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Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients

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Abstract

Good evidence exists to suggest that individuals on opioid maintenance for the treatment of addiction (i.e. methadone) are less tolerant of experimental pain than are matched controls or ex-opioid addicts, a phenomenon theorized to reflect opioid-induced hyperalgesia (OIH). Agonist activity at the excitatory ionotropic N-methyl-D-aspartate (NMDA) receptor on dorsal horn neurons has been implicated in the development of both OIH and its putative expression at the clinical level—opioid tolerance. The aim of this study was to evaluate the potential utility of the NMDA-receptor antagonist, dextromethorphan (DEX), to reverse or treat OIH in methadone-maintenance (MM) patients. Utilizing a clinical trial design and double-blind conditions, changes in pain threshold and tolerance [cold pressor (CP) and electrical stimulation (ES)] following a 5-week trial of DEX (titrated to 480 mg/day) in comparison with placebo was evaluated in a well-characterized sample of MM patients. The sample ($n = 40$) was 53% male and ethnically diverse (53% Latino, 28% African American, 10% White, 9% other), with a mean age of 48.0 years ($SD = 6.97$). Based on t -test analyses, no difference was found between groups on CP pain threshold, CP pain tolerance, ES pain threshold or ES pain tolerance, both pre- and postmedication. Notably, DEX-related changes significantly differed by gender, with women tending to show diminished tolerance for pain with DEX therapy. These results support that chronic high-dose NMDA antagonism does not improve tolerance for pain in MM patients, although a gender effect on DEX response is suggested.

Keywords

Cold-pressor pain; dextromethorphan; electrical stimulation pain; hyperalgesia; methadone; opioids

INTRODUCTION

Good evidence exists to support the hypothesis that individuals on the opioid maintenance agent methadone for the treatment of opioid addiction are relatively hyperalgesic to experimental pain. Across electrical and thermal (cold) nociceptive stimuli, methadone

patients reliably demonstrate poor tolerance for experimental pain and are, on average, between 42 and 76% less tolerant of cold-pressor (CP) pain than are normal controls matched on age, gender and ethnicity (Compton *et al.* 2000; Doherty *et al.* 2001; Athanasos *et al.* 2006; Pud *et al.* 2006). These data have implications for the management of pain in methadone patients and support increased analgesic need in patients receiving this addiction pharmacotherapy (Newshan 2000; Scimeca *et al.* 2000; Alford, Compton & Samet 2006).

It has been suggested that the relative pain intolerance noted in these opioid-maintained individuals is the result of an increasingly appreciated consequence of ongoing opioid exposure—opioid-induced hyperalgesia (OIH) (see reviews Mao 2002; Ossipov *et al.* 2005; Angst & Clark 2006). Convergent lines of pre-clinical and clinical evidence indicate that opioid administration not only provides a rapid and powerful analgesia but concurrently sets into motion certain anti-analgesic or hyperalgesic opponent processes, which can be observed both during opioid activity and withdrawal (Li, Angst & Clark 2001; Vanderah *et al.* 2001a; Mao, Sung & Lim 2002; Angst *et al.* 2003; Koppert *et al.* 2003; Simonnet 2005; Chu, Clark & Angst 2006). In that OIH and opioid analgesic tolerance may occur simultaneously by a similar mechanism (Colpaert 1996; Laulin *et al.* 1999; Gardell *et al.* 2006; Mao 2006), the implications of this altered pain state have become of interest to investigators and clinicians involved in the prescription of opioid analgesics for chronic pain (Mercadante *et al.* 2003a; Wilder-Smith & Arendt-Nielsen 2006; Chang, Chen & Mao 2007; Koppert & Schmelz 2007).

Much work has been done implicating agonist activity at the excitatory ionotropic N-methyl-D-aspartate (NMDA) receptor on dorsal horn neurons in the development of OIH. As eloquently demonstrated in the work of Mao and colleagues (Mao, Price & Mayer 1995; Mayer *et al.* 1999; Mao *et al.* 2002), binding of opioids to the G-protein linked μ -opioid receptors on spinal neurons induces intracellular molecular changes such that co-localized excitatory NMDA receptors are essentially upregulated or more sensitive to glutamate, thus resulting in increased transmission of nociceptive signals.

