner. However, these two hypotheses are not mutually exclusive—it is entirely consistent with prior findings that opioids can produce both anti- and pro-nociceptive effects, and the overall clinical situation may be a balance between these competitive actions.

It is reassuring, however, that COT was not associated with a potentiated effect of CS on non-crisis clinical pain, which would have suggested a potentiation effect, possibly due to the compounding cycle mentioned previously. It also suggests that any opioid-induced increase in CS may represent a qualitative or "threshold" relationship rather than a dose-dependent one, whereas anti-nociceptive effects appear to be related to the potency of opioid agonism and to dose,[74] although there is some evidence that neuropathic pain mechanisms are relatively refractory to opioids.[75] These data may be built upon in the future and could have implications for prescription of COT. For example, those already high in CS may not benefit as much from COT. One exciting potential future direction may be tempering COT dosing in those high in CS and examining whether a corresponding reduction is observed in clinical pain.

A principal strength of the study was the use of standardized measures of CS and other QST indices, as well as a highly detailed daily diary and information regarding participants' clinical characteristics. The principal limitations of the study are lack of randomization to COT category and no knowledge of pain-related variables prior to initiating COT, which limits the capacity to infer the direction of causation of the findings. Included in this uncertainty is topography and duration of COT therapy, as participants undoubtedly varied in prior opioid exposure and duration of therapy. This could only be addressed either in a randomized trial for COT in SCD chronic pain or in an opioid cessation study. In addition, there was a reduced sample size for the QST analyses, owing to failure to complete certain pain tests among some participants in the COT group, which resulted in a loss of power for some analyses. Overall, this study highlights the potential drawbacks of COT and suggests that measurement of CS and other disease- and pain-related factors could be used in clinical decision making. These data also suggest that further assessment of COT in pain-related outcomes for SCD patients is warranted.

Publication of this article was supported by the Centers for Disease Control and Prevention.

DHHS Funder/Grant NHLBI R01 HL098110-04 (PI Dr. Haythornthwaite); NIH/National Institute of Nursing Research T32NR012704 and F31NR014598 (Dr. Moscou-Jackson); NHLBI K01HL108832 (Dr. Haywood), NINDS K23 NS070933 (Dr. Campbell).

No financial disclosures were reported by the authors of this paper.

## References

1. Moll S, Orringer EP. Hemoglobin SC disease. *Am J Hematol*. 1997; 54(4):313. http://dx.doi.org/10.1002/(SICI)1096-8652(199704)54:4<313::AID-AJH9>3.0.CO;2-Y.
2. Powars DR, Hiti A, Ramicone E, Johnson C, Chan L. Outcome in hemoglobin SC disease: a four-decade observational study of clinical, hematologic, and genetic factors. *Am J Hematol*. 2002;70(3):206–215. http://dx.doi.org/10.1002/ajh.10140.
3. Hassell K. Sickle cell disease population estimation: application of available contemporary data to traditional methods [Abstract]. Paper presented at: 35th Anniversary Convention of the National Sickle Cell Disease Program; September 17–22, 2007. Washington, DC. Baltimore: Sickle Cell Disease Association of America, 2007: 173 Abstract no.: 275.
4. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. *Am J Epidemiol*. 2000;151(9):839–845. http://dx.doi.org/10.1093/oxfordjournals.aje.a010288.
5. Ballas SK. Pathophysiology and principles of management of the many faces of the acute vaso-occlusive crisis in patients with sickle cell disease. *Eur J Haematol*. 2015;95(2):113–123. http://dx.doi.org/10.1111/ejh.12460.
6. Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. *Blood*. 1992;79(8):2154–2163.
7. Charache S, Barton FB, Moore RD, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *Medicine (Baltimore)*. 1996;75(6):300–326. http://dx.doi.org/10.1097/00005792-199611000-00002.
8. Shiu YT, Udden MM, McIntire LV. Perfusion with sickle erythrocytes up-regulates ICAM-1 and VCAM-1 gene expression in cultured human endothelial cells. *Blood*. 2000;95(10):3232–3241.
9. Smith BD, La Celle PL. Erythrocyte-endothelial cell adherence in sickle cell disorders. *Blood*. 1986;68(5):1050–1054.
10. Assis A, Conran N, Canalli AA, Lorand-Metze I, Saad ST, Costa FF. Effect of cytokines and chemokines on sickle neutrophil adhesion to fibronectin. *Acta Haematol*. 2005;113(2):130–136. http://dx.doi.org/10.1159/000083451.
11. Michaels LA, Ohene-Frempong K, Zhao H, Douglas SD. Serum levels of substance P are elevated in patients with sickle cell disease and increase further during vaso-occlusive crisis. *Blood*. 1998;92(9):3148–3151.
12. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med*. 1991;325(1):11–16. http://dx.doi.org/10.1056/NEJM199107043250103.
13. Krishnan S, Setty Y, Betal SG, et al. Increased levels of the inflammatory biomarker C-reactive protein at baseline are associated with childhood sickle cell vasocclusive crises. *Br J Haematol*. 2010;148(5):797–804. http://dx.doi.org/10.1111/j.1365-2141.2009.08013.x.
14. Mohammed FA, Mahdi N, Sater MA, Al-Ola K, Almawi WY. The relation of C-reactive protein to vasoocclusive crisis in children with sickle cell disease. *Blood Cells Mol Dis*. 2010;45(4):293–296. http://dx.doi.org/10.1016/j.bcmd.2010.08.003.
15. Graido-Gonzalez E, Doherty JC, Bergreen EW, Organ G, Telfer M, McMillen MA. Plasma endothelin-1, cytokine, and prostaglandin E2 levels in sickle cell disease and acute vaso-occlusive sickle crisis. *Blood*. 1998;92(7):2551–2555.
16. Brandow AM, Stucky CL, Hillery CA, Hoffmann RG, Panepinto JA. Patients with sickle cell disease have increased sensitivity to cold and heat. *Am J Hematol*. 2013;88(1):37–43. http://dx.doi.org/10.1002/ajh.23341.
17. Hillery CA, Kerstein PC, Vilceanu D, et al. Transient receptor potential vanilloid 1 mediates pain in mice with severe sickle cell disease. *Blood*.

