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Randomized, Placebo-Controlled Pilot Trial of Gabapentin During an Outpatient, Buprenorphine-Assisted Detoxification Procedure[1]

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Abstract

This pilot study examined the efficacy of the N-type calcium channel blocker gabapentin to improve outcomes during a brief detoxification protocol with buprenorphine. Treatment-seeking opioid-dependent individuals were enrolled in a 5-wk, double blind, placebo-controlled trial examining the effects of gabapentin during a 10-day outpatient detoxification from buprenorphine. Participants were inducted onto buprenorphine sublingual tablets during week 1, were randomized and inducted onto gabapentin or placebo during week 2, underwent a 10-day buprenorphine taper during weeks 3–4 and then were tapered off gabapentin/placebo during week 5. Assessments included thrice-weekly opioid withdrawal scales, vitals, and urine drug screens. Twenty-four individuals (13 male, 17 Caucasian, 3 African American, 4 Latino, mean age 29.7 yrs) participated in the detoxification portion of the study (gabapentin, N=11; placebo, N=13). Baseline characteristics did not differ significantly between groups. Self-reported and observer-rated opioid withdrawal ratings were relatively low and did not differ between groups during the buprenorphine taper. Urine results showed a drug x time interaction, such that the probability of opioid-positive urines significantly decreased over time in the gabapentin versus placebo groups during weeks 3–4 (OR=0.73, p=0.004). These results suggest that gabapentin reduces opioid use during a 10-day buprenorphine detoxification procedure.

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Keywords

Buprenorphine; gabapentin; detoxification; Opioid withdrawal; humans

Opioid dependence is a severe public health problem. Nearly 2,000,000 Americans are currently believed to be opioid dependent (SAMHSA, 2011). Moreover, the estimated number of emergency room visits involving narcotic analgesic abuse rose from 166,338 in 2004, to 425,247 in 2010, indicating a dramatic increase of 156% (SAMHSA, 2012). In 2001, dependence on a narcotic analgesic was the most frequently reported motive (44%) for these visits (Crane, Stouffer, Lee, & Lemanski, 2003). These figures indicate the need to continue investigating strategies aimed at improving treatments for opioid dependence.

After chronic use of an opioid agonist, abrupt abstinence or administering an opioid antagonist, such as naloxone, produces a particular set of symptoms (e.g., nausea, fever, dizziness) indicative of opioid withdrawal. Traditional methods of detoxification from opioids, including tapering off the opioid agonist methadone and supportive treatment of symptomatology with the alpha-adrenergic receptor agonists, are limited by the high relapse rate and lack of efficacy in relieving subjective symptoms (Amato, Davoli, Minozzi, Ali, & Ferri, 2005; Broers, Giner, Dumont, & Mino, 2000; Gossop, Green, Phillips, & Bradley, 1989; L. R. Gowing, Farrell, Ali, & White, 2002; Jasinski, Johnson, & Kocher, 1985; Kleber et al., 1985; T. R. Kosten, Rounsaville, & Kleber, 1985; Rounsaville, Kosten, & Kleber, 1985). Moreover, although the partial agonist buprenorphine has been thought to produce fewer withdrawal symptoms of a lower intensity than full agonists such as methadone (Stotts, Dodrill, & Kosten, 2009), a recent review concluded that, while buprenorphine may help resolve symptoms faster, buprenorphine relieves withdrawal symptoms and intensity of withdrawal symptoms to a similar extent as methadone (L. Gowing, Ali, & White, 2009). In addition, increased prescriptions of narcotic analgesics to chronic non-cancer pain patients raise concern about withdrawal symptoms. Indeed, one UK survey reported that 14.4% of respondents who abruptly terminated opioid use after at least 7 days of opioid use experienced withdrawal (Cowan, Wilson-Barnett, Griffiths, & Allan, 2003). Thus, improving upon treatments for opioid withdrawal in particular is of great importance, not only for opioid detoxification purposes in opioid-dependent prescription opioid abusers and pain patients, but also for providing a smooth transition from opioid agonist to naltrexone maintenance.

