Objective pain sensitivity affects sleep quality in opioid dependent males on methadone maintenance therapy

Aim Pain associated poor sleep quality has been reported among opioid dependent patients on methadone maintenance therapy (MMT) but objective pain data are lacking. This study aimed to investigate the rate of objective pain sensitivity and the relationship between pain sensitivity and sleep quality in this susceptible male population. **Methods** A total of 168 male patients from MMT clinic in Kelantan, Malaysia were included into the study. Objective pain tolerance to cold pressor test (CPT) was evaluated at 0 hour and at 24 hours after the first CPT. Malay version of the Pittsburgh Sleep Quality Index – PSQI and the subjective opiate withdrawal scale (SOWS) questionnaires were administered to evaluate the quality of sleep and withdrawal symptoms, respectively. **Results** The mean age of the study participants was 37.22 (SD 6.20) years old. The mean daily methadone dose was 76.64 (SD 37.63) mg/day. The mean averaged SOWS score was 5.43 (SD 6.91). The averaged pain tolerance time ranged from 7 to 300 s with a mean time of 32.16 (SE 2.72) s, slightly below the cut-off score of 37.53 s. More specifically, 78.6% (n = 132) of patients were identified as 'pain-sensitive' (averaged pain tolerance time ≤ 37.53 s), and 36 (21.4%) were 'pain-tolerant' patients (averaged pain tolerance time > 37.53 s). The mean global PSQI score was 5.47 (SD 2.74). The pain-sensitive patients reported poorer sleep quality with mean (SD) of 5.78 (2.80) compared with pain-tolerant patients with mean (SD) of 4.31 (2.18) ($p = 0.005$). With analysis of covariance, pain-sensitive patients were found to have higher global PSQI scores (adjusted mean 5.76, 95% CI 5.29; 6.22) than pain-tolerant patients (adjusted mean 4.42, 95% CI 3.52; 5.32) ($p = 0.010$).
Conclusions Many opioid dependent male patients on MMT are pain-sensitive. A poorer sleep quality is associated with objective pain sensitivity. Pain and sleep complaints in this susceptible population should not be overlooked.

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ABSTRACT

Aim Pain associated poor sleep quality has been reported among opioid dependent patients on methadone maintenance therapy (MMT) but objective pain data are lacking. This study aimed to investigate the rate of objective pain sensitivity and the relationship between pain sensitivity and sleep quality in this susceptible male population.

Methods A total of 168 male patients from MMT clinic in Kelantan, Malaysia were included into the study. Objective pain tolerance to cold pressor test (CPT) was evaluated at 0 hour and at 24 hours after the first CPT. Malay version of the Pittsburgh Sleep Quality Index – PSQI and the subjective opiate withdrawal scale (SOWS) questionnaires were administered to evaluate the quality of sleep and withdrawal symptoms, respectively.

Results The mean age of the study participants was 37.22 (SD 6.20) years old. The mean daily methadone dose was 76.64 (SD 37.63) mg/day. The mean averaged SOWS score was 5.43 (SD 6.91). The averaged pain tolerance time ranged from 7 to 300 s with a mean time of 32.16 (SE 2.72) s, slightly below the cut-off score of 37.53 s. More specifically, 78.6% (n = 132) of patients were identified as 'pain-sensitive' (averaged pain tolerance time ≤ 37.53 s), and 36 (21.4%) were 'pain-tolerant' patients (averaged pain tolerance time > 37.53 s). The mean global PSQI score was 5.47 (SD 2.74). The pain-sensitive patients reported poorer sleep quality with mean (SD) of 5.78 (2.80) compared with pain-tolerant patients with mean (SD) of 4.31 (2.18) ($p = 0.005$). With analysis of covariance, pain-sensitive patients were found to have higher global PSQI scores (adjusted mean 5.76, 95% CI 5.29; 6.22) than pain-tolerant patients (adjusted mean 4.42, 95% CI 3.52; 5.32) ($p = 0.010$).

Conclusions Many opioid dependent male patients on MMT are pain-sensitive. A poorer sleep quality is associated with objective pain sensitivity. Pain and sleep complaints in this susceptible population should not be overlooked.