A clinical population for which the efficacy of NMDA antagonists on OIH has not been evaluated is pain-free individuals receiving ongoing opioid therapy, patients on MM therapy for the treatment of opioid addiction. As noted, MM patients evidence significant OIH to experimental pain, but evidence for NMDA receptor-mediated mechanisms in its development have not been established. The aim of this study was to evaluate the ability of the NMDA-receptor antagonist, DEX, to diminish OIH to experimental pain in a well-characterized sample of MM individuals. Given the ability of the potent NMDA antagonists, ketamine (Celerier *et al.* 2000; Duncan & Spiller 2002; Angst *et al.* 2003; Mercadante, Villari & Ferrera 2003b; Anghelescu & Oakes 2005; Holtman & Wala 2005; Van Elstraete *et al.* 2005) and MK801 (in animals) (Laulin *et al.* 1999; Li *et al.* 2001), to counteract OIH and opioid tolerance, the well-tolerated, but weaker, DEX was chosen for evaluation. It was hypothesized that DEX therapy would effectively increase tolerance for experimental pain in this sample, and thus suggest an excitatory amino acid mechanism underlying their notable hyperalgesia.

MATERIALS AND METHODS

The ability of the NMDA antagonist, DEX, to decrease OIH in MM patients was tested using a placebo-controlled randomized clinical trial design. Threshold and tolerance to CP and electrical-stimulation (ES) pain were measured prior to and following 5 weeks of continuous DEX/placebo therapy; although pain threshold has not been shown to be a reliable indicator of OIH, evaluation of the specific effects of DEX on pain responses supported keeping the measure in the design. To control for the effects of methadone dosing on pain responses, pre- and post-DEX pain measures were collected on two separate occasions, at trough (immediately prior to dose) and peak (150 minutes postdose) methadone blood levels.

Sample

A convenience sample of study participants was recruited from a single methadone clinic affiliated with UCLA Integrated Substance Abuse Programs, providing a recruitment pool of approximately 300 patients. Enrolled participants were selected so as to be between the ages of 18 and 55, in good general physical and psychological health, compliant in MM treatment and on a stable dose of methadone for at least 6 weeks. Based upon previous demonstrations (Compton *et al.* 2000; Doverty *et al.* 2001; Athanasos *et al.* 2006; Pud *et al.* 2006), it was anticipated, although not confirmed a priori, that all subjects would demonstrate some degree of OIH by virtue of their prolonged and ongoing exposure to opioids.

Individuals were excluded from study participation if they met DSM-IV dependence criteria for alcohol, benzodiazepine, CNS stimulant, marijuana or other drug of abuse; had a neurologic or psychiatric condition (i.e. peripheral neuropathy, schizophrenia, neuropathic pain, Raynaud's disease, urticaria) known to affect pain responses; or were currently taking analgesic medication (opioid or otherwise) for a painful condition on a regular basis. Before participation, all potential subjects provided informed consent in strict adherence with UCLA Institutional Review Board standards. Subjects were compensated for their time and compliance. Based upon extant data describing the effect of DEX therapy on postoperative (Helmy & Bali 2001; Weinbroum *et al.* 2001) and putative neuropathic (Sindrup & Jensen 1999, 2000) hyperalgesia, a large effect size (0.80) for DEX on OIH was assumed, indicating that 20 subjects per group would provide 80% power to detect group differences with a 0.05 one-sided significance level.

Measures

Collected prior to and 5 weeks following medication administration, two separate experimental pain induction methods, CP and ES, were utilized to evaluate the ability of DEX to diminish putative OIH in MM patients. Both are well established pain induction techniques, demonstrated to be analogous to clinical types of pain, and provide quantifiable measures of pain threshold and tolerance.

