Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain

Ajay D. Wasan, M.D., M.Sc., Edward Michna, M.D., J.D., Robert R. Edwards, Ph.D., M.P.H., Jeffrey N. Katz, M.D., M.S., Srdjan S. Nedeljkovic, M.D., Andrew J. Dolman, B.S., David Janfaza, M.D., Zach Isaac, M.D., Robert N. Jamison, Ph.D.

ABSTRACT

Background: Opioids are frequently prescribed for chronic low back pain (CLBP), but there are little prospective data on which patient subgroups may benefit. Psychiatric comorbidity, such as high levels of depression and anxiety symptoms (termed comorbid negative affect [NA]), is a common presentation and may predict diminished opioid analgesia and/or increased opioid misuse.

Methods: The authors conducted a 6½-month prospective cohort study of oral opioid therapy, with an active drug/placebo run-in period, in 81 CLBP patients with low, moderate, and high levels of NA. Treatment included an opioid titration phase with a prescribing physician blinded to NA group assignment and a 4-month continuation phase, during which subjects recorded daily pain levels using an electronic diary. The primary outcome was the percent improvement in average daily pain, summarized weekly.

Results: There was an overall 25% dropout rate. Despite the high NA group being prescribed a higher average daily dose of morphine equivalents, linear mixed model analysis revealed that the 24 study completers in each of the high NA and low NA groups had an average 21 *versus* 39% improvement in pain, respectively ($P < 0.01$). The high NA group also had a significantly greater rate of opioid misuse (39 *vs.* 8%, $P < 0.05$) and significantly more and intense opioid side effects ($P < 0.01$).

Conclusions: These results indicate that the benefit and risk considerations in CLBP patients with high NA *versus* low NA are distinctly different. Thus, NA is an important phenotypic variable to characterize at baseline, before deciding whether to prescribe opioids for CLBP. **(Anesthesiology 2015; 123:861-72)**

DESPITE the controversies regarding their effectiveness in chronic noncancer pain,[1] opioids are frequently prescribed for chronic low back pain (CLBP), a condition which affects 50 million adults in the United States.[2] In a recent study of 1,860 patients with CLBP from clinics across the United States, 52% were prescribed opioids.[3] Although clinicians report significant interindividual differences in opioid analgesia, there is a dearth of studies comparing whether certain patient subgroups are more or less likely to have significant pain improvement, side effects, and/or increased rates of opioid misuse.[4]

Although no such prospective studies of oral opioids have been conducted, using an intravenous opioid administration study design[5] and in a *post hoc* analysis of an oral opioid randomized controlled trial,[6] we have shown that CLBP patients with high levels of comorbid negative affect (NA) have 40% diminished opioid analgesia compared with CLBP patients with low levels of NA. NA is a cluster of related, concurrent negative emotions and thoughts (such as high levels of depression, anxiety, and pain catastrophizing), which can occur in response to chronic pain.[7] These psychologic conditions, despite their distinct features, may

What We Already Know about This Topic

- Negative affect, a constellation of anxiety, depression, and catastrophizing cognitive style, is associated in chronic pain patients with poor analgesic response to opioids and with opioid misuse, but prospective studies have not been performed to confirm this association

What This Article Tells Us That Is New

- In 81 patients with chronic low back pain prospectively studied for 6½ months with placebo followed by opioids, those with high negative affect were prescribed larger average daily doses of opioids, had less improvement in pain, and had a greater rate of opioid misuse than those with low negative affect
- These prospective data support previous cross-sectional data to suggest that negative affect presents an important risk factor in inadequate analgesia from opioids and opioid misuse

This article is featured in "This Month in Anesthesiology," page 1A.

Submitted for publication November 2, 2014. Accepted for publication April 8, 2015. From the Departments of Anesthesiology and Psychiatry (A.D.W.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and Departments of Anesthesiology (A.D.W., E.M., R.R.E., S.S.N., A.J.D., D.J., R.N.J.), Psychiatry (R.R.E., R.N.J.), Internal Medicine (J.N.K.), Orthopaedic Surgery (J.N.K.), and Physical Medicine and Rehabilitation (Z.I.), Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2015; 123:861-72

be grouped, because depression, anxiety, and catastrophizing are highly comorbid among patients with chronic pain, with correlations of 0.60 to 080, which points to an underlying construct of NA.[8–13]

High levels of NA are the most frequent presenting symptoms of a comorbid major depression or anxiety disorder, which afflict 30 to 50% of patients with CLBP receiving medical care.[14,15] Given the phenomenology of depression–anxiety spectrum disorders, focusing on the sum total of NA symptoms as an indicator of significant psychopathology is endorsed by the National Institutes of Mental Health Research Domain Criteria initiative, which identifies "NA" as one of the five primary neurobiologic domains of mental illness.[16,17] Our group and others also have shown in large cohorts with chronic musculoskeletal pain that high levels of depression and anxiety most frequently co-occur and is the most common clinical presentation of NA symptoms.[11,13] High levels of NA afflict at least 40% of CLBP patients[14] and are associated with higher levels of pain, poor functioning, and worse treatment outcomes, such as with spine surgery, nerve blocks, physical therapy, or opioids.[5,6,18–24]

The prevalent subgroup of CLBP patients with high NA is prescribed opioids at an even greater rate, in part because of their treatment resistance.[25–27] High NA in CLBP patients is also associated with greater opioid misuse,[4] with rates ranging from 50 to 60%,[28,29] and heightened craving for opioids;[30,31] although these studies are retrospective, cross-sectional, or from insurance claims databases. Consensus-based recommendations from the Food and Drug Administration define opioid misuse as, "the taking of medication with a therapeutic intent in a manner other than as prescribed,"[32] which includes using opioids at higher doses and/or frequency than prescribed, obtaining opioids from multiple providers to improve pain, and/or concurrent use of illegal drugs. In our previous studies, pain intensity level was not a predictor of prescription opioid misuse.[33,34] Rather, high NA was the most prevalent and powerful risk factor.[28,35]

Hence, it is important to understand prospectively and longitudinally whether high NA (an indicator of psychiatric comorbidity) is associated with treatment failure in CLBP patients initiating treatment with opioids. We hypothesized that in the treatment of CLBP, patients with high NA would have diminished opioid analgesia and greater rates of opioid misuse compared with CLBP patients with low NA.

Materials and Methods

Study Design and Population

This was a 6½-month prospective cohort study of oral opioid therapy, conducted from 2009 to 2012, with an active drug/placebo run-in period, in CLBP patients with low, moderate, and high levels of NA (ClinicalTrials.gov Identifier: NCT01502644). Inclusion criteria were (1) age ranging from 21 to 75 yr; (2) CLBP of at least 6 months duration with an average pain score of more than 3/10 (established with a 1-week baseline pain observation period, using daily, electronic pain ratings); (3) low back pain (LBP) meeting Quebec Task Force Criteria for Grades I to III (LBP only to LBP with intermittent radicular pain [not constant or daily] and no neurologic signs);[36] (4) no back surgery within the past year; (5) having degenerative disc disease as a component of a pain syndrome of mixed etiology, confirmed by history, examination, and a previous lumbar magnetic resonance imaging; (6) no opioid use or use of short-acting opioids only, and less than 90 mg/day in morphine equivalents and those subjects taking opioids must also have agreed to a 2-week opioid washout period before beginning medication; (7) no pregnancy or intent to become pregnant during the study period; (8) no intent to begin new pain or psychiatric treatments during the study (such as pain medication, nerve blocks, physical therapy, or psychiatric medication) or increase in any current medications; (9) no current, active substance use disorder and no history of an opioid substance use disorder (assessed with the Mini International Neuropsychiatric Interview);[37] and (10) no active suicidality or psychosis (assessed by the Mini International Neuropsychiatric Interview as well).