2011;118(12):3376–3383. http://dx.doi.org/10.1182/blood-2010-12-327429.
18. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639–1644. http://dx.doi.org/10.1056/NEJM199406093302303.
19. Lorenzi EA. The effects of comprehensive guidelines for the care of sickle-cell patients in crisis on the nurses' knowledge base and job satisfaction for care given. *J Adv Nurs*. 1993;18(12):1923–1930. http://dx.doi.org/10.1046/j.1365-2648.1993.18121923.x.
20. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease. *JAMA*. 2014;312(10):1033. http://dx.doi.org/10.1001/jama.2014.10517.
21. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med*. 2008;148(2):94–101. http://dx.doi.org/10.7326/0003-4819-148-2-200801150-00004.
22. Garrison SR, Kramer AA, Gerges NZ, Hillery CA, Stucky CL. Sickle cell mice exhibit mechanical allodynia and enhanced responsiveness in light touch cutaneous mechanoreceptors. *Mol Pain*. 2012;8(1):62. http://dx.doi.org/10.1186/1744-8069-8-62.
23. Zappia KJ, Garrison SR, Hillery CA, Stucky CL. Cold hypersensitivity increases with age in mice with sickle cell disease. *Pain*. 2014;155(12):2476–2485. http://dx.doi.org/10.1016/j.pain.2014.05.030.
24. Ezenwa MO, Molokie RE, Wang ZJ, et al. Safety and utility of quantitative sensory testing among adults with sickle cell disease: indicators of neuropathic pain? *Pain Pract*. January 12, 2015. http://dx.doi.org/10.1111/papr.12279.
25. Cataldo G, Rajput S, Gupta K, Simone DA. Sensitization of nociceptive spinal neurons contributes to pain in a transgenic model of sickle cell disease. *Pain*. 2015;156(4):722–730. http://dx.doi.org/10.1097/j.pain.0000000000000104.
26. Akinyoola AL, Adediran IA, Asaleye CM, Bolarinwa AR. Risk factors for osteonecrosis of the femoral head in patients with sickle cell disease. *Int Orthop*. 2009;33(4):923–926. http://dx.doi.org/10.1007/s00264-008-0584-1.
27. Mont MA, Zywiel MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. *J Bone Joint Surg Am*. 2010;92(12):2165–2170. http://dx.doi.org/10.2106/JBJS.I.00575.
28. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113–130. http://dx.doi.org/10.1016/j.jpain.2008.10.008.
29. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain Off J Am Pain Soc*. 2009;10(2):147–159. http://dx.doi.org/10.1016/j.jpain.2008.10.007.
30. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372–380. http://dx.doi.org/10.1016/j.pain.2004.09.019.
31. Merrill JO, Von Korff M, Banta-Green CJ, et al. Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. *Gen Hosp Psychiatry*. 2012;34(6):581–587. http://dx.doi.org/10.1016/j.genhosppsych.2012.06.018.
32. Sullivan MD, Von Korff M, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. *Pain*. 2010;149(2):345–353. http://dx.doi.org/10.1016/j.pain.2010.02.037.
33. Choinière M, Dion D, Peng P, et al. The Canadian STOP-PAIN project —Part 1: who are the patients on the waitlists of multidisciplinary pain treatment facilities? *Can J Anaesth*. 2010;57(6):539–548. http://dx.doi.org/10.1007/s12630-010-9305-5.