CP pain—A standardized CP pain induction procedure as adapted by Eckhardt *et al.* (1998) was utilized to assess the anti-hyperalgesic effects of DEX. Specifically, participants were seated in a comfortable chair and a blood pressure cuff was placed on the non-dominant

limb. Eye patches were placed over the eyes to minimize distraction. Participants first placed their forearm into a bath of room-temperature water for 2 minutes, and during the final 15 seconds the blood pressure cuff was inflated to 20 mm Hg below diastolic pressure. At exactly 2 minutes, participants were assisted in removing the forearm from the warm bath and placing it immediately in an adjacent ice bath ($1.0 \pm 0.5^{\circ}\text{C}$). A water pump in the ice water was utilized to prevent laminar warming around the immersed limb. Participants were not spoken to during the cold-water immersion in order to minimize any distraction or cues for time that could adversely influence pain threshold and tolerance levels. Participants held an event-marker button in their dominant hand to indicate when (1) pain was initially detected (threshold); and (2) when pain could be no longer tolerated and the arm was voluntarily removed from the ice bath (tolerance); both were operationalized as time in seconds from initial ice bath immersion. All trials were truncated at 5 minutes, as after this time point, pain perception diminishes as numbness sets in.

ES technique—ES pain was induced using a commercially available SD9 Square Pulse Stimulator (Grass Technologies, West Warwick, RI). As with the CP protocol, participants were seated in a comfortable chair, eye patches were placed and they were not spoken to during the pain induction period. Following the application of electro-conductive gel to the earlobe and placement of an ear clip, electrical pulses (frequency 0.7 pulses per second) of 14 milliseconds duration were increased by 2-V increments (starting at 0 V) every 1.5 seconds (Dyer *et al.* 1999). Participants were asked to press the event marker when each of the following sensations occurred: (1) the onset of pain (threshold); and (2) when pain could no longer be tolerated (tolerance) and the stimulation immediately stopped; corresponding voltages were entered into the data analysis.

Procedures

Following a screening visit to establish study eligibility, consenting participants were familiarized with the CP and ES procedures, and baseline pain measures were collected. Subjects were randomized to DEX or matched lactose placebo and titrated up to a total oral daily dose of 480 mg DEX over a 1-week period ($120 \text{ mg} \times 2 \text{ days}$, $200 \text{ mg} \times 2 \text{ days}$, $320 \text{ mg} \times 2 \text{ days}$); the placebo group underwent an identical ‘titration’. The maximum DEX dose was selected based on that shown to be tolerable in MM patients with chronic oral administration (Cornish *et al.* 2002); the 5-week dosing period was chosen to approximate the effective dosing period for the treatment of neuropathic pain suggested by the meta-analyses of Sindrup & Jensen (1999, 2000). Subjects were then maintained at this dose for the next 4 weeks and evaluated weekly by a blinded study clinician for health status and side effect assessment and concomitant medications use. Subjects were encouraged to refrain from illicit drug use over the course of the study and received a small monetary bonus for submitting a clean (free from illicit opioid, cocaine, amphetamine/methamphetamine, benzodiazepine or marijuana metabolites) specimen for urine toxicology weekly. Medication compliance was evaluated at each visit with pill counts.

At baseline and immediately following 5 weeks of medication, CP and ES pain responses were measured on two occasions separated by 72 hours, at both methadone trough (just prior to methadone dosing) and peak (150 minutes following methadone dosing) blood levels. All

pain testing sessions took place in a private setting and the pain stimulus administered by one of two trained research assistants. Subjects were instructed to refrain from caffeine and nicotine for 1 hour prior to testing and throughout the testing session. Prior to each pain testing session, subjects underwent a brief screening to ensure physical and psychological stability. First day of menstrual cycle was recorded for all female subjects.

Within each pain session, ES was administered first followed by CP, separated by at least 15 minutes to control for carryover effects. Respiration, electrocardiogram (EKG), pulse oximetry, heart rate and blood pressure were continuously monitored prior, during and for at least 10 minutes following each pain test to ensure return to baseline. Testing occurred at approximately the same time each morning around clinic methadone dosing hours. Immediately following pain testing, approximately 10 cc of blood was drawn to enable measurement of methadone and DEX plasma levels at the time of testing.