Eligibility was determined by investigator (A.D.W.) at the first visit through a review of a history and physical examination and magnetic resonance imaging findings confirming the presence of degenerative disc disease. Patients were included if this evaluation found that there was at least one degenerated, herniated, or torn lumbar disc with either a minimum grade III disc degeneration,[38] abnormal morphology,[39] or a hyperintense zone.[40] These inclusion criteria, used by the authors in the previous studies,[5,41,42] narrow the heterogeneity of CLBP phenotypes by including those with the commonly presenting mixed syndrome of LBP with underlying degenerated discs, and possibly spinal stenosis or facet disease, and excluding those with pain due to purely nonspecific or myofascial causes.

Subject Enrollment

Institutional review board–approved procedures were used (Brigham and Women's Hospital, Boston, Massachusetts). Volunteers were recruited from the Pain Medicine and Physiatry Spine clinics of Brigham and Women's Hospital. In addition, the hospital's research database of patients with CLBP International Classification of Diseases, ninth revision diagnosis codes was queried to generate lists of potential subjects, and their corresponding treating providers. Letters were sent to those providers requesting permission to contact their specific patients. On approval from providers, informational letters about the study were sent to these potential subjects. After telephone and medical record prescreening, subjects were enrolled at visit 1 and signed written informed consent. The consent document included opioid therapy instructions regarding the appropriate use of prescription opioids.

Visit 1

The lead investigator (A.D.W.) confirmed subject eligibility, and subjects completed baseline self-report questionnaires, along with a history and physical examination. The primary predictor was the likely presence or absence of psychiatric comorbidity. This was determined by the levels of NA symptoms within the past week, which were assigned as low, moderate, or a high level to each subject by the combined depression and anxiety subscale scores of the Hospital Anxiety and Depression Scale (HADS) total score.[43] We have used the HADS total score as an operational measure of NA and a grouping variable in previous CLBP treatment outcome studies.[23] The HADS does not include somatic items that may be attributable to medical illness, and thus, it is more appropriate for screening in chronic pain.[43] High NA was defined as more than 8 on both the depression and the anxiety subscales, Low NA was less than 6 on each subscale, and moderate NA was all other scores in between these cutoffs.[44] In CLBP specifically, scores meeting high NA criteria are highly correlated with a patient having a comorbid major depression or generalized anxiety disorder, and those meeting low NA criterion are highly unlikely to have psychiatric comorbidity.[43,44] Recent reviews have concluded that the HADS functions best as a unidimensional measure of NA, while retaining excellent psychiatric case-finding ability.[45,46]

Other baseline measures included the Brief Pain Inventory (BPI; for 24-h pain and pain interference levels),[47] the Oswestry Disability Index (for self-reported function),[48] the Neuropathic Pain Questionnaire Short Form (for symptoms of burning, shooting, and sensitivity to touch),[49] the Neuroticism Subscale of the NEO personality inventory,[50] the Pain Catastrophizing Scale,[51] and the Screener and Opioid Assessment for Patients with Pain, revised (SOAPP, for estimating the risk of opioid misuse).[33] These measures were chosen to conform to the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials Group recommendations for analgesic clinical studies.[52]

During visit 1, a urine drug test (UDT) was collected to confirm that subjects were not taking opioids and not using illegal drugs. For those subjects prescribed opioids before enrollment, they underwent a 2-week weaning period and remained off of opioids for at least 7 days before beginning medication at visit 2 (a period similar to other studies).[53] Compliance with the wean was confirmed with a UDT at visit 2.

Baseline Pain Observation Period

In between visits 1 and 2, subjects rated their average pain level (0 to 10) over the past 24 h (question 5 of the BPI) each day for 7 days using an electronic diary, triggered by an alarm. These data were inspected and downloaded at visit 2 and were averaged to determine the mean level of baseline pain for each subject. Subjects had to provide data for at least 4 of 7 days to continue in the study.

Visit 2

Subjects completed the HADS again to establish the stability of the self-reported NA symptoms and to continue so that they could not have fallen out of the group (low, moderate, or high NA) to which they were assigned (no subjects changed group). UDT results were reviewed, and a psychiatrist administered a structured psychiatric interview to determine any *Diagnostic and Statistical Manual-IV Axis 1* diagnosis, including a current substance use disorder.[37]

Active Drug/Placebo Run-in

During visit 2, subjects could choose to be prescribed morphine or oxycodone based on any previous experience with these drugs. In a double-blinded, randomized order, subjects then received either placebo or morphine/oxycodone 1 to 2 tablets up to three times a day as needed for 1 week each (crossover), dispensed by the hospital research pharmacy (all pills looked identical). The hospital research pharmacy followed up block randomization in groups of eight and maintained the double blind until the conclusion of the study. The doses for morphine were immediate-release tablets of 15 to 30 mg and for oxycodone were 5 to 10 mg three times daily as needed for pain. Subjects completed the electronic diary daily for the average pain rating as well as noting the number of medication doses they took each day. The run-in period allowed subjects to acclimate to opioid medication and to become familiar with the daily pain rating procedures. It also could clarify the role of placebo responses in predicting opioid analgesia. Subjects continued completing the electronic diaries daily in all remaining phases of the study, which were inspected at each study visit.

Opioid Treatment Periods

Visits 3 to 6, Titration of Opioids (Weeks 1 to 3). This open-label portion of the trial was conducted by a pain medicine physician–investigator (E.M.) blinded to group assignment who used a standardized titration schedule for morphine or oxycodone over a 3-week period. If a subject could not tolerate morphine or oxycodone during the run-in period (assessed at the weekly study visits), the blind was broken and they were allowed to switch to the other opioid for the rest of the study. The average pain intensity target was less than 4 of 10, and dosing was individually adjusted each week to maximize pain relief with acceptable side effects according to subject tolerability. At each weekly visit, the subject completed the BPI and a medication log (inspected by the study physician). In discussion with the subject, the dosing was adjusted using standardized parameters for long-acting and breakthrough medication for morphine or oxycodone. At the end of the titration period, the maximum allowable daily dose in morphine equivalents was 30 and 60 mg of short- and long-acting medication, respectively, three times a day (270 mg, no subjects reached the maximum possible dose).

