Gabapentin improves Cold-pressor Pain Responses in Methadone-maintained Patients

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Abstract

Individuals on methadone maintenance for the treatment of addiction (MM) are demonstrated to be hyperalgesic to cold-pressor pain in comparison to matched controls and ex-opioid addicts, a finding described as clinical evidence of opioid-induced hyperalgesia (OIH). Interestingly, opioids induce hyperalgesia via many of the same neuro-inflammatory and central sensitization processes that occur with the development of neuropathic pain. Evaluated in this study was the efficacy of a key pharmacotherapy for neuropathic pain, gabapentin (GPN), to reverse OIH in MM patients. Utilizing a clinical trial design and double blind conditions, changes in cold-pressor pain threshold and tolerance following a five-week trial of GPN (titrated to 2400mg/day) were evaluated at peak and trough methadone plasma levels in a well-characterized MM sample. Drug abstinence was encouraged via an escalating payment schedule, and compliance monitored via pill counts and GPN plasma levels; entered into the analyses were only those subjects compliant and abstinent throughout the study (approx 45%). Utilizing change scores from baseline, significant improvements in cold-pressor pain threshold and pain tolerance were observed at both peak and trough methadone levels ($p < 0.05$). Notably, drop-out rates due to medication side effects were low (2%) and the medication was well-tolerated. These results support that GPN, as prescribed for the treatment of neuropathic pain, is effective in decreasing OIH in patients who are abstinent and stable in methadone treatment.

Keywords

gabapentin; hyperalgesia; methadone; treatment

1. Introduction

Abundant evidence exists to support that individuals on the opioid maintenance agent methadone for the treatment of opioid addiction are relatively hyperalgesic to experimental pain. First noted in the literature 40 years ago, Ho and Dole (1979) observed that methadone-maintained heroin addicts were significantly more sensitive to cold pressor-induced pain as compared to drug-free controls. Since that time, significantly diminished tolerance to experimental (electrical stimulation, cold-pressor [CP]) pain has been reliably demonstrated in methadone patients' in comparison to matched drug-free addicts (Compton, 1994) and

controls (Athanasos et al., 2006; Compton et al., 2000; 2001; Doverty et al., 2001; Pud et al., 2006), at both peak and trough methadone blood levels. Cross-sectional data suggest a large effect size, indicating that methadone-maintained patients (MM) are 42% – 76% less tolerant of CP pain than are normal controls matched on age, gender and ethnicity. These findings have implications for the management of pain in methadone patients, and support increased analgesic need in patients receiving this addiction pharmacotherapy (Alford et al., 2006; Newshan, 2000; Scimeca et al., 2000).

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 Angst and Clark, 2006; Chu et al., 2008; Fishbain et al., 2009; Mao, 2006; Ossipov et al., 2005). Convergent lines of preclinical 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 (Angst et al., 2003; Chu et al., 2006; Koppert et al., 2003; Li et al., 2001; Mao et al., 2002; Simonnet, 2005; Vanderah et al 2001a), and which have been suggested to contribute to opioid tolerance (Colpaert, 1996; Gardell et al., 2006; Laulin et al., 1999; Mao, 2006). The implications of this altered pain state have become of interest to investigators and clinicians who prescribe opioid analgesics for chronic pain (Ballantyne and Shin, 2008; Chang et al., 2007; Koppert and Schmelz, 2007; Wilder-Smith and Arendt-Nielsen, 2006).

Phenomenological similarities between OIH and the hyperalgesia associated with neuropathic pain have been appreciated. In both, central ascending hyperexcitability and/or diminished descending supraspinal inhibition have been posited to underlie the hypersensitivity to noxious stimuli (see reviews, Chu et al, 2008; Finnerup, 2008; Harvey and Dickinson, 2008; Taylor, 2009). More recent work has demonstrated a common immune mechanism underlying the development of both opioid-induced and neuropathic hyperalgesia, and related to glial activation (Hutchinson et al., 2007; 2008; Mika, 2008; Watkins et al., 2007). Due to the overlap between the central neuroplastic processes underlying OIH and neuropathic pain, it is reasonable to suspect that an effective pharmacotherapy for the treatment of the latter might generalize to treatment of the former.