Data analysis

Following description of the sample characteristics, group differences were evaluated to ensure the adequacy of random assignment. A correlation matrix was inspected to detect relationships among patient demographics, methadone dose and pain responses. To evaluate the effect of DEX on putative OIH, difference in pain response from baseline to after treatment were compared for the group treated with DEX and that treated with placebo for CP and ES methods for pain threshold and pain tolerance, at peak and trough methadone blood levels, separately. Comparison of the two treatment groups was done using *t*-test at 95% level of significance.

RESULTS

A total of 40 subjects were randomized to group and completed the study (see Table 1); four missed one of the four data collection points and are noted in the Table (*n*). The mean age of participants was 48 years, and the average methadone dose was 69 mg/day. The sample was fairly evenly divided by gender (53% male) and reflected the primarily Latino community in which the clinic was situated. Study groups were essentially identical with the exception that those assigned to DEX were approximately 4 years older than those assigned to the placebo group. Indicators of protocol adherence were good: plasma levels of DEX were well within therapeutic levels ($\bar{x}$ = 130.8 ng/mL), and weekly pill counts showed that 88% of the sample was (90% compliant in taking the study medication as prescribed. Seventy-six percent of urines submitted by subjects over the course of the study were free of illicit drugs (opioids other than methadone, cocaine, amphetamine, methamphetamine, benzodiazepines and/or marijuana). The average peak methadone plasma level was 203.3 (SD = 88.39), and average trough was 137.9 (SD = 69.88).

Table 2 lists the CP and ES pain responses of all subjects prior to and following medication treatment at peak and trough methadone levels. All pain responses were approximately normally distributed. Pre- and post-methadone cold pressor and pre-methadone pain ES responses were unrelated to the demographics of the sample at baseline and week 5, whereas baseline ES pain threshold post-methadone was significantly related to race (Latino > African American > White > American Indian; $F = 3.94$; $P < 0.05$).

Evaluating the effect of DEX on pain responses OIH, changes in mean CP and ES threshold and tolerance were compared between medication groups. The difference of pain responses between pre- and post-treatment was not significant between the two treatment groups on any of the pain responses when compared at trough and peak methadone level ($P > 0.05$ for all tests; see Fig. 1). Age (but not methadone dose) was positively and significantly related to difference in number of volts of ES pain tolerance between pre- and post-DEX at trough methadone level ($r = 0.39$, $P = 0.02$). Interestingly, although a trend for increased CP pain tolerance with DEX treatment was evident in the male participants, female subjects evidenced just the opposite, with a diminished tolerance of pain on DEX, and to a degree significantly different than men ($t = (2.12; P = 0.04$; see Fig. 2). There were no other significant relationships between characteristics of the subject and DEX pain (ES and CP) responses.

In general, DEX was well tolerated by study subjects. Of those adverse effects deemed as related to the study medications, 82% were classified as mild. Approximately 14% of the adverse events reported were either 'probably' or 'definitely' related to the study medication. Out of these, 18 (50%) were complaints of drowsiness, 11 (31%) of dizziness/lightheadedness and 3 (8%) of lethargy. The remaining symptoms (constipation, head pressure, intoxication and upset stomach) were each reported only once. Of the three most commonly occurring adverse events, the number of dizziness/lightheadedness reports was significantly higher in the DEX group (91%) than in the placebo group (90%) ($\chi^2 = 6.08$, $P < 0.05$).

DISCUSSION

This study sought to determine if the NMDA antagonist, DEX, would be effective in treating the previously described pain intolerance of MM patients. Hypothesized to be a latent hyperalgesia secondary to chronic opioid exposure, it was hoped that this pharmacotherapy might normalize the pain responses of opioid-dependent patients and thus provide a tool for improving the treatment of clinical pain in this at-risk population.