Visits 7 to 10, Opioid Continuation Period (Weeks 4 to 20). Subjects remained at their individualized dose throughout this period, except that doses could be reduced (*e.g.*, because of side effects). They received monthly prescriptions for the short- and long-acting opioids at monthly visits. They met with a study physician and completed questionnaires at each visit (including global impression of change ratings and an opioid side effects checklist used in our previous studies).[54] In addition, at 2 and 4 months into the continuation period, opioid adherence measures were collected: the Current Opioid Misuse Measure (for self-reported misuse, score >13 highly predicts misuse using revised criteria),[55] the Addiction Behaviors Checklist (for physician-rated misuse assessment, positive score >2),[56] and a UDT. Subjects found misusing were continued in the study. We asked that subjects not begin any new pain or psychiatric treatments during the study, and we tracked this issue at monthly visits.

Opioid Tapering (Visits 11 to 13, Weeks 21 to 24)

Subjects returned for weekly visits during this period, and the individualized opioid dose was decreased by approximately 25% each week. Subjects were off of opioids by the end of the study.

Statistical Methods

Sample size calculations were based on a power of 0.80 and a 5% significance level using a two-tailed *t* test to test the hypothesis that opioids confer diminished analgesia in the high NA *versus* in the low NA group. The primary outcome measure was the percent improvement in average daily pain during the opioid continuation period (measured with daily pain ratings on the electronic diary and calculated on a weekly basis), in comparison with the average baseline pain level. Based on our previous data from intravenous morphine administration in CLBP patients with low NA *versus* high NA,[5] 20 subjects each were needed in the low and high groups to find a 33% difference in average percent improvement in pain between groups. The primary comparisons of interest were the outcomes differences between the low and the high groups. Target study completer rates in these groups were 24 subjects/group so that we would be adequately powered using multiple comparison corrections to examine our main secondary outcome of interest, the rates of drug misuse between groups. Those in the moderate group continued in all phases of the study, because little is known about their opioid analgesic outcomes as well, and their data are presented for descriptive purposes only. Data from the moderate group were also included in multiple secondary "sensitivity analyses" to further interrogate our findings.

Statistical analyses were based on a "modified intent-to-treat principle," such that subjects had to complete at least 50% of the opioid treatment period to have their data included for analysis. Otherwise, they were termed a "dropout," and these data were not included. Sources of missing data that were tracked include subject dropout, subjects missing study visits, or subjects not completing the electronic diaries at home. We also inspected the case report forms to understand whether there was any pattern to the missing data. For the primary outcome measure, we used linear mixed modeling (LMM) in SPSS version 22 (SPSS Inc., USA) to compare the low NA *versus* high NA groups over time. LMM "borrows" information pertaining to the relationship between the weekly outcomes, such that subjects missing some weekly data (but not all) can still be used for analyses. Generally, in longitudinal trials, this approach allows for inclusion in the analysis of the majority of subjects with any missing data.[57] For the LMM model, group, group × week, average baseline pain, and opioid use at baseline (yes/no) were entered as fixed effects using an autoregressive covariance structure. Subject, intercept, and week were entered as random effects, using a compound symmetry covariance structure. This approach controls for possible differences in baseline pain level and opioid use between subjects. To further address the possible impacts of missing data (those who completed at least 50% but not 100% of the opioid treatment period), we imputed data using Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) methods as part of a secondary, sensitivity analysis. For LOCF, we used the percent improvement in pain for the last week the subject was in the trial during the opioid continuation period and the first week of this period for the BOCF value.

For the secondary outcome of rates of opioid misuse between groups, similar to our previous studies,[58,59] we determined the Drug Misuse Index (DMI) at 2 and 4 months into the opioid continuation period. The DMI triangulates three domains (patient self-report [Current Opioid Misuse Measure], provider assessment of misuse [Addiction Behaviors Checklist], and UDT results) to determine adherence to opioids (adherence *vs.* misuse, a categorical outcome). A positive DMI is a positive finding of misuse on any of these three measures. Of note, positive misuse at 2 and 4 months was counted as one episode of misuse. Chi-square test was used to analyze the relationship between group and opioid misuse. Comparisons of demographics, pain history data, baseline questionnaires, and additional secondary outcome measures in relation to group were analyzed using Pearson correlations, Chi-square test, and ANOVA, depending on whether the variables were ordinal or numerical. Furthermore, sensitivity analyses using analysis of covariance (ANCOVA) were conducted to test whether any baseline variables were significant univariate or covariate predictors when added to the group of total average percent improvement in pain during the opioid continuation period. We also analyzed HADS scores as a continuous predictor of pain treatment outcomes.

Results

Figure 1 displays the study flow diagram. After assessing the eligibility in 298 volunteers, 81 subjects enrolled in the study and 72 received medication during the run-in and/or