Gabapentin (GPN), a γ-aminobutyric acid (GABA) agonist anticonvulsant, is increasingly considered a first-line medication for the treatment of chronic neuropathic pain (Dobecki et al., 2006; Dworkin et al., 2007; Knotkova and Pappagallo, 2007; Moulin et al., 2007; Vadalouca et al., 2006). Attributed to its ability to hyperpolarize neurons via activity at voltage-gated Ca^{2+} channels (see Cheng and Chiou, 2006; Rose and Kam, 2002), the analgesic effect of GPN has been demonstrated in animal models of nerve injury (Blackburn-Munro and Erichsen, 2005), and in clinical trials of patients with diabetic neuropathy, post-herpetic neuralgia, and trigeminal neuralgia (Backonja and Glanzman, 2003; Sindrup and Jensen, 1999; Mellegers et al., 2001; Wiffin et al., 2009). Detailed evaluation of its ability to decrease neuropathic pain in animal models shows that GPN acts primarily by diminishing the hyperalgesia associated with nerve injury (Cesena and Calcutt, 1999; De la O-Arciniega et el., 2009; Gustafsson et al., 2003; Jones and Sorkin, 1998; Jun and Yaksh, 1998; Patel et al., 2001; Yasuda et al., 2005); similar findings have been demonstrated in humans under experimental (Dirks et al., 2002; Gottrup et al., 2004; Gustorff et al., 2004; Iannetti et al., 2005; Segerdahl, 2006; Wallace and Schulteis, 2008) and clinical pain conditions (Attal et al., 1998; Berry and Petersen, 2005; Cuignet et al., 2006). This anti-hyperalgesic effect is proposed to account for accumulating clinical observations that preoperative GPN administration results in decreased post-operative opioid requirement (Giron, 2007; Hayashida et al., 2007; Kong and Irwin, 2007; Tiippana et al., 2007).

That GPN can treat the mechanistically similar hyperalgesia associated with opioid use has been recently supported by animal data collected in the laboratories of Van Elstraete (2008), which showed that fentanyl-induced hyperalgesia could be prevented by the administration of GPN in a dose-dependent manner. The apparent large effect size of GPN on OIH warrants translation of these findings to the clinical setting for patients on opioid therapy. The aim of this study was to evaluate the ability of GPN to diminish OIH to experimental pain in a well-characterized sample of MM individuals. It was hypothesized that chronic GPN therapy would effectively increase tolerance for experimental pain in this sample, and thus support a gabaminergic mechanism by which to treat their notable hyperalgesia.

2. Methods

2.1 Design

The ability of the GPN to decrease OIH in MM patients was tested using a placebo-controlled, randomized clinical trial design. Threshold and tolerance to cold-pressor (CP) pain were measured prior to and following five weeks of continuous GPN vs. placebo therapy. To control for the effects of methadone dosing on pain responses, pre- and post-GPN pain measures were collected at peak and trough methadone blood levels.

2.2 Sample

A convenience sample 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. Being in MM therapy, all met DSM-IV criteria for opioid dependence. Based upon previous demonstrations in comparison to controls (Athanasos et al., 2006; Compton et al., 2000; Doverty et al., 2001; Pud et al., 2006), it was anticipated 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. Prior to participation, all potential subjects provided informed consent in strict adherence with UCLA Institutional Review Board standards. Subjects were compensated for their time and compliance.

2.3 Gabapentin (GPN)

GPN was titrated to a total daily dose of 2400mg PO over a one week period (120mg QID × 2 days, 200mg QID × 2 days, 320mg QID × 2 days). As suggested by the meta-analyses of Dworkin and colleagues (2007) and Wiffen and colleagues (2009), GPN dose was selected so as to be safe and tolerable, and the five-week dosing period used to capture the effective dosing period for the treatment of neuropathic pain

2.4 Cold Pressor (CP) Pain

Prior to and 5 weeks following medication administration, pain responses to a standardized cold-pressor (CP) test were observed to evaluate the ability of GPN to diminish OIH in MM patients. Over 60 years of use (Edes and Dallenbach, 1936; Hines and Brown, 1932), this pain induction procedure has been demonstrated to have excellent reliability (Blitz, 1968; Garcia

de Jalon et al., 1985; Tassorelli et al., 1995; Wolff et al., 1976) and analogous in nature to various types of clinical pain (Chen et al., 1989).