Providing pre-clinical support of this hypothesis, NMDA antagonists have been shown to diminish (Li *et al.* 2001) or prevent (Larcher *et al.* 1998; Celerier *et al.* 1999, 2000; Laulin *et al.* 1999, 2002; Mao *et al.* 2002; Richebe *et al.* 2005; Van Elstraete *et al.* 2005) morphine, fentanyl and heroin OIH in mouse and rat models. Koppert and colleagues (Angst *et al.* 2003; Koppert *et al.* 2003) extended this finding to healthy human controls, demonstrating that concurrent or subsequent administration of the NMDA-receptor antagonist S-ketamine diminished or reversed remifentanyl-induced hyperalgesia to experimental pain.

Evidence for the efficacy of the relatively weak NMDA antagonist, DEX, to offset OIH in clinical samples with pain, however, has been mixed. Acute DEX dosing has been shown to decrease opioid analgesic requirement (putative OIH) in postoperative patients (Helmy & Bali 2001; Weinbroum *et al.* 2001), but appears less effective in doing so for patients with chronic malignant and non-malignant pain (Heiskanen *et al.* 2002; Galer *et al.* 2005; Dudgeon *et al.* 2007). The pre-clinical data of Chaplan, Malmberg & Yaksh (1997) show

DEX to be less effective in treating formalin-induced hyperalgesia than the more potent MK801, suggesting that the weak activity of the former may account for negative findings.

However, OIH to experimental pain has been prospectively demonstrated in a small sample of well characterized chronic pain patients undergoing a 1-month trial of morphine therapy (Chu *et al.* 2006), suggesting that the apparent lack of effect of DEX in previous trials might be related to the use of outcome measures (morphine analgesia, average daily pain scores, reduced analgesic need) not directly reflective of OIH.

Extending this literature to evaluate the effects of NMDA-receptor antagonists on putative OIH in methadone patients, these data indicate that chronic high-dose DEX therapy had no effect on subjects' overall ability to tolerate experimental cold and electrical pain. Utilizing a different patient population and more direct measure of hyperalgesia (tolerance to experimental pain), this study provides further evidence that NMDA antagonism with DEX does not mitigate OIH in the clinical setting.

These negative findings support continued consideration of alternate hypothesized mechanisms underlying the development of OIH (see Fig. 3). Porreca and colleagues have provided good pre-clinical evidence (Vanderah *et al.* 2001a) that OIH may in fact be the result of the activation of supraspinal descending pain facilitation systems arising from μ -opioid receptor activation (Gardell *et al.* 2006) in the rostral ventromedial medulla (RVM) (see Vanderah *et al.* 2001a; Ossipov *et al.* 2004, 2005; King *et al.* 2005a). Specifically implicated are opioid-induced increased levels of the pronociceptive peptide cholecystokinin (CCK) in the RVM, increases that appear to play a role in the development of opioid analgesic tolerance as well (Xie *et al.* 2005). It is suggested that CCK activity in the medulla drives descending pain facilitatory mechanisms, resulting in spinal hyperalgesic responses to nociceptive input (Vanderah *et al.* 2000, 2001b).

Various spinal neuropeptides, distinct from excitatory amino acid systems, have also been implicated in the development of OIH. Over a decade ago, Simonnet's laboratory showed that a single dose of parenteral heroin resulted in significant release of the anti-opioid neuropeptide FF from the spinal cord in rats, an effect blocked by the subsequent administration of opioid antagonist naloxone, and induction of hyperalgesia 30% below baseline noted 30 minutes later (DeVillers *et al.* 1995). More recent animal work in Porreca's laboratory has demonstrated increased levels of lumbar dynorphin, a kappa opioid agonist with pronociceptive activity, following sustained spinal administration of opioid. (Vanderah *et al.* 2000; Gardell *et al.* 2002). Interestingly, the hyperalgesic effects of opioids were reversed 15 minutes following the administration of an antagonist to the neurokinin-1 receptor, the site of activity for the nociceptive neuropeptide substance P (King *et al.* 2005a,b). Particularly active in pain of inflammatory origin, substance P involvement suggests a neuro-inflammatory component to the development of OIH (see Ossipov *et al.* 2005).