34. Strigo IA, Simmons AN, Matthews SC, Craig ADB, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Arch Gen Psychiatry*. 2008;65(11):1275–1284. http://dx.doi.org/10.1001/archpsyc.65.11.1275.
35. 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(5):1577–1584. http://dx.doi.org/10.1002/art.21008.
36. Strigo IA, Simmons AN, Matthews SC, Craig ADB, Paulus MP. Increased affective bias revealed using experimental graded heat stimuli in young depressed adults: evidence of "emotional allodynia. *Psychosom Med*. 2008;70(3):338–344. http://dx.doi.org/10.1097/PSY.0b013e3181656a48.
37. Hagen K, Albretsen C, Vilming ST, et al. Management of medication overuse headache: 1-year randomized multicentre open-label trial. *Cephalalgia*. 2009;29(2):221–232. http://dx.doi.org/10.1111/j.1468-2982.2008.01711.x.
38. Saper JR, Lake 3rd. Continuous opioid therapy (COT) is rarely advisable for refractory chronic daily headache: limited efficacy, risks, and proposed guidelines. *Headache*. 2008;48(6):838–849. http://dx.doi.org/10.1111/j.1526-4610.2008.01153.x.
39. De Felice M, Porreca F. Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache. *Cephalalgia*. 2009;29(12):1277–1284. http://dx.doi.org/10.1111/j.1468-2982.2009.01873.x.
40. Townsend CO, Kerkvliet JL, Bruce BK, et al. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. *Pain*. 2008;140(1):177–189. http://dx.doi.org/10.1016/j.pain.2008.08.005.
41. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. 2013;29(2):109–117. http://dx.doi.org/10.1097/AJP.0b013e3182579935.
42. Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK. Withdrawal of analgesic medication for chronic low-back pain patients: improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. *Am J Phys Med Rehabil*. 2008;87(7):527–536. http://dx.doi.org/10.1097/PHM.0b013e31817c124f.
43. Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD. Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. *Pain Med*. 8(1):8–16. 10.1111/j.1526-4637.2007.00253.x.
44. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *J Pain*. 2006;7(1):43–48. http://dx.doi.org/10.1016/j.jpain.2005.08.001.
45. Chen L, Malarick C, Seefeld L, Wang S, Houghton M, Mao J. Altered quantitative sensory testing outcome in subjects with opioid therapy. *Pain*. 2009;143(1-2):65–70. http://dx.doi.org/10.1016/j.pain.2009.01.022.
46. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood*. 2012;120(18):3647–3656. http://dx.doi.org/10.1182/blood-2012-04-383430.
47. Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. *Drug Alcohol Depend*. 2006;82(3):218–223. http://dx.doi.org/10.1016/j.drugalcdep.2005.09.007.
48. Ram KC, Eisenberg E, Haddad M, Pud D. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain—new perspective of opioid-induced hyperalgesia. *Pain*. 2008;139(2):431–438. http://dx.doi.org/10.1016/j.pain.2008.05.015.
49. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain*. 2009;10(3):316–322. http://dx.doi.org/10.1016/j.jpain.2008.10.003.