Key words: Methadone maintenance therapy (MMT); opioid dependence; pain; pain tolerance, pain sensitivity; sleep quality

INTRODUCTION

Pain is a complex, subjective and has wide inter-individual variability (Fillingim, 2005). Recent studies indicated that acute and chronic pain were common among a largely male patients on methadone maintenance therapy (MMT) (Peles *et al.*, 2006; Eyler, 2013). For example, a one-time self-report survey found that, out of 227 methadone-maintained patients from a single clinic setting in Baltimore, 137 patients (60%) had chronic pain (Dunn *et al.*, 2014). Inadequate pain management may contribute to failure in achieving overall treatment outcomes with MMT (Hines *et al.*, 2008; Eyler, 2013).

In recent years, attention has shifted its focus to quality of sleep in methadone maintenance patients (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009; Sharkey *et al.*, 2009; Sharkey *et al.*, 2010; Liao *et al.*, 2011; Sharkey *et al.*, 2011). For example, in a study that systematically studied the prevalence of sleep disorders among 135 heroin-dependent Chinese on MMT in Hunan Province, China found a majority of the patients (n = 134 subjects, 99.23%) had a total PSQI score of > 5, suggestive of sleeping problems (Liao *et al.*, 2011). It is possible that the relationship between sleep disturbance and pain might be circular or reciprocal, with disturbed sleep contributing to enhanced pain sensitivity, or disturbed sleep is caused by pain (Smith and Haythornthwaite, 2004; Edwards *et al.*, 2008).

Although a number of studies have assessed the association between patients' experiences of pain and sleep in patients on MMT (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009), less is known about the relationship of patients' pain sensitivity or pain tolerance on sleep quality. Existing studies only evaluated patients' experiences of pain using subjective self-reported pain questionnaires (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009), but not with quantitative studies. Using cold pressor test (CPT) and pain tolerance time to quantify pain experience, patients can be categorized into pain-sensitive and pain-tolerant groups (Chen *et al.*, 1989). The CPT is a standardized and naturalistic pain model, producing pain analogous to naturally occurring type of pain and effectively mimics chronic pain conditions such as dental and back pain, thus allowing valid generalization into clinical pain (Chen *et al.*, 1989). The reliability and validity of the cold pain model has been established with good validity and test-retest reliability (Chen *et al.*, 1989; Ruscheweyh *et al.*, 2010; Lewis *et al.*, 2012).

The objectives of our study were to determine the rate of pain sensitivity among male patients on MMT and the relationship between pain sensitivity and sleep quality. Quantitative experimental pain method was used to measure pain sensitivity in the current study.

METHODS

Participants

The sample population consisted of opioid dependent male patients who were undergoing treatment between March and October 2013 at Hospital Universiti Sains Malaysia (USM) and other MMT clinics in the state of Kelantan including Kota Bharu, Pasir Mas, Pasir Puteh and Bachok. Opioid dependency was defined according to the DSM IV criteria (American Psychiatric Association, 1994). Study participants were included if they were (a) in the national MMT programme with a duration of participation of more than one month; (b) more than 18 years of age; (c) free of regular use of alcohol; (d) free of intoxication; (e) able to understand study protocols and to follow simple study instructions; and (f) willing to sign written informed consent. Exclusion criteria included the following: (a) presence of acute medical, surgical or psychiatric illness; (b) current intake of benzodiazepines, cannabinoids and barbiturates; (c) on regular anticonvulsants, neuroleptics or analgesics; (d) history of chronic or ongoing acute pain; (e) history of analgesics ingestion within 3 days before the CPT; and (f) presence of severe cognitive impairment which might interfere with pain assessments and/or communication.

This prospective study was approved by the Human Research Ethics Committee (HREC), Universiti Sains Malaysia (USM) in Kelantan, Malaysia (Reference number: USMKK/PPP/JEPeM (253.3 [14]) and the Medical Research & Ethics Committee (MREC) at the Ministry of Health (MOH), Malaysia (Reference number: NMRR-13-524-16614).