Similarly, neuro-immune mechanisms for the development of OIH have been posited (Watkins & Maier 2000; DeLeo, Tanga & Tawfik 2004). In this model, exogenously administered opioids are theorized to bind to μ -opioid receptors located on the astrocytes of

the blood–brain barrier, activating these, and resulting in the subsequent expression and release of pro-inflammatory chemokines and cytokines. In support of this hypothesis, Song & Zhao (2001) and Johnston & Westbrook (2005) have demonstrated that the administration of a glial cell inhibitor (fluorocitrate) reversed the hyperalgesic effect of morphine in acute and chronically treated rats up to 2 hours following infusion. Furthermore, administration of the cytokine inhibitors interleukin-1 (receptor antagonist) and interleukin-6 neutralizing antibody have been shown to reverse and/or block morphine-induced hyperalgesia 6 days following treatment. (Raghavendra, Rutkowski & DeLeo 2002; Johnston *et al.* 2004). Interestingly, co-administration of the tricyclic antidepressant amitriptyline with morphine in an animal model preserved the opioid's antinociceptive effect 5 days following treatment, theorized to be due to the ability of amitriptyline to suppress opioid-induced glial cell activation and subsequent cytokine expression (Tai *et al.* 2006). Although the effects of spinal neuropeptides on OIH are evident acutely (15–30 minutes following treatment), immune-mediated mechanisms of OIH reversal have been shown to be relatively enduring (5–6 days following treatment). In the present study, no DEX effect on OIH was detected after 5 weeks of active treatment, providing further evidence that NMDA-mediated processes are not central to the hyperalgesic response.

Noted was a difference between ethnic groups with respect to their electrical pain threshold at baseline following methadone dosing. These results were unexpected in that experimental pain threshold has been shown to be relatively similar across racial groups (Edwards & Fillingim 1999; Campbell, Edwards & Fillingim 2005), with differences in response more consistent on measures of pain tolerance (Edwards *et al.* 2001; Kim *et al.* 2004; Campbell *et al.* 2005; Mechlin *et al.* 2005; Rahim-Williams *et al.* 2007). In that testing was performed following methadone dosing, it may be that differential analgesic response to methadone among the ethnic groups accounted for these results. However, notwithstanding the demonstrated ethnic differences in the metabolism and plasma levels of the morphine derivatives (Cepeda *et al.* 2001; Gaedigk *et al.* 2005), surprisingly little research exists to predict differential analgesic response to the synthetic opioids, such as methadone.

Despite the overall lack of effect of DEX on pain responses in MM patients, a significant gender effect on response was noted, such that DEX had a *negative* effect on CP pain tolerance during the pre-methadone condition in females. Acknowledging notable gender differences in opioid analgesic response (see Sun 1998; Kest, Sarton & Dahan 2000) and the relative contribution of NMDA-system activity to pain responses in males versus females (Mogil & Belknap 1997; Vendruscolo, Pamplona & Takahashi 2004), it is not unexpected that methadone-maintained women might have a differential DEX response effect to OIH. These findings parallel those of Bryant *et al.* (2006), who describe a poorer response to the NMDA-receptor antagonist MK-801 in attenuating the development of morphine analgesic tolerance in female as compared with male mice, but contrast the pre-clinical data of Holtman & Wala (2005) that show that the ability of ketamine to mitigate OIH is more robust in female versus male rats. In that women have an opposite analgesic response to opioids than do female rodents, it is entirely likely that these pre-clinical data cannot be integrated with the present findings.

Clearly, the small sample size in the study precludes confirmation of a gender-specific effect of DEX on the pain experience of methadone patients; a poorer response to DEX is suggested in women but requires replication in a larger clinical sample powered to test for the effect of gender. Noting the previously reviewed data of Chaplan *et al.* (1997), it is possible that the relatively weak NMDA-antagonist activity of DEX generates a medium or small (as opposed to large) effect size on OIH, thus is undetectable in the small sample. The overrepresentation of a single ethnic group (Latino) in the sample precludes adequate evaluation of the effect of ethnicity on DEX response across the sample. Finally, the lack of a control group in the design calls for cautious interpretation of these data; although the sample appeared hyperalgesic based upon the extant data, hyperalgesia was not strictly established in the subjects in comparison with matched individuals not on methadone therapy. The effect of DEX on hyperalgesic pain responses may appear more robust or clear in a sample in which OIH has been confirmed.