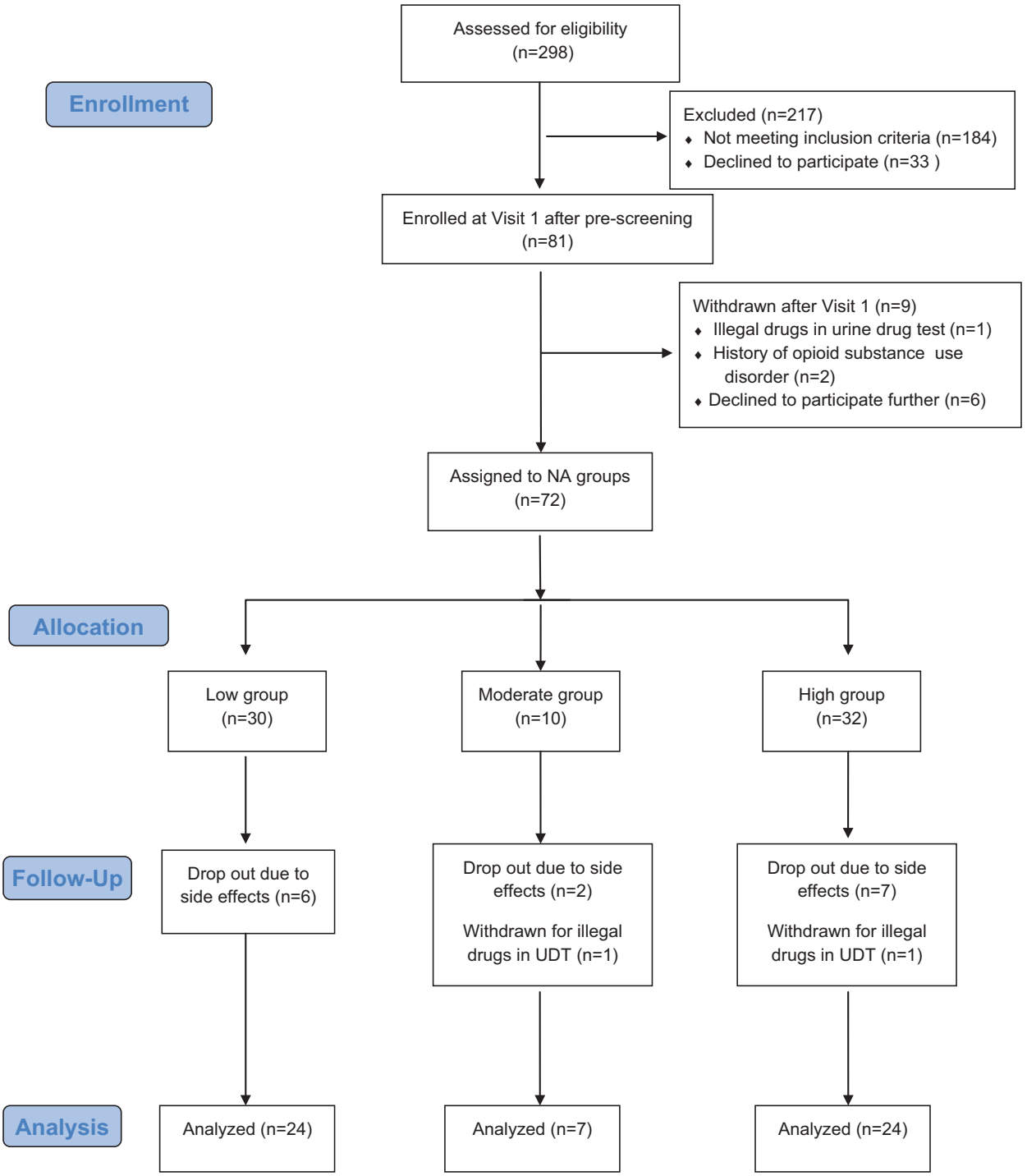

Fig. 1. Study flow diagram: This follows Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized and observational cohort studies. Note that 76% of subjects who began medication treatment completed the study. NA = negative affect; UDT = urine drug test.

opioid treatment phases. In these 72 subjects, there were 20, 30, and 25% rates of dropout/study withdrawal in the low, moderate, and high NA groups, respectively. The majority of these dropouts were due to side effects of opioid medication. Consequently, data analysis included 24 subjects each in the low and high groups and 7 in the moderate group. There were no significant differences in average age, gender distribution, average baseline pain level, and duration of pain between those who dropped out and those who completed the study. Among the 55 subjects with data suitable for analysis following a modified intent-to-treat principle: 10 of 55 finished at least half, but not the entire opioid continuation period, the distribution of these subjects was not skewed between NA groups (4 each in the low and high

groups and 2 in the moderate group), and no pattern to the missing data were found.

Table 1 displays the baseline characteristics of the three NA groups, with the moderate group being included for descriptive purposes only. The low and high groups were similar on average age, gender, and marital status distributions. The high NA group had a significantly lower percentage of those working. Average baseline pain, the duration of pain, and the percentages taking opioids or having intermittent radicular and other neuropathic pain complaints were similar between groups. Those on opioids before enrollment were taking an average of 28 mg of morphine equivalents per day (range, 5 to 80 mg). The average baseline pain levels just before treatment and after any wean were not significantly different between those taking or not taking opioids at baseline. Although the low NA group tended to have intermittent radicular pain more frequently, the high NA group tended to have a more frequent composite presentation of neuropathic symptoms. The high NA group did report significantly greater pain interference, more disability, and were at a higher risk of opioid misuse. The high group also tended to have a more frequent history of substance abuse. Every subject in the high group had a psychiatric diagnosis of some type of an affective disorder (table 1, psychiatric diagnoses). The group of subjects with major depression is mainly composed of those with major depression with anxious features (90% of cases). The high NA group also had significantly greater pain catastrophizing and neuroticism scores, which were significantly correlated with total HADS scores (Pearson correlation coefficients 0.58 and 0.66, respectively, $P < 0.01$ for both).

For the run-in period, table 2 displays the means of the percent improvement in pain per group for the active and placebo weeks. The high NA group had less analgesia with active drug or placebo than the low NA group, and there was a significant difference between groups for placebo analgesia ($P = 0.025$). During the run-in period, those in the low group used an average of 64 mg/day of oral morphine equivalents, whereas the high group used 75 mg/day (nonsignificant difference).

During the opioid titration phase, the high group was titrated to a higher average daily amount of morphine equivalents (94.7 *vs.* 75.6 mg). For the continuation phase,

Table 1. Demographics and Baseline Pain History

Variable	Psychiatric Group			*P* Value (Low NA *vs.* High NA)
	Low NA (n = 24)	Moderate NA (n = 7)	High NA (n = 24)	
Age, mean (yr)	55	54	49	0.08
Gender (% female)	67	43	58	0.38
Work status (% working)	42	29	12	0.03
Marital status (% married)	54	57	58	0.6
Taking opioids at baseline (% yes)	33	14	42	0.38
Baseline pain (mean, 0–10)	7.1	6.6	7.5	0.39
Pain duration (mean, yr)	7.3	12.4	8	0.72
Radicular pain (% yes)*	75	57	54	0.31
Neuropathic pain (% yes)†	58	71	81	0.09
Pain interference (mean, 0–10)‡	5.6	6.6	7.5	0.002
Function (% disability)§	35.6	40.1	50.3	0.007
Opioid misuse risk score (mean, 0–96)‖	10.7	14.7	24	0.0001
Substance abuse history (% yes)	12	14	21	0.35
Comorbid major depression (% yes)#	4	0	67	0.0001
Generalized anxiety disorder (% yes)	4	14	8	0.64
Posttraumatic stress disorder (% yes)	0	0	21	0.018
Obsessive-compulsive disorder (% yes)	0	0	8	0.61
Panic disorder (% yes)	0	0	8	0.61
Bipolar disorder (% yes)	0	0	8	0.61
Dysthymia (% yes)	0	0	46	0.001
Adjustment disorder (% yes)	0	29	12	0.2
Depression symptoms (mean, 0–21)**	4	7.5	11.7	0.0001
Anxiety symptoms (mean, 0–21)††	4.7	9.5	12.7	0.0001
Pain catastrophizing (mean, 0–52)‡‡	20.9	33	32.7	0.0001
Neuroticism (mean, T score)§§	42.4	44.9	60	0.0001

* Intermittent only per history (not constant or daily). † Composite measure of burning, shooting, and sensitivity to touch symptoms, assessed with the Neuropathic Pain Questionnaire. ‡ Average of the pain interference items on the Brief Pain Inventory. § Oswestry Disability Index. ‖ Screener for Opioid Assessment in Patients with Pain, Revised. Score >17 predicts a high likelihood of future opioid misuse. # Results of the mini-international neuropsychiatric interview (MINI). ** Depression subscale of the Hospital Anxiety and Depression Scale (HADS). †† Anxiety subscale of the HADS. ‡‡ Pain catastrophizing scale. §§ Neuroticism subscale of the NEO Personality Inventory "T" scores above 60 ≥85th percentile for neuroticism (NEO-FFI-Personality Inventory, Costa P, 1985).