50. Hay JL, Kaboutari J, White JM, Salem A, Irvine R. Model of methadone-induced hyperalgesia in rats and effect of memantine. *Eur J Pharmacol*. 2010;626(2-3):229–233. http://dx.doi.org/10.1016/j.ejphar.2009.09.056.
51. Cohen SP, Christo PJ, Wang S, et al. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. *Reg Anesth Pain Med*. 2008;33(3):199–206. http://dx.doi.org/10.1016/j.rapm.2007.10.009.
52. Prosser JM, Steinfeld M, Cohen LJ, et al. Abnormal heat and pain perception in remitted heroin dependence months after detoxification from methadone-maintenance. *Drug Alcohol Depend*. 2008;95(3):237–244. http://dx.doi.org/10.1016/j.drugalcdep.2008.01.012.
53. Sandkühler J, Ruscheweyh R. Opioids and central sensitisation: I. Preemptive analgesia. *Eur J Pain*. 2005;9(2):145–148. http://dx.doi.org/10.1016/j.ejpain.2004.05.012.
54. Ruscheweyh R, Sandkühler J. Opioids and central sensitisation: II. Induction and reversal of hyperalgesia. *Eur J Pain*. 2005;9(2):149–152. http://dx.doi.org/10.1016/j.ejpain.2004.05.011.
55. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D. *Am J Prev Med*. 1994;10(2):77–84.
56. Wison Schaeffer JJ, Gil KM, Burchinal M, et al. Depression, disease severity, and sickle cell disease. *J Behav Med*. 1999;22(2):115–126. http://dx.doi.org/10.1023/A:1018755831101.
57. Butler SF, Budman SH, Fernandez KC, et al. Development and validation of the Current Opioid Misuse Measure. *Pain*. 2007;130(1-2):144–156. http://dx.doi.org/10.1016/j.pain.2007.01.014.
58. Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. *Clin J Pain*. 2010;26(9):770–776. http://dx.doi.org/10.1097/AJP.0b013e3181f195ba.
59. Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). *Pain*. 2011;152(2):397–402. http://dx.doi.org/10.1016/j.pain.2010.11.006.
60. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3)(suppl):S2–S15. http://dx.doi.org/10.1016/j.pain.2010.09.030.
61. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders—pathways of vulnerability. *Pain*. 2006;123(3):226–230. http://dx.doi.org/10.1016/j.pain.2006.04.015.
62. Campbell CM, Buenaver LF, Finan P, et al. Sleep, pain catastrophizing, and central sensitization in knee osteoarthritis patients with and without insomnia. *Arthritis Care Res (Hoboken)*. 2015;67(10):1387–1396. http://dx.doi.org/10.1002/acr.22609.
63. Hayes AF. PROCESS: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling. www.afhayes.com. Published 2012.
64. Johnson PO, Fay LC. The Johnson-Neyman technique, its theory and application. *Psychometrika*. 1950;15(4):349–367. http://dx.doi.org/10.1007/BF02288864.
65. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med*. 2011;155(5):325–328. http://dx.doi.org/10.7326/0003-4819-155-5-201109060-00011.
66. Celerier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology*. 2000;92(2):465–472.
67. Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. *J Neurosci*. 2001;21(11):4074–4080.
68. Celerier E, Laulin J, Larcher A, Le Moal M, Simonnet G. Evidence for opiate-activated NMDA processes masking opiate analgesia in rats. *Brain Res*. 1999;847(1):18–25.
69. Laulin JP, Larcher A, Celerier E, Le Moal M, Simonnet G. Long-lasting increased pain sensitivity in rat following exposure to heroin for the first time. *Eur J Neurosci*. 1998;10(2):782–785.
70. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J. Differential modulation of remifentanil-induced analgesia and post-infusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology*. 2003;99(1):152–159.
71. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenwolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. *Pain Med*. 2011;12(12):1720–1726. http://dx.doi.org/10.1111/j.1526-4637.2011.01276.x.
72. Carcoba LM, Contreras AE, Cepeda-Benito A, Meagher MW. Negative affect heightens opiate withdrawal-induced hyperalgesia in heroin dependent individuals. *J Addict Dis*. 2011;30(3):258–270. http://dx.doi.org/10.1080/10550887.2011.581985.
73. Gebhart GF. Descending modulation of pain. *Neurosci Biobehav Rev*. 2004;27(8):729–737. http://dx.doi.org/10.1016/j.neubiorev.2003.11.008.
74. Furlan AD, Sandoval Ja, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006;174(11):1589–1594. http://dx.doi.org/10.1503/cmaj.051528.
75. Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. *Neurology*. 1994;44(5):857. http://dx.doi.org/10.1212/WNL.44.5.857.


## Appendix

## Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.amepre.2016.02.012.