The CP pain induction procedure as adapted by Eckhardt et al. (1998) was utilized to assess the anti-hyperalgesic effects of GPN. Specifically, study participants were seated in a comfortable chair, asked to roll up their sleeve and remove watches or jewelry from their non-dominant arm and hand, and a blood pressure cuff applied. Eye patches were placed over the eyes to minimize distraction. Participants were instructed to first place their forearm into a bath of room temperature water with fingers wide apart, and no contact with the side or bottom of the container. At 1 minute and 45 seconds, the blood pressure cuff was inflated to 20 mm Hg below the obtained diastolic BP so as to induce mild tissue hypoxia. At exactly 2 minutes, participants were assisted in removing the forearm from the lukewarm bath and placing it immediately in an adjacent circulating ice bath (1.0 +/− 0.5C). Participants were not spoken to during the cold-water immersion to minimize distraction or cues for time

Participants held an event marker button in their dominant hand to indicate when (a) pain was initially detected (threshold), and (b) 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. Once the hand was removed from the cold water, eye patches and blood pressure cuff were removed and a warm towel given to gently dry the forearm. All trials were truncated at 5 minutes, so as to avoid the onset of numbness.

2.5 Procedures

Following a screening visit to establish study eligibility, consented participants were familiarized with the CP procedures and baseline pain measures were collected. Subjects were randomized to GPN or matched placebo, and titrated up to the target dose as described above; the placebo group underwent an identical "titration." Subjects were evaluated weekly by a blinded study clinician for health status, side effect assessment, and concomitant medication use. To encourage abstinence from illicit drug use over the course of the study, subjects received an escalating monetary weekly bonus for submitting a "clean" specimen (free from illicit opioid, cocaine, amphetamine/methamphetamine, benzodiazepine, or marijuana metabolites), beginning at $5 week 1 and increasing by $5/wk for each drug-free sample provided. Medication compliance was evaluated at each visit with pill counts and plasma levels were collected at week 5.

At baseline and immediately following five weeks of medication, CP pain responses were measured on two occasions separated by 72 hours, at both methadone trough (just prior to methadone dosing) and peak (approximately 150min following methadone dosing) blood levels. All pain testing sessions took place in a private setting and the CP administered by one of two trained research assistants. Subjects were instructed to refrain from caffeine and nicotine for one 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, including a measure of subjective opioid withdrawal. First day of menstrual cycle was recorded for all female subjects.

For each pain session, respiration, EKG, pulse oximetry, heart rate and blood pressure were continuously monitored prior to, during, and for at least ten 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 10cc's of blood was drawn to enable measurement of methadone and GPN plasma levels at the time of testing.

2.6 Data Analysis

To evaluate the effect of the GPN on putative OIH, difference on pain responses from baseline to after treatment were compared for the treatment group to the control group at peak and trough methadone blood levels separately. Only those subjects who were abstinent (as confirmed by urine toxicology) and compliant (as evidenced by GPN blood level) were entered into the analyses. The outcome variables of interest were change scores in pain tolerance and threshold at both peak and trough blood levels, and measured by the difference in pain responses between week 5 and baseline. Differences in change scores between the experimental and control groups were assessed using t-tests. Chi-square tests were used to assess statistical differences between the two groups for categorical demographic variables and two-sample independent t-tests were conducted to detect significant differences in continuous outcome variables between groups. Assumptions for statistical tests were checked and met. Analyses were performed with SAS/STAT.

3. Results

Characteristics of the overall sample as well as categorized by the experimental and control groups are as described in Table 1. Data are presented as mean ± SE for continuous measures and percentages for categorical variables. Overall there were 26 subjects in the sample that were compliant and abstinent during the entire study (experimental: 10; placebo: 16). Subjects in the treatment group were marginally younger (45.5) compared to the control group (49.5). Half of the sample was Hispanic (50%), and the rest were primarily Caucasian (19%) or African Americans (15%). The majority had at least a high school education, and about half were married and/or had partners. The mean daily dose of methadone was 72mg, and at baseline, peak and trough R-methadone blood levels averaged 177.5ng/ml and 128.8ng/ml respectively.