Study procedure

All included study participants would be interviewed to obtain detailed demographic and clinical data including details related to their past drug history and recent drug use, and other treatment variables. All interviews were conducted by one interviewer (ZZ), with experience of five or more years of managing opioid dependence. Subjects were also asked to complete the validated

Malay version of the Pittsburgh Sleep Quality Index (PSQI-M) and subjective opiate withdrawal scale (SOWS). The SOWS was scored at 0 hour (i.e. approximately 30 minutes before taking their morning dose of methadone), and at 24 hours after the dose intake. Participants would be asked for any history of analgesics consumption within 72 hours prior to CPT testing and for a history of any chronic and acute painful conditions. The CPT took place in a quiet, dedicated area at the Clinical Trial Unit (CTU), USM and was administered by a trained research assistant (SHH). Details of the instruments used in the current study are described below.

Instruments

Cold pressor test

The CPT method utilized in the current study was adapted based on previous reports from Chen *et al.* (1989) and Compton *et al.* (2001a). The CPT apparatus consisted of a 48 quart cool box filled with a mixture of two-thirds crushed ice and one-third tap water. The resulting ice-water mix was stirred to maintain a constant temperature of 0 – 2 °C by adding ice with temperature constantly being monitored by a digital indoor-outdoor-thermometer (TFA Dostmann GmbH & Co.KG, Wertheim).

A standardized written instruction was read out aloud to all the participants before conducting the first CPT. They were instructed to place their non-dominant hand and also forearm in the ice bath with their palm flat at the bottom of the tank; so that ice water would cover the hand and approximately 10 cm of the forearm. The test was truncated at 300 s, since after this time point, the numbness would set in and the pain diminished (Wolf and Hardy, 1941; Harris and Rollman, 1983; Compton *et al.*, 2001b).

Pain tolerance was defined as the most severe pain that a participant was willing to tolerate (i.e. the time elapsed when the participant withdrew his hand after immersion). Pain tolerance to CPT was evaluated at 0 hour and repeated at 24 hours. Pain tolerance was quantified in seconds. Time for pain tolerance in participants who did not withdraw their hand even after 300 seconds was recorded as 300 s. After withdrawal of the immersed hand, each subject was given a piece of dry towel to dry their hand.

Malay version of the Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-administered written questionnaire to measure subjective sleep quality and disturbances during the previous month and to discriminate between 'good' and 'poor' sleepers (Buysse *et al.*, 1989). The PSQI is a validated questionnaire that has been translated into several languages including the Malay language (PSQI-M). Permission for use of the Malay version of the PSQI was first obtained from the author (Buysse *et al.*, 1989). Information on the administration and scoring instructions are available from the website of the Sleep Medicine Institute, University of Pittsburgh (University of Pittsburgh Sleep Medicine Institute (UPSMI), 2013).

The 19 individual items of the PSQI were used to generate seven component scores: subjective sleep quality (one item), sleep latency (two items), sleep duration (one item), habitual sleep efficiency (three items), sleep disturbances (nine items), use of sleep medications (one item), and daytime dysfunction (two items). Each of the seven component scores was determined based on scoring guidelines, with the seven component scores each with a potential score range of $0 - 3$, where '3' reflected the negative extreme on the Likert Scale. The sum of these seven component scores yielded one global score with a score range of $0 - 21$, with higher scores indicating a poorer subjective sleep quality.

Subjective Opiate Withdrawal Scale

The SOWS was used to measure the severity of the opiate withdrawal syndrome over a wide range of common signs and symptoms (Jain *et al.*, 2011; Salehi *et al.*, 2011; Chawla *et al.*, 2013; Mustafa *et al.*, 2013). A valid and reliable instrument (Handelsman *et al.*, 1987), SOWS was available in the Malay language (Mohamed Nazar, 2013) with permission acquired prior to use.

The SOWS is a self-administered scale which contains 16 symptoms. Patients were asked to rate each symptom according to severity. Each item is rated on a 4 point Likert scale where zero (0) is not at all, one (1) is a little, two (2) is moderately, three (3) is quite a bit and four (4) is extremely, with a total score between 0 to 64. The researcher's role here is to assist the patient to complete the evaluation, not to do it for them or to interpret their symptomology. In the current study, for most participants, the 16 item SOWS took less than 10 minutes to complete. The SOWS was

administered at two time points (at 0 hour i.e. approximately 30 minutes before taking their morning dose of methadone and at 24 hours after the dose intake) during the study.