Given that L-type calcium channel blockers have been shown to attenuate naloxone-precipitated withdrawal in nonhumans (Barrios & Baeyens, 1991; Bongianni, Carla, Moroni, & Pellegrini-Giampietro, 1986; Seth, Upadhyaya, Moghe, & Ahmad, 2011) and humans (Oliveto, Poling, Kosten, & Gonsai, 2004), as well as attenuate withdrawal during opioid detoxification (Jimenez-Lerma et al., 2002; Shulman, Jagoda, Laycock, & Kelly, 1998), this pilot study examined the tolerability and initial efficacy of gabapentin, an N-type calcium channel blocker (Eroglu et al., 2009; e.g., Maneuf et al., 2003; Snutch, Sutton, & Zamponi, 2001) and GABA analogue that promotes release of GABA (Bertrand, Morin, & Lacaille, 2003; Kuzniecky et al., 2002), to attenuate withdrawal and illicit opioid use in opioid dependent volunteers undergoing a buprenorphine detoxification protocol. Gabapentin is indicated for the treatment of post herpetic neuralgia and as adjunct therapy for epilepsy (Pfizer, 2012a). It has been shown to attenuate morphine-induced conditioned place preference in rats (Andrews et al., 2001); enhance the analgesic effect of morphine in rats (Shimoyama, Shimoyama, Inturrisi, & Elliott, 1997) and healthy volunteers (Eckhardt et al., 2000); decrease postoperative morphine consumption and movement-related pain after radical mastectomy (Dirks et al., 2002); and block, as well as reverse, tolerance to the antinociceptive effects of morphine in the rat paw-pressure and tail-flick tests (Gilron,

Biederman, Jhamandas, & Hong, 2003). These findings indicate a relationship between gabapentin and the opioid system that is similar to that observed with L-type calcium channel blockers (e.g., Santillan, Hurle, Armijo, de los Mozos, & Florez, 1998) and should be explored further. Moreover, given that the GABA system has been implicated in the expression of withdrawal (e.g. Hack, Vaughan, & Christie, 2003; Kruszewska, 1988; Williams, Christie, & Manzoni, 2001; Zarrindast & Mousa-Ahmadi, 1999), the GABAergic actions of gabapentin may also contribute to its efficacy in attenuating the behavioral effects of naloxone. In addition, gabapentin has a favorable side effect profile, minimal, if any, drug interactions, and a relatively short elimination half-life of 5–9 hours (Bourgeois, 2000). The favorable side effect profile of this agent and limited drug interactions should make it a potentially good candidate for combination therapy for opioid withdrawal.

Gabapentin at low doses (i.e., ≤400 mg) significantly attenuated naloxone-induced increases in ratings of “drug strength” in opioid maintained humans responding under a naloxone discrimination procedure, although naloxone-induced discriminative stimulus effects were attenuated in a non-significant, dose-related manner (Oliveto et al., 2010). These findings suggest that higher doses of gabapentin may be necessary to attenuate naloxone-induced withdrawal in this population. Indeed, adjunct gabapentin administration of 1,600 mg/day (Kheirabadi, Ranjkesh, Maracy, & Salehi, 2008), but not 900 mg/day (Salehi, Kheirabadi, Maracy, & Ranjkesh, 2011), during a methadone-assisted detoxification significantly reduced several withdrawal symptoms. Thus, this randomized, double blind, placebo-controlled pilot clinical trial examined the effects of gabapentin at 1,600 mg/day on treatment outcomes in opioid-dependent participants undergoing a buprenorphine-assisted detoxification.