In conclusion, these data do not support that ongoing NMDA-receptor antagonist therapy, as provided by DEX and under the dosing conditions evaluated, reduces or mitigates OIH in MM patients, and may in fact worsen pain responses in female patients. As noted, these negative findings are not inconsistent with an increasing literature on the lack of clinical efficacy of the NMDA antagonist, DEX, to prevent or reduce OIH, which may, in part, be attributed to its weak antagonist activity at the NMDA receptor. As Drogul *et al.* (2005) observe, multiple pharmacologic agents (only one of which are the NMDA antagonists) have been identified as able to antagonize OIH via the final common pathway of reducing activity at dorsal horn neuron calcium channels. For patients on methadone maintenance, the contribution of an NMDA-mediated excitatory mechanism to clinical OIH appears to be negligible.

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Figure 1.

Change scores for cold-pressor (CP) pain threshold and tolerance at peak and trough methadone plasma levels, dextromethorphan (DEX) versus placebo (a) and for electrical stimulation (ES) pain threshold and tolerance at peak and trough methadone plasma levels, DEX versus placebo (b)

Figure 2.

Gender versus treatment on cold-pressor pain tolerance at trough methadone plasma levels (* $P = 0.04$). DEX = dextromethorphan

Figure 3. Potential mechanisms underlying the development of opioid-induced hyperalgesia (adapted from Angst & Clark 2006). NMDA = N-methyl-D-aspartate

Table 1

Sample demographics.

	Treatment		
	Overall (n = 40)	Active (n = 18)	Placebo (n = 22)
Age *	48.01 (6.97)	50.54 (7.23)	45.94 (6.15)
Methadone dose	69.05 (19.52)	75.28 (16.64)	63.95 (20.56)
Gender			
Male	52 (21)	50 (9)	55 (12)
Female	43 (19)	50 (9)	45 (10)
Race			
Hispanic	53 (21)	39 (7)	64 (14)
American Indian/Alaskan	7 (3)	6 (1)	9 (2)
African American	27 (11)	44 (8)	14 (3)
White	11 (4)	6 (1)	13 (3)
Other	2 (1)	5 (1)	. (.)

Numbers presented are either mean (SD) or % (*n*);* $P < 0.01$.

Table 2

Pain threshold and tolerance for cold pressor (CP) and electrical stimulation (ES) at baseline and at Week 5.

	Baseline		Week 5					
	Trough methadone		Peak methadone		Trough methadone		Peak methadone	
	DEX (n = 18)	Placebo (n = 22)	DEX (n = 18)	Placebo (n = 22)	DEX (n = 18)	Placebo (n = 21)	DEX (n = 17)	Placebo (n = 20)
CP threshold (seconds)	13.13 (8.83)	12.06 (5.44)	13.49 (11.33)	11.80 (6.23)	13.84 (9.24)	13.62 (6.36)	12.68 (8.30)	12.98 (6.83)
CP tolerance (seconds)	20.07 (12.83)	19.57 (9.30)	19.71 (11.90)	21.23 (10.54)	19.30 (10.74)	21.73 (13.10)	19.84 (9.90)	23.83 (21.50)
ES threshold (V)	42.96 (17.05)	41.03 (15.82)	49.06 (22.10)	37.43 (16.45)	43.53 (21.72)	36.86 (13.94)	49.21 (21.67)	38.58 (16.18)
ES tolerance (V)	56.42 (17.75)	50.51 (20.75)	62.81 (21.53)	48.91 (20.08)	53.60 (19.76)	48.13 (19.47)	60.98 (21.22)	50.33 (21.30)

Numbers presented are mean (SD); DEX = dextromethorphan.