Urine drug test

Urine drug screens for morphine, tetrahydrocannabinol, amphetamines and benzodiazepines using drugs of abuse rapid test, F.A.C.T.S [TM] 4 in 1 Combo Dipcard Rapid Test (MOR/THC/AMP/BZO) (Scientifacts Sdn. Bhd., Malaysia) were performed for each subject twice in one week prior to the CPT. Subjects with two consecutive negative urine tests (during the first and second urine drug screening test) would be included into the study.

Data and statistical analysis

Descriptive analysis with mean and standard deviation (SD) for continuous variables was calculated unless otherwise stated. The averaged pain tolerance time and SOWS score were determined (i.e. the average of two measurements taken at 0 hour and at 24 hours). By using the averaged pain tolerance time cut-off of '37.53 seconds' (taken as the mean plus two standard error, i.e. upper bound of 95% confidence interval for mean), participants were categorized into pain-sensitive ($\leq$ 37.53 seconds) and pain-tolerant (> 37.53 seconds) groups (Neziri *et al.*, 2011).

An unpaired independent t-test was used to compare differences in characteristics between pain-sensitive and pain-tolerant groups including age, age of first illicit drug use, age of first opioid abuse, duration of opioid exposure, duration of opioid addiction, duration of illicit drug use prior to joining MMT, duration in MMT, methadone dose and averaged SOWS score.

Likewise, the unpaired independent t-test was applied to compare the mean global PSQI scores between pain-sensitive and pain-tolerant groups without adjusting for other effects. The difference of mean global PSQI scores between pain-sensitive and pain-tolerant groups was further elucidated using an analysis of covariance (ANCOVA) test by taking the duration of opioid addiction as a covariate because this variable was significantly different between the two groups. All analyses were performed using SPSS version 22 (SPSS Inc., Chicago, US). The limit of significance was set to 0.05.

RESULTS

Demographic and clinical characteristics

Of 169 eligible patients, 168 (99.4%) agreed to participate in this study. One patient did not participate in the study due to a lack of interest. Most patients were Malays (98.8%) and only two were Chinese. The mean age of study participants was 37.22 (SD = 6.20, range: 25 - 55) years old. The mean duration for patients in the MMT program was 2.92 (SD = 2.09, range: 0.33 – 9.00) years. The mean daily methadone dose was 76.64 (SD = 37.63, range: 20 - 360) mg/day. The mean averaged SOWS score was 5.43 (SD = 6.91, range: 0 – 48). The comparisons between pain-sensitive and pain-tolerant groups in demographic and clinical patient characteristics are shown in Table 1. The two groups were well matched with respect to age, age of first illicit drug use, age of first opioid abuse, duration of opioid exposure, duration of illicit drug use prior to joining MMT, duration in MMT, methadone dose, averaged SOWS score and monthly income. However, duration of opioid addiction was significantly different between pain-sensitive and pain-tolerant groups (p = 0.044).

The Pittsburgh Sleep Quality Index (PSQI) and pain tolerance time

Table 2 shows the mean global PSQI scores, pain tolerance time of the opioid dependent patients at 0 hour and at 24 hours after the first CPT, and averaged pain tolerance time (i.e. the average of two measurements taken at 0 hour and at 24 hours). Of 168 patients, three patients did not complete the PSQI questionnaire and therefore, their global PSQI scores were not calculated. Based on the available data, the mean global PSQI score was 5.47 (SD = 2.74), slightly above a cut-off score of 5, thus indicating poor overall sleep quality among patients.

The averaged pain tolerance time ranged from 7 to 300 s with a mean time of 32.16 (SD = 35.25) s, only slightly below a cut-off score of 37.53 s. More specifically, 78.6% (n = 132) of patients were identified as 'pain-sensitive' (averaged pain tolerance time ≤ 37.53 s), and 36 (21.4%) had averaged pain tolerance time > 37.53 s, indicating 'pain-tolerant' patients.

Comparison of global PSQI scores between pain-sensitive and pain-tolerant patients

The pain-sensitive patients reported poorer sleep quality, with a mean PSQI score (SD) of 5.78 (2.80) compared with pain-tolerant patients with a mean score (SD) of 4.31 (2.18) (p = 0.005).