METHODS

Participants

Thirty-three male and female opioid-dependent individuals (aged 18–58 years) seeking treatment of opioid-dependence were recruited from Central Arkansas in October of 2010 and January 2011 through December of 2011. Written informed consent was obtained from all subjects. In order to participate in the study, participants had to be available to attend clinic 6 days a week for approximately 30–60 minutes; fulfill DSM-IV criteria for opioid dependence, as determined by a physician; submit a urine negative for drugs of abuse other than opioids or marijuana prior to entering the study; have no unstable medical condition or stable medical condition that would interact with study medications or participation; have no history of psychosis, schizophrenia, or bipolar disorder; no plan to become pregnant and adequate birth control; have no present or recent use of psychoactive medications or medications that would have major interactions with the study drugs; have liver function tests no greater than 3 times normal with BUN and creatinine within the normal range; have no EKG abnormalities; and have no physical dependence on alcohol or drugs other than opioids or tobacco. Eligibility was ascertained through a comprehensive evaluation, which included complete physical, neurological, and clinical psychiatric examinations, routine laboratory studies, and an electrocardiogram. Participants were compensated under a low-cost contingency management procedure that utilized the “fishbowl” (Petry, 2000; Petry & Martin, 2002). Participants that completed at least the fourth week of the study earned an average of approximately $180. This protocol was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Design and Procedures

Thirty-three participants were initially determined as being eligible to participate in this 5-week randomized, double blind, clinical trial through a 1-week, centralized recruitment/

screening procedure. Once participants were determined eligible they completed an intake procedure with a research assistant and/or clinician. During the first week of the study all participants were inducted onto buprenorphine and then randomized to receive gabapentin or placebo using a computerized urn randomization program (Wei & Lachin, 1988), balancing groups on primary opiate of abuse, sex, opioid withdrawal symptoms score, and THC urine drug screen (UDS) results. Only the research pharmacist and data manager were aware of the medication condition. Participants were inducted on to gabapentin or placebo during week 2, began a 10-day buprenorphine taper starting week 3, and tapered off gabapentin during week 5 (see table1). Supervised urines, objective and subjective withdrawal symptoms scores, self-reported adverse effects, body temperature, pupil diameter, and vital signs were obtained thrice weekly; drug use measures were obtained once weekly. Regardless of treatment group, all participants were scheduled to meet with a research counselor weekly for 30–60 minutes. These sessions provided the participant an opportunity to review critical issues and problem areas. Participants attended study visits Monday through Saturday to receive buprenorphine and study medication through the University of Arkansas for Medical Sciences' Substance Abuse Treatment Clinic (SATC), complete scheduled research assessments and attend any scheduled counseling session. At the end of five weeks participants were transferred to SATC or referred to other treatment programs if they so desired.

Drugs

The dosing schedules for buprenorphine tablets and gabapentin/placebo are shown in table 1. Participants were typically inducted onto the targeted buprenorphine stabilization dose of 12 mg/day during the first 3 days of week 1 and continued to receive 12 mg/day (with a double dose of 24 mg administered on Saturday to cover Sunday). Participants continued to receive 12 mg/day of buprenorphine (24 mg on Saturday) through week 2. The 10-day buprenorphine detoxification began on Monday of week 3, such that the buprenorphine dose was gradually tapered until Wednesday of week 4 when the final dose of 2 mg was administered. Meanwhile, starting on Monday of Week 2, participants began induction onto either gabapentin or placebo, which was administered orally, twice daily, via blue opaque capsules, until the maintenance dose of 1600 mg/day was reached on Friday of week 2. The participants continued taking the maintenance dose of gabapentin (or placebo) until Monday of week 5, at which time the dose gradually tapered until Thursday of week 5 when they were given their final dose of 200 mg/day of gabapentin. In order to ensure medication compliance and control for medication diversion participants were observed at the SATC dosing window taking their gabapentin/placebo morning dose, followed by their buprenorphine dose. Participants were required to demonstrate to the dosing nurse that the buprenorphine had dissolved, prior to leaving the clinic. Participants were given a daily zipper bag of study medication to take in the evening. Participants were compensated for returning their weekend take-home packages back on Monday mornings. Compliance with taking evening doses was assessed via pill counts and self-reports. Participants were discharged from the study if they missed 2 consecutive days of dosing.