Change scores in pain tolerance and threshold are listed in Table 2 and illustrated in the Figure. As noted, the experimental group showed statistically significant improvements in both pain threshold and tolerance compared to the control group at both peak and trough methadone levels. Using generalized linear modeling, no differences in change scores were noted by age, gender or ethnicity. Change scores were not correlated to methadone dose or its plasma peak or plasma trough levels.

In general, GPN was well-tolerated by study subjects. Of 149 adverse effects deemed as related to the study medications, 99% were classified as mild to moderate severity and 93% anticipated. Table 3 shows the frequencies for adverse events that were coded as probably or definitely related to the study drug, with the most commonly reported event being nausea.

4. Discussion

This study sought to determine if the GABA agonist, gabapentin, 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. Albeit a small sample, these data provide support for the efficacy of GPN to do so for both measures of pain threshold and pain tolerance at methadone peak and trough blood levels.

Importantly, the focus of this paper is specifically to compare those subjects who were compliant in taking the study medication and who remained abstinent from illicit drug use over the course of the 5 week study to controls. Although subjects were encouraged to provide drug-free urine samples via an escalating payment schedule, less than half were able to do so completely. It is well-known that many drugs of abuse, including the CNS stimulants, illicit

opioids, and marijuana, can acutely decrease pain, while withdrawal from the same can make nociceptive stimuli feel more painful. Although no overt opioid withdrawal symptoms were noted prior to pain testing, it is unclear how uncontrolled concomitant drug use might have influenced pain responses and GPN efficacy. For this reason, the focus was kept only on abstinent and compliant subjects.

Similar to previous work (Compton et al, 2008; Doverty et al., 2001), at baseline, subjects tended to be more sensitive to CP stimulation at peak relative to trough methadone plasma levels. It is possible that these non-significant differences reflect a measurable opioid analgesic effect following methadone dosing, enabling subjects to tolerate the ice bath longer. Alternatively, at trough plasma levels, patients may have been experiencing a mild opioid withdrawal hyperalgesia (see Basbaum, 1991; Compton et al., 2003; Kaplan & Fields, 1991) prior to methadone dosing, thus subjects appeared more sensitive to the cold-pressor. Regardless, these differences did not carry over to the post–treatment measures, with significant improvements noted at both peak and trough testing, suggesting that methadone effects on pain responses were not substantively involved in the improvements noted with GPN therapy.

These data are the first to demonstrate that a GABA agonist effectively treats putative opioid-induced hyperalgesia in a clinical sample of methadone patients. Not unlike the considerable effect of GPN on chronic neuropathic pain (Mellegers et al., 2001; Wiffin et al., 2009), the general inhibitory effect of GPN on neuronal transmission is evident in central pain systems which have been unregulated secondary to opioid exposure. Singler and colleagues (2007) observation that the GABA agonist, propofol, mitigates remifentanil-induced hyperalgesia in normal human subjects further supports gabaminergic approaches for the treatment of OIH. Further, these data are also among the first published to demonstrate the effectiveness of GPN to treat OIH in a human model of opioid exposure. Van Elstraete and colleagues (2008) recently demonstrated that both intrathecal and intraperitoneal GPN administration dose-dependently prevents the hyperalgesia induced by repeated fentanyl administration in uninjured rats; the current findings translate these preclinical observations to a clinical population of humans who receive opioid therapy in the absence of injury or pain.

Pharmacotherapies with activity at non-GABA sites have also been suggested as treatment for OIH. Probably best studied is the relatively weak NMDA-antagonist dextromethorphan, although evidence for its efficacy to offset OIH in clinical samples with pain has been mixed (Compton et al., 2008; Dudgeon et al., 2007; Galer et al., 2005; Haugan et al., 2008; Heiskanen et al., 2002; Helmy and Bali, 2001; Weinbroum et al., 2001). Other potential agents include CCK antagonists to block descending pain facilitory processes (Gardell et al., 2002; Vanderah et al., 2001), and the α2-receptor agonists which attenuated OIH in a small sample of healthy human subjects (Koppert et al., 2003). Of increasing interest in the literature is the use of low-dose opioid antagonists in conjunction with opioid agonists to counteract the development of OIH (Cepeda et al. 2004; Chindalore et al., 2005; and Terner, 2006; Wang et al., 2005; Webster, 2007; Webster et al., 2006), and the use of glial antagonists (i.e., ibudilast) to mitigate the neuroimmune activation associated with opioid administration (Hutchinson et al., 2007; 2008; Watkins et al., 2007).