Table 2. Secondary Outcomes

Variable	Psychiatric Group		
	Low NA (n = 24)	Moderate NA (n = 7)	High NA (n = 24)
Active drug run-in period analgesia (mean, % improvement in pain)	18.3 (±29.2)*	26.4 (±39.9)	6.8 (±14.2)
Placebo run-in period analgesia (mean, % improvement in pain)	14.9 (±29.1)	11.1 (±14.7)	−1.9 (±15.3); *P* = 0.025†
Changes from beginning of study to end of continuation phase			
Maintenance opioid dose (mean, mg daily morphine equivalents)	75.6 (±44.6)	72.2 (±52.9)	94.7 (±47.8)
Negative affect (% change)‡	27.5 (±45.6)	4.2 (±24.6)	31.1 (±27.1)
Pain interference (% change)§	39.5 (±42.7)	30.4 (±25.7)	20.2 (±27.6); *P* = 0.0001
Function (% change disability score)‖	1 (±12.2)	4.0 (±8.6)	5.8 (±15.1)
Patient global impression of change (median distribution of seven categories)#	Much improved	Much improved	Minimally improved; *P* = 0.026
Drug Misuse Index (% positive)	8.3	14.3	39.1; *P* = 0.013
Opioid side effects (mean total, 0–18)**	4.1 (±3.8)	4.7 (±.6)	7.0 (±5.2); *P* = 0.0001
Opioid side effects (mean intensity, 0–10)**	1.8 (±1.6)	2.3 (±2.0)	3.1 (±2.0); *P* = 0.0001

* ±SD. † *P* values are comparisons of low *vs*. high. ‡ Measured with monthly administration of the Hospital Anxiety and Depression Scale. § Measured by averaging the pain interference items on the Brief Pain Inventory collected monthly. ‖ Measured by averaging the Oswestry Disability Index Score collected monthly. # Measured by averaging the impression of change ratings collected monthly. ** Measured by the Opioid Side Effects Checklist collected monthly.

figure 2 displays the group differences in average percent improvement in pain by week and the estimated means for each group from the LMM analysis. The high group had significantly less average percentage improvement in pain (20.6 *vs*. 38.6%, *P* = 0.01, F = 6.5, the 95% CI for the differences in mean analgesia between groups = 3.7 to 32.2). The moderate group had an average 30% improvement in pain during the continuation phase. Those with missing data in the low group had an average of 41.9% improvement in pain (n = 4), whereas those in the high group with missing data had an average 14.9% improvement in pain (n = 4).

For the secondary outcomes (table 2), the low NA group reported: (1) significantly greater change in pain interference (items 9A to G of the BPI, which includes general activity, walking, work, sleep, and social relations, *P* = 0.0001); (2) "much improved" global impression of change *versus* "minimally improved" in the high NA group, *P* = 0.026; and (3) lower total number of opioid side effects (*P* = 0.0001) and a lower intensity of side effects (*P* = 0.0001). Within the low and high groups, those on opioids at baseline did report a lower total number of side effects (*P* = 0.001). There were no differences in either group in self-reported changes in physical function. Both groups reported similar degrees of improvements in NA during the course of the study. The high NA group had a significantly greater rate of opioid misuse (39.1 *vs*. 8.3%, *P* = 0.013) and significantly more craving for opioids than the low NA group (item 11 of the SOAPP, revised, *P* = 0.041).

Sensitivity Analyses

First, total scores on the HADS in all subjects (low, moderate, and high groups, n = 55) were treated as a continuous predictor of average weekly percent improvement in pain during the opioid continuation period (outcome). Linear regression indicated that HADS score accounted for 15% of the variance in analgesic outcomes, such that a higher HADS score was associated with less improvement in pain with opioid treatment ($R^2 = 0.15$; std $\beta = -0.38$, *P* = 0.005). This result is consistent with the LMM results in the low and high groups.

Next, Pearson correlation coefficients between analgesia for the active and placebo run-in periods *versus* analgesia for the opioid continuation period (average percent improvement in pain) were 0.60 and 0.75, respectively (*P* < 0.01 for both). An analysis of partial correlation coefficients revealed that these correlations were not significantly different within psychiatric groups. In other words, regardless of NA group assignment, pain improvements during either the active or the placebo run-in weeks were significant predictors of subsequent opioid analgesia. Furthermore, six subjects in the low NA group had more than 20% pain improvement during the placebo run-in week and a corresponding average 49.7% improvement in pain in the continuation period (*vs*. the 37.8% low group mean). This indicates that those six subjects with low NA who had heightened placebo analgesia were not the drivers of the robust analgesic responses for the group as a whole.

Using ANOVA, table 3 displays the analysis of baseline pain history and demographic variables that were significant univariate predictors of analgesia during the continuation period (average percent improvement in pain), such as age, gender, working status, baseline pain, intermittent radicular pain, the composite neuropathic pain score, opioid misuse risk score (SOAPP scores), and the levels of pain catastrophizing or neuroticism. Baseline pain interference scores, SOAPP scores, and taking opioids before study entry were significant predictors (*P* < 0.05 for both). In addition, opioid dose during the study and the specific psychiatric diagnosis