The analysis of covariance revealed that pain-sensitive patients have higher global PSQI scores (adjusted mean 5.76, 95% CI 5.29; 6.22) than pain-tolerant patients (adjusted mean 4.42, 95% CI 3.52; 5.32) ($p = 0.010$) (Table 3).

DISCUSSION

Sleep disorders are frequently reported by opioid dependent patients during methadone treatment but it is unknown if pain sensitivity plays a significant role. Sleep disturbances could have a profound impact on quality of life, health and even impair engagement with treatment programme leading to continued illicit drug use (Staedt *et al.*, 1996; Hsu *et al.*, 2012; Pud *et al.*, 2012).

In the present study, we found, as hypothesized, that pain-sensitive male patients on MMT had a poorer sleep quality compared to pain-tolerant patients. The aetiology of sleep disorders among patients in methadone treatment is likely multifactorial and complex. Pain, co-morbid psychiatric symptoms, concomitant drug abuse problems and methadone dose were found to be associated with increased subjective sleep disorders among patients on methadone treatment (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009). However, it can be difficult to determine whether sleep disorder is related to the methadone, the pain, the co-morbid psychiatric illnesses, the patients' history of substance misuse, current medications and drug abuse, other causes, or a mixture of the sleep-disturbing factors. It is noteworthy that our result confirms the existence of a poorer sleep quality among those patients on MMT with pain sensitivity that is measured quantitatively.

The importance of the present study is that it uses the cold pressor test (CPT) as an objective measurement of pain sensitivity. Previous studies, measured subjective pain experiences and did not objectively measure pain (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009).

In many cases where patients complaining about pain, it can be difficult to know who is faking a pain complaint ("drug-seeking") to get an opioid prescription (Fields, 2011). Thus, it is possible that without any objective test, patient in this high risk population can fake their pain experiences. The fact that a significant percentage of patients on MMT reported chronic pain is

intriguing (Dunn *et al.*, 2014), therefore an objective measure like CPT is clearly important in providing further support to subjective pain questionnaires. Our result showed that opioid dependent male patients on MMT represent a pain-sensitive subset of clinical patients. From a clinical point of view, it is important to highlight that the percentage of patients "being pain-sensitive" is higher than "being pain-tolerant".

The results of our study did not only add to the growing evidence on the relationship of pain and sleep quality in opioid dependent patients on methadone maintenance therapy (MMT) but also provided new evidence on the effect of objective pain sensitivity on sleep quality in this susceptible largely male population. Previous studies have included patients with co-morbid psychiatric illnesses such as depression and anxiety (Stein *et al.*, 2004; Peles *et al.*, 2006; Peles *et al.*, 2009). In this study, we had excluded patients with psychiatric illnesses, individuals who were taking benzodiazepines, cannabinoids and barbiturates, and individuals with chronic or ongoing acute pain, in order to minimize the possible effects of co-morbid illnesses had on sleep parameters.

As with all studies, this study has limitations. Our study did not use an objective sleep evaluation test such as polysomnography (PSG). However, a study reported that objective sleep measures concur with subjective sleep experience in MMT patients (Sharkey *et al.*, 2011). Future studies should consider using PSG hand in hand with objective pain measure in addition to other sleep parameters such as sleep architecture. Only male subjects were included in the current study but this reflected the cohort population of drug abusers in Malaysia where more than 90% of them are males (Manan *et al*., 2013). Furthermore, this can minimise the possible effects of gender had on cold pressor pain response (Fillingim and Maixner, 1995; Fillingim *et al.*, 2009; Alabas *et al.*, 2012; Racine *et al.*, 2012) and sleep (Krishnan and Collop, 2006).

Based on the results of our study, the PSQI scores should probably be evaluated in every opioid dependent patient on methadone therapy complaining of pain that is confirmed using objective measure. When they indicate a poor sleep quality, we recommend referring these patients to a sleep laboratory in order to identify sleep problems through a polysomnographic evaluation, if available, so that an intervention or a suitable treatment protocol can be established.

To conclude, pain sensitivity is associated with impaired sleep quality in opioid dependent patients on MMT. Sleep disturbance and pain sensitivity in this population should not be disregarded.