Absolute improvements in cold-pressor responses to GPN were small (2 – 3 seconds), calling into question the clinical significance of these findings. Relative to the short pain threshold and tolerance responses noted at baseline (approx. 7 – 21 seconds), a 3-second change represents a 14% to 43% increase in cold-pressor immersion, thus is clearly significant in this context. Yet, the extrapolation of magnitude of analgesic responses from experimental pain to the clinical pain experience remains an ongoing issue in pain research, (Arendt-Nielsen et al., 2007; Petersen-Felix and Arendt-Nielsen, 2002), and one which may never fully be resolved.

To the authors' knowledge there is not a clear cut method for determining the clinical equivalence of changes in cold-pressor pain responses. To provide perspective, CP pain threshold improvement in normal healthy controls to an analgesic dose of morphine (10mg PO) is 5 seconds (Jones et al., 1988), while improvements in CP tolerance to a 0.5mg/kg dose of morphine PO averaged 10 seconds (Cleeland et al., 1996; Grach et al., 2004), thus lengthy changes in cold-pressor pain responses are not associated with clinically potent analgesics.

Several limitations are evident in this work. Firstly, baseline hyperalgesia was not established in this group of subjects, although their average CP pain threshold and tolerance times were consistent with those reported in previous work on this population (Athanasos et al., 2006; Compton, 1994; Compton et al., 2000; 2001; Doverty et al., 2001). Although these data support changes in CP pain threshold and tolerance on GPN, conclusions about changes to OIH specifically must be drawn cautiously. Also, the trial lasted for five weeks, and then subjects were titrated off study mediation; future studies should evaluate the longer-term effects of GPN therapy in this population. Finally, these findings can only be generalized to those MM who are able to abstain from illicit drug use over an extended period of time. In that complete and ongoing drug abstinence is a relatively uncommon outcome of methadone treatment (Johansson et al., 2007; Maremmani et al., 2007), the clinical utility of GPN may be limited.

In conclusion, these data support that ongoing GABA agonist therapy, as provided by GPN and under the dosing and clinical conditions evaluated, reduces or mitigates OIH in MM patients. Although the analyzable sample size was small, impressive is the large effect of GPN on CP pain responses in this sample (Cohen's d = 1.01 [threshold peak methadone]; 1.73 [threshold trough methadone]; 1.11 [tolerance peak methadone]; 0.30 [tolerance trough methadone]). Like the hyperalgesia of neuropathic pain, OIH appears to respond to GABA-agonist therapy. Gabapentin therapy, in clinically tolerated doses, significantly improved cold-pressor pain responses in methadone patients. These findings suggest that gabapentin might be a useful adjuvant for the significant number of methadone patients who also have chronic pain (Clark et al., 2008; Rosenblum et al., 2003; Sheu et al., 2009).

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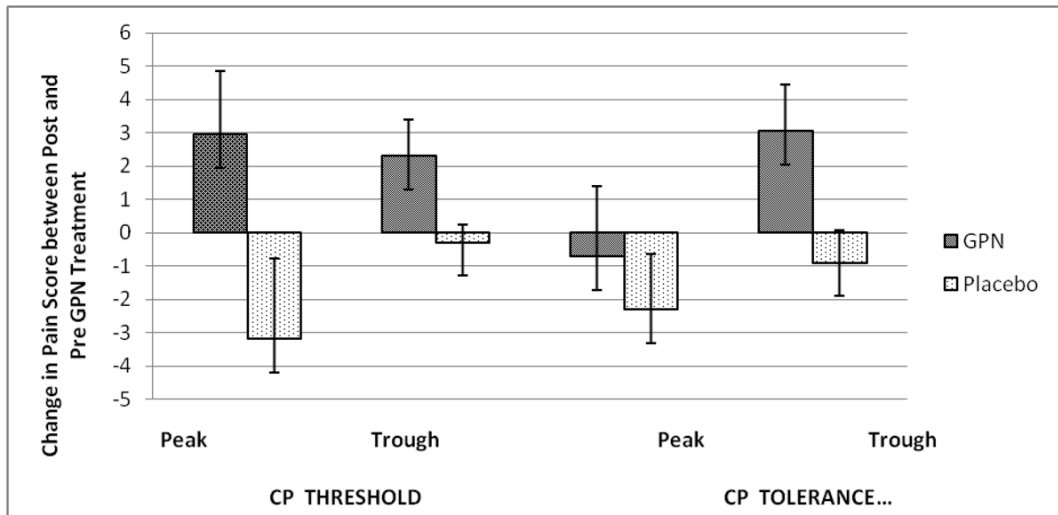
Figure.
Change in pain threshold and pain tolerance from baseline to week 5 for placebo and gabapentin groups at peak and trough methadone levels.