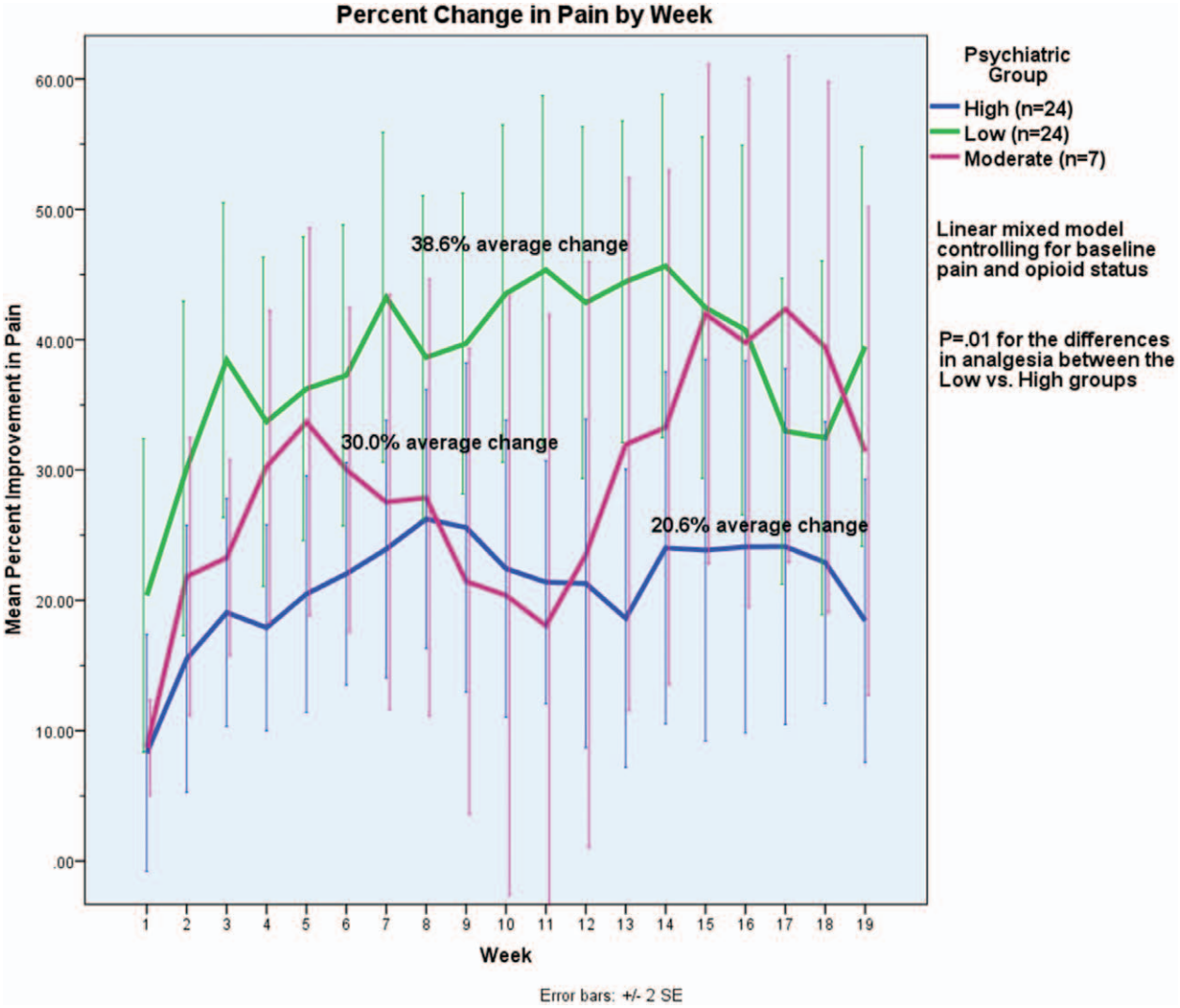

Fig. 2. Percent change in pain by week and by group: These curves depict the average percent improvement in pain per group for each week of the trial. Weeks 1 to 3 are the titration weeks, and the end of week 3 through week 19 is the continuation (maintenance) period. Note that there are only seven subjects in moderate group and that the primary comparison is between the low *versus* high negative affect groups.

were tested and neither were significant predictors of analgesia. Next, pain interference, SOAPP score, and opioid status at baseline were continued to the next stage of modeling and entered into separate ANCOVA models with group to test main and interaction effects that may predict analgesia during the continuation period. Pain interference and SOAPP score were not significant main or interaction effects.

However, opioid use at baseline was a significant confounder to analgesic responses in the low NA group only. In the low group, the 33% of subjects on opioids at baseline had an average 22% improvement in pain during the opioid continuation period, whereas those not on opioids in this group had 48% improvement. In the high group, those on opioids before study had an average of 20% improvement in pain, whereas those not on opioids had 19% improvement. In an ANCOVA model with group, baseline opioid status, and group × opioids as predictors and average percent improvement in pain during the continuation period as the outcome, only group ($F = 5.35$, $P = 0.026$) and the interaction term (group × opioids, $F = 5.34$, $P = 0.026$) were significant (R^2 for the model = 0.29). In addition, the adjusted means of percent improvement in pain in each group was decreased by approximately 10% in the low group, but not in the high group, compared with an ANOVA model with group as the only predictor. These analyses indicate that opioid use at baseline affects analgesia responses in the low group only and that NA group still remains a significant predictor of analgesia.

In terms of missing data in the eight subjects who did not complete the entire opioid continuation period, imputation using LOCF into the LMM model resulted in the high group having 20.5% average percentage improvement

Table 3. Univariate Analysis of Baseline Predictors of Pain Improvement*

Variable (Units)	R^2	F	Significance
Age (yr)	0.005	0.26	0.61
Gender (female and male)	0.001	0.06	0.82
Work status (yes, no, and retired)	0.014	0.23	0.87
Marital status (yes and no)	0.001	0.07	0.8
Taking opioids at baseline (yes and no)	0.09	4.7	0.04†
Baseline pain (0–10)	0	0.01	0.91
Pain duration (yr)	0.01	0.57	0.46
Radicular pain (yes and no)‡	0.009	0.24	0.79
Neuropathic pain (yes and no)§	0.04	0.94	0.4
Pain interference (0–10)‖	0.12	7.2	0.01†
Function (0–100%)#	0.003	0.16	0.67
Opioid misuse risk score (0–96)**	0.17	9.9	0.003†
Substance abuse history (yes and no)	0.015	0.78	0.38
Pain catastrophizing (0–52)††	0.05	0.12	0.74
Neuroticism (T score)‡‡	0.02	1.2	0.28

* Average weekly percent improvement in pain during the opioid continuation period. † Continued to analysis of covariance stage of testing. ‡ Intermittent only per history (not constant or daily). § Composite measure of burning, shooting, and sensitivity to touch symptoms, assessed with the Neuropathic Pain Questionnaire. ‖ Average of the pain interference items on the Brief Pain Inventory. # Oswestry Disability Index. ** Screener for Opioid Assessment in Patients with Pain, Revised. Score >14 predicts a high likelihood of future opioid misuse. †† Pain Catastrophizing Scale. ‡‡ Neuroticism Subscale of the NEO Personality Inventory "T" scores above 60 ≥85th percentile for neuroticism (NEO-FFI-Personality Inventory, Costa P, 1985).

in pain during the opioid continuation period *versus* 39.8% in the low group ($P = 0.01$, F = 7.4, the 95% CI for the differences in mean analgesia between groups = 5.0 to 33.6). For BOCF, the high group had 20.1 *versus* 40.1% average percentage improvement in pain in the low group ($P = 0.01$, F = 7.8, the 95% CI for the differences in mean analgesia between groups = 5.6 to 34.3). Both imputation methods resulted in model estimates of analgesia between groups that were highly similar to the model without imputation.

Discussion

In this prospective cohort study of patients with CLBP, we found that psychiatric comorbidity (specifically, high NA) was a significant predictor of poor opioid treatment outcomes compared with CLBP patients with low NA, including almost 50% less improvement in pain, increased side effects, and 75% more opioid misuse. Subjects were carefully phenotyped to have the commonly presenting mixed CLBP syndrome of disc disease, facet, stenosis, and/or neuroforaminal components possibly contributing to their chronic pain. They were also phenotyped psychiatrically to fall into distinct groups of low, moderate, and high levels of NA (and no active substance use disorder), with corresponding higher rates of psychiatric comorbidity and higher levels of pain catastrophizing, and neuroticism in the high NA group. As a result, the low and high groups had a similar underlying pain condition and only differed significantly on their psychologic characteristics.

Despite being prescribed a higher daily dose of opioid compared with the low NA group, patients in the high NA group experienced almost 50% less improvement in pain during the opioid continuation phase of the study (20.6 *vs.* 38.6% improvement) and tended to have tolerance (diminishing analgesia over time). Interestingly, the high NA group reported a greater benefit to their mood (31% improvement in NA symptoms) than to their pain (19%). However, the improvement in mood is far less than the 50% improvement in symptoms benchmark used to determine effective treatments for NA.[60] Our findings do not suggest that opioids are a potential treatment for high NA or depression or anxiety disorders. Although we have shown previously that patients with chronic pain prescribed opioids tend to self-medicate anxious and depressive feelings with opioids,[30] we are unaware of any studies that have examined specifically whether CLBP patients with depression or anxiety disorders prescribed opioids obtain differential effects on their mood *versus* pain.