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Table 1. Demographic and clinical patient characteristics

Variable	Total (N = 168)		Pain-tolerant (N = 36)		Pain-sensitive (N = 132)		Mean difference (95% CI)	t-statistic (df)	p-value[a]
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	37.22	6.20	36.11	5.68	37.52	6.32	-1.41 (-3.71, 0.89)	-1.21 (166)	0.227
Age of first illicit drug use (years)	19.24	4.17	20.20	5.05	18.98	3.88	1.22 (-0.34, 2.78)	1.55 (163)	0.124
Age of first opioid abuse (years)	22.24	4.86	22.80	5.15	22.08	4.78	0.72 (-1.11, 2.54)	0.77 (163)	0.441
Duration of opioid exposure (years)	15.03	6.95	13.37	7.50	15.48	6.76	-2.11 (-4.71, 0.50)	-1.60 (163)	0.112
Duration of opioid addiction (years)	14.24	7.00	12.13	7.59	14.81	6.75	-2.68 (-5.29, -0.07)	-2.03 (163)	**0.044**
Duration of illicit drug use prior to joining MMT (years)	15.08	6.91	13.47	7.68	15.52	6.65	-2.04 (-4.63, 0.54)	-1.56 (163)	0.121
Duration in MMT (years)	2.92	2.09	2.43	1.54	3.05	2.21	-0.62 (-1.26, 0.03)	-1.91 (76)	0.060
Methadone dose (mg)	76.64	37.63	78.00	32.29	76.27	39.05	1.73 (-12.46, 15.92)	0.24 (163)	0.810
Averaged SOWS score*	5.43	6.91	4.26	8.65	5.74	6.35	-1.48 (-4.04, 1.08)	-1.14 (166)	0.256
Monthly income (RM)	844.42	474.71	968.57	501.48	811.00	463.57	157.57 (-19.81, 334.96)	1.75 (163)	0.081

* The average of two measurements taken at 0 hour (i.e. immediately (approximately 30 minutes) before taking their morning dose of methadone), and at 24 hours after the dose intake.
[a]p values were obtained using an unpaired independent t-test
N, number of subject; MMT, methadone maintenance therapy; SOWS, subjective opiate withdrawal scale; RM, Ringgit Malaysia; SD, standard deviation; CI, confidence interval; df, degree of freedom

Table 2: **The Pittsburgh Sleep Quality Index (PSQI) and pain tolerance data in opioid dependent patients**

Variable	Mean	SD	SE	95% CI Lower limit	Upper limit
Global PSQI score (N = 165)	5.47	2.74	0.21	5.05	5.89
Pain tolerance (second)					
At 0 hour (N = 168)	36.09	37.11	2.86	30.44	41.74
At 24th hour (N = 163)	27.87	36.36	2.85	22.24	33.49
Averaged* (N = 168)	32.16	35.25	2.72	26.79	37.53

* The average of two measurements taken at 0 hour and at 24 hours after the first CPT

N, number of subject; PSQI, Pittsburgh Sleep Quality Index (PSQI); SD, standard deviation; SE, standard error; CI, confidence interval

Table 3: Comparison of global PSQI scores between pain-sensitive and pain-tolerant patients with and without controlling for duration of opioid addiction

A: Without controlling for duration of opioid addiction

Group	Global PSQI		Mean difference (95% CI)	t-statistic (df)	p-value[a]
	Mean	SD			
Pain-tolerant (N = 35)	4.31	2.18	-1.47 (-2.48, -0.46)	-2.88 (163)	0.005
Pain-sensitive (N = 130)	5.78	2.80			

[a]p values were obtained using an unpaired independent t-test
N, number of subject; PSQI, Pittsburgh Sleep Quality Index (PSQI); SD, standard deviation; CI, confidence interval; df, degree of freedom

B: Controlling for duration of opioid addiction

Group	Adj. mean[a] (95% CI)	Adj. mean difference (95% CI)[b]	F stat. (df)	p-value[c]
Pain-tolerant (N = 35)	4.42 (3.52, 5.32)	-1.34 (-2.35, -0.32)	6.73 (1, 162)	0.010
Pain-sensitive (N = 130)	5.76 (5.29, 6.22)			

[a]Adjusted mean controlling for duration of opioid addiction
[b]Bonferroni adjustment for 95% confidence interval for difference
[c]p values were obtained using an analysis of covariance
N, number of subject; CI, confidence interval; df, degree of freedom