Table 1

Sample Demographics of Abstinent and Compliant Study Subjects

	Gabapentin (n = 10)	Placebo (n = 16)	Overall (n = 26)
Demographic Characteristics			
Continuous Variable	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)[*]	45.5 (4.46)	49.5 (4.96)	47.9 (5.05)
Methadone Dose (mg)	73.0 (20.02)	70.9 (23.16)	71.7 (21.62)
Peak Methadone plasma level (baseline ng/ml)	191.5 (57.08)	168.8 (62.32)	177.5 (60.22)
Trough Methadone plasma level (baseline ng/ml)	125.8 (39.91)	130.7 (43.16)	128.8 (41.20)
Categorical Variables	%	%	%
Gender			
Males	50.0	56.3	53.9
Race			
Hispanic	60.0	43.8	50.0
American Indian	10.0	0.0	3.9
African American	0.0	25.0	15.4
Caucasian	30.0	12.5	19.2
Other	0.0	18.8	11.5
Marital Status			
Married / Living-with-partner	50.0	50.0	50.0
Separated / Divorced	30.0	31.3	30.1
Widowed / Never-married	20.0	18.8	19.2
Education			
< High School	36.0	40.0	38.0
High School	32.0	40.0	36.0
> High School	32.0	20.0	26.0

[*] Significant group difference observed at alpha = 0.049 level of significance

Table 2

Average Pain Threshold and Tolerance for Cold-Pressor at Baseline and Week 5

		Time	Group	
		Mean (SE)	Gabapentin (n = 10) Mean (SE)	Placebo (n = 14) Mean (SE)
CP Threshold (Seconds)	Trough Methadone	Baseline	7.61 (1.23)	14.23 (1.40)
		Week 5	9.90 (1.56)	13.78 (1.71)
Within-group difference in pain between Week 5 and baseline **			2.29 (1.58)	−0.45 (2.21)
	Peak Methadone	Baseline	7.54 (1.54)	15.82 (2.24)
		Week 5	10.49 (1.86)	12.33 (1.77)
Within-group difference in pain between Week 5 and baseline *			2.95 (2.41)	−3.49 (2.85)
CP Tolerance (Seconds)	Trough Methadone	Baseline	11.15 (1.04)	20.72 (1.76)
		Week 5	14.19 (1.79)	19.73 (2.42)
Within-group difference in pain between Week 5 and baseline ***			3.04 (2.07)	−0.99 (2.99)
	Peak Methadone	Baseline	13.43 (3.02)	21.90 (2.40)
		Week 5	15.71 (1.90)	19.63 (2.96)
Within-group difference in pain between Week 5 and baseline *			−0.72 (3.57)	−2.27 (3.81)

Significant group difference observed at

*
p = 0.04,

**
p = 0.02,

***
p = 0.01

levels of significance using two-sample independent t-tests to test that the change scores are the same between groups versus not.

Table 3

Adverse events Probably or Definitely related to Gabapentin among abstinent and compliant subjects (n = 26)

ADVERSE EVENTS[*]	Overall	GPN	Placebo
NAUSEA	7	6	1
GAS	4	3	1
CONSTIPATION	6	3	3
LETHARGY/TIREDNESS	7	4	3
INSOMNIA/TROUBLE SLEEPING	6	1	5
HEADACHE	3	1	2
DIZZINESS/ LIGHTHEADEDNESS	5	5	0

[*]
: Some subjects experienced more than one AE or the same AE over multiple study visits.