Regarding other secondary outcomes, the high NA group rated opioids as less beneficial to them compared with the low NA group and reported less improvement in pain interference, with a corresponding greater incidence and intensity of opioid side effects. Furthermore, the high NA group had significantly more opioid misuse and reported more cravings for prescription opioids. We have shown that craving for prescription opioids is a risk factor predicting misuse and a potential psychologic mechanism by which high NA may lead to prescription opioid misuse.[31,59]

Interrogation of our findings through sensitivity analyses revealed that they are robust. The active/placebo run-in period analysis addresses the issue that differences in placebo *versus* active drug responses between groups might explain our findings. This unique crossover/cohort hybrid study provides a methodology for examining placebo responses in an otherwise uncontrolled study, with the understanding that a brief placebo run-in period is not equivalent to an efficacy study with a true "placebo arm." In terms of other possible confounders,

the ANCOVA analyses only uncovered previous opioid use as a significant covariate, which affected the low NA group only. NA group remained a significant predictor of opioid analgesia. Perhaps the reason why the risk of opioid misuse at baseline (increased SOAPP scores in the high NA group) was only a significant univariate predictor was that there are several items regarding mood symptoms on the SOAPP. Thus, the SOAPP and HADS questionnaires do not form entirely separate constructs and share a significant overlapping variance. Given the baseline differences in pain catastrophizing and neuroticism between groups, it was surprising that neither of these were significant univariate or multivariate predictors of average pain improvement during the continuation phase. Our data and analysis indicate that if symptoms of depression and anxiety are controlled for, neither pain catastrophizing nor neuroticism are constructs predicting independently the responses to opioid therapy. These results, as well as numerous other published studies from our group,[5,6,11,23,31] highlight the importance of NA being a strong, independent predictor of pain treatment responses. In addition, although catastrophizing and neuroticism are powerful predictors in patients with chronic pain of the levels of pain and function,[19,61] fewer studies have prospectively examined these as predictors of outcomes for specific pain treatments. One of the relevant studies is by Smeets *et al.*[62] who compared physical therapist–directed exercise or advice-based treatment for LBP, and they also found that pain catastrophizing levels did not predict clinical treatment responses.

Our results indicate that the outcomes of opioid therapy in CLBP patients with a high or low degree of psychiatric comorbidity (as categorized by levels of NA) are distinctly different, with less benefit, more side effects, and greater risks in patients with high levels of NA. This prospective longitudinal study confirms findings from retrospective and cross-sectional studies by our group and others. Moreover, the 5-month opioid treatment period in this study is substantially longer than the majority of oral opioid studies in CLBP, which typically average 3 months in length.[63,64] This longer treatment period enabled a better study of longitudinal issues, such as the development of tolerance and opioid misuse, which cannot be well studied in the shorter trials. Our findings address the controversy over long-term opioid prescribing for CLBP through showing prospectively that there may be subgroups who can potentially do well on this therapy long-term and a distinct subgroup with psychiatric comorbidity who tends to do poorly.

Our data suggest that in deciding to prescribe opioids, it is prudent to assess for psychiatric comorbidity and, more specifically, high levels of NA. We have now demonstrated in 3 studies, each with a different study design and totaling more than 250 subjects,[5,6] that comorbid high NA predicts poor opioid treatment outcomes in patients with CLBP.

Rather than refusing to prescribe opioids for this subgroup, we suggest that comorbid high NA be identified and treated early in the course of CLBP and preferably even before LBP becomes chronic. Large randomized controlled trials testing a variety of NA treatments, such as antidepressant medications,[60] cognitive behavioral therapy,[65] or fear of movement physical therapy,[66] have each shown efficacy for improving LBP, function, and mood. One implication of this work is that if high NA is identified and treated early in the course of LBP, one could prevent this vulnerable subgroup from being prescribed opioids if pain and function were improved through NA treatment. Furthermore, for those prescribed opioids, successful treatment of NA may improve opioid analgesia and reduce the chances of opioid misuse. These suppositions merit further testing in clinical studies.

There are a number of important limitations to consider in our study. First, although analgesia from opioids was lower in the high NA group, these participants may still have felt that the therapy was beneficial to them because of possible nonanalgesic opioid effects and may have wished it to continue. Second, this study does not explore what effect the chronicity of high NA (from months to years in duration) has on opioid analgesia. Although our results are statistically significant, one could argue that the sample size is too small to be a definitive, confirmatory trial.

In summary, high NA predicts poor opioid treatment outcomes in CLBP. This finding provides an impetus for conducting further studies of patients with CLBP and high NA to improve opioid analgesia in this population and to reduce or prevent opioid misuse.

Acknowledgments

This study was supported by the National Institute of Drug Abuse of the National Institutes of Health grant K23 DA020682 (Bethesda, Maryland; to Dr. Wasan, Principal Investigator), and Investigator Award from the Arthritis Foundation (Atlanta, Georgia; to Dr. Wasan, Principal Investigator).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Wasan: UPMC Pain Medicine, 5750 Centre Avenue, 400, Pittsburgh, Pennsylvania 15232. awasan@partners.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Ballantyne JC, Mao J: Opioid therapy for chronic pain. N Engl J Med 2003; 349:1943–53
2. Fourney DR, Andersson G, Arnold PM, Dettori J, Cahana A, Fehlings MG, Norvell D, Samartzis D, Chapman JR: Chronic low back pain: A heterogeneous condition with challenges for an evidence-based approach. Spine (Phila Pa 1976) 2011; 36(21 suppl):S1–9

3. Taylor-Stokes G, Lobosco S, Pike J, Sadosky AB, Ross E: Relationship between patient-reported chronic low back pain severity and medication resources. Clin Ther 2011; 33:1739–48
4. Howe CQ, Sullivan MD: The missing 'P' in pain management: How the current opioid epidemic highlights the need for psychiatric services in chronic pain care. Gen Hosp Psychiatry 2014; 36:99–104
5. Wasan AD, Davar G, Jamison R: The association between negative affect and opioid analgesia in patients with discogenic low back pain. Pain 2005; 117:450–61
6. Jamison RN, Edwards RR, Liu X, Ross EL, Michna E, Warnick M, Wasan AD: Relationship of negative affect and outcome of an opioid therapy trial among low back pain patients. Pain Pract 2013; 13:173–81
7. Mounce C, Keogh E, Eccleston C: A principal components analysis of negative affect-related constructs relevant to pain: Evidence for a three component structure. J Pain 2010; 11:710–7
8. Turk DC: The potential of treatment matching for subgroups of patients with chronic pain: Lumping *versus* splitting. Clin J Pain 2005; 21:44–55
9. Watson D, Clark AC: Affects separable and inseparable: On the hierarchical arrangements of the negative effects. J Pers Soc Psychol 1992; 62:489–505
10. Fernandez E: Interactions between Pain and Affect, Anxiety, Depression, and Anger in Pain. Dallas, Advanced Psychological Resources, 2002, pp 13–32
11. Wasan AD, Anderson NK, Giddon DB: Differences in pain, psychological symptoms, and gender distribution among patients with left- vs right-sided chronic spinal pain. Pain Med 2010; 11:1373–80
12. Janssen SA: Negative affect and sensitization to pain. Scand J Psychol 2002; 43:131–7
13. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K: Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med 2008; 70:890–7
14. Dersh J, Gatchel RJ, Mayer T, Polatin P, Temple OR: Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. Spine (Phila Pa 1976) 2006; 31:1156–62
15. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R: Chronic spinal pain and physical-mental comorbidity in the United States: Results from the national comorbidity survey replication. Pain 2005; 113:331–9
16. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P: Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 2010; 167:748–51
17. Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Wang PS, Cuthbert BN: Developing constructs for psychopathology research: Research domain criteria. J Abnorm Psychol 2010; 119:631–9
18. Linton S: A review of psychological risk factors in back and neck pain. Spine 2000; 25:1148–56
19. Pincus T, Burton AK, Vogel S, Field AP: A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine (Phila Pa 1976) 2002; 27:E109–20
20. Chou R, Shekelle P: Will this patient develop persistent disabling low back pain? JAMA 2010; 303:1295–302
21. Celestin J, Edwards RR, Jamison RN: Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: A systematic review and literature synthesis. Pain Med 2009; 10:639–53
22. Daubs MD, Norvell DC, McGuire R, Molinari R, Hermsmeyer JT, Fourney DR, Wolinsky JP, Brodke D: Fusion *versus* nonoperative care for chronic low back pain: Do psychological factors affect outcomes? Spine (Phila Pa 1976) 2011; 36(21 suppl):S96–109
23. Wasan AD, Jamison RN, Pham L, Tipirneni N, Nedeljkovic SS, Katz JN: Psychopathology predicts the outcome of medial branch blocks with corticosteroid for chronic axial low back or cervical pain: A prospective cohort study. BMC Musculoskelet Disord 2009; 10:22
24. Karp JF, Yu L, Friedly J, Amtmann D, Pilkonis PA: Negative affect and sleep disturbance may be associated with response to epidural steroid injections for spine-related pain. Arch Phys Med Rehabil 2014; 95:309–15
25. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB: Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 2006; 166:2087–93
26. Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK: Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. Pain 2010; 151:625–32
27. Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, Rutter CM, Weisner C, Banta-Green C, Campbell C, Von Korff M: Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry 2009; 31:564–70
28. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN: Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain 2007; 23:307–15
29. Grattan A, Sullivan MD, Saunders KW, Campbell CI, Von Korff MR: Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. Ann Fam Med 2012; 10:304–11
30. Wasan AD, Ross EL, Michna E, Chibnik L, Greenfield SF, Weiss RD, Jamison RN: Craving of prescription opioids in patients with chronic pain: A longitudinal outcomes trial. J Pain 2012; 13:146–54
31. Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD: The association between negative affect and prescription opioid misuse in patients with chronic pain: The mediating role of opioid craving. J Pain 2014; 15:90–100
32. Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH; Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership: Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013; 154:2287–96
33. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN: Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). J Pain 2008; 9:360–72
34. Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, Jamison RN: Development and validation of the Current Opioid Misuse Measure. Pain 2007; 130:144–56
35. Martel MO, Wasan AD, Jamison RN, Edwards RR: Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. Drug Alcohol Depend 2013; 132:335–41
36. Werneke MW, Hart DL: Categorizing patients with occupational low back pain by use of the Quebec Task Force Classification system *versus* pain pattern classification procedures: Discriminant and predictive validity. Phys Ther 2004; 84:243–54
37. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic

psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33

38. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N: Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976) 2001; 26:1873–8
39. Fardon DF, Milette PC; Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology: Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine (Phila Pa 1976) 2001; 26:E93–113
40. Aprill C, Bogduk N: High-intensity zone: A diagnostic sign of painful lumbar disc on magnetic resonance imaging. Br J Radiol 1992; 65:361–9
41. Wasan AD, Loggia ML, Chen LQ, Napadow V, Kong J, Gollub RL: Neural correlates of chronic low back pain measured by arterial spin labeling. Anesthesiology 2011; 115:364–74
42. Wasan AD, Kong J, Pham LD, Kaptchuk TJ, Edwards R, Gollub RL: The impact of placebo, psychopathology, and expectations on the response to acupuncture needling in patients with chronic low back pain. J Pain 2010; 11:555–63
43. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361–70
44. Bjelland I, Dahl AA, Haug TT, Neckelmann D: The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002; 52:69–77
45. Cosco TD, Doyle F, Ward M, McGee H: Latent structure of the Hospital Anxiety And Depression Scale: A 10-year systematic review. J Psychosom Res 2012; 72:180–4
46. Doyle F, Cosco T, Conroy R: Why the HADS is still important: reply to Coyne & van Sonderen. J Psychosom Res 2012; 73:74
47. Cleeland CS, Ryan KM: Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singapore 1994; 23:129–38
48. Fairbank JC, Pynsent PB: The Oswestry Disability Index. Spine (Phila Pa 1976) 2000; 25:2940–52
49. Backonja MM, Krause SJ: Neuropathic pain questionnaire—Short form. Clin J Pain 2003; 19:315–6
50. Costa PT, McCrae RR: The NEO Personality Inventory Manual. Orlando, Psychological Assessment Resources, 1985, pp 1–131
51. Sullivan MJ, Pivik J: The Pain Catastrophizing Scale: Development and validation. Psych Assess 1995; 7:524–32
52. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113:9–19
53. Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H: Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996; 347:143–7
54. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP: Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine 1998; 23:2591–600
55. Meltzer EC, Rybin D, Saitz R, Samet JH, Schwartz SL, Butler SF, Liebschutz JM: Identifying prescription opioid use disorder in primary care: Diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011; 152:397–402
56. Wu SM, Compton P, Bolus R, Schieffer B, Pham Q, Baria A, Van Vort W, Davis F, Shekelle P, Naliboff BD: The addiction behaviors checklist: Validation of a new clinician-based measure of inappropriate opioid use in chronic pain. J Pain Symptom Manage 2006; 32:342–51
57. Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP: Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inform J 2008; 42:303–19
58. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD: Substance misuse treatment for high-risk chronic pain patients on opioid therapy: A randomized trial. Pain 2010; 150:390–400
59. Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN: Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain 2009; 25:193–8
60. Kroenke K, Bair MJ, Damush TM, Wu J, Hoke S, Sutherland J, Tu W: Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: A randomized controlled trial. JAMA 2009; 301:2099–110
61. Goubert L, Crombez G, Van Damme S: The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: A structural equations approach. Pain 2004; 107:234–41
62. Smeets RJ, Maher CG, Nicholas MK, Refshauge KM, Herbert RD: Do psychological characteristics predict response to exercise and advice for subacute low back pain? Arthritis Rheum 2009; 61:1202–9
63. Rauck RL, Nalamachu S, Wild JE, Walker GS, Robinson CY, Davis CS, Farr SJ: Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: A randomized double-blind, placebo-controlled study. Pain Med 2014; 15:975–85
64. Hale M, Khan A, Kutch M, Li S: Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin 2010; 26:1505–18
65. Eccleston C, Williams AC, Morley S: Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2009: CD007407
66. George SZ, Zeppieri G Jr, Cere AL, Cere MR, Borut MS, Hodges MJ, Reed DM, Valencia C, Robinson ME: A randomized trial of behavioral physical therapy interventions for acute and subacute low back pain (NCT00373867). Pain 2008; 140:145–57