Assessments

Staff-rated opiate withdrawal symptoms were recorded thrice weekly (MWF) using the Objective Opiate Withdrawal Scale (OOWS) (Handelsman et al., 1987), which consisted of thirteen items describing withdrawal symptoms. For each symptom that was present during a 5-minute period and fit the given criteria, one point was scored. The OOWS has been shown to have good reliability with self-reported opiate withdrawal scales (Handelsman, et al., 1987; Loimer, Linzmayer, & Grunberger, 1991). Participant-reported opioid withdrawal symptoms were measured thrice weekly using the Opiate Withdrawal Symptoms Checklist (OWSC) (T. Kosten et al., 2003), which consisted of twenty-two items describing possible

opioid withdrawal symptoms rated on a scale from 0 (not at all) to 4 (very much). Self-report assessments of opioids and heroin use (e.g., days during which either was used; number of pills for opioids or bags for heroin used) were obtained at intake and on day 1 of each week using 7-day recall method instruments developed in previous studies (T. Kosten, et al., 2003; Oliveto et al., 2005). Physiological signs (vital signs, pupil diameter, and body temperature) were measured thrice weekly. Blood pressure and heart rate were taken using a CARESCAPE V100 Dinamap monitor (GE Healthcare, Waukesha, WI). Pupil diameter was measured by using a NeurOptics PLR-200 pupillometer (NeurOptics, Irvine, CA). Body temperatures were assessed using an AccuSystem FILAC* F-1500 and FILAC-3000 thermometers (Moore Medical, Farmington, CT).

Because the contingency management procedure was, in part, based on current drug use of opiate/opioid, benzodiazepine, cocaine, and amphetamine, Instant-View multi-test drugs of abuse panel dipsticks (CLIAwaived.com, San Diego, CA) were used to immediately test supervised urine samples obtained thrice weekly. Urine samples were rated positive if the quantity of drug or metabolite was ≥500 ng/mL for methamphetamines; ≥ 300 ng/ml for benzoylecognine, propoxyphene, benzodiazepines, morphine and methadone; ≥ 100 ng/mL for oxycodone. If any dipstick reading was questionable, the participant was treated as though the urine was clean, for the sake of the contingency management procedure. The sample was then sent off to be analyzed using EMIT (Redwood Toxicology Laboratories, Santa Rosa, CA). In the EMIT procedure a urine was rated positive for if the quantity of drug or metabolite is ≥1000 ng/mL for Amphetamines; ≥ 300 ng/ml for benzoylecognine, propoxyphene, and opiates; > 200 ng/ml for barbiturates and benzodiazepine; ≥ 150 ng/mL for methadone; ≥ 50 ng/mL for THC.

Data Analyses

Differences in retention were determined by entering the length of study participation into a Wilcoxon Rank-sum test due to non-normality of the data. Because the effects of gabapentin on the 10-day buprenorphine detoxification were of the greatest interest in this pilot study, the data collected during the buprenorphine detoxification (weeks 3–4) were analyzed. Continuous data collected thrice weekly (e.g., OWSC ratings), were analyzed using proc MIXED in SAS 9.3 (SAS System for Windows, SAS Institute Inc., Cary, NC) to run a 2×6 repeated measures ANOVA with drug (placebo vs. gabapentin) and time point (weekday visits 7–12) as factors. Dichotomous UDS data (positive or negative for opiates/opioids) were analyzed using proc GENMOD in SAS 9.3 to run a repeated measures logistical regression fit by generalized estimating equations with drug and time (number of days from visit 7 through visit 12) as factors. Baseline characteristics were analyzed using a t-test for continuous variables and a χ^2-test for categorical variables to determine whether any significant baseline differences have accrued despite randomization. For all analyses, significance was set at $p<0.05$ and a trend toward significance was set at $0.05 \leq p \leq 0.1$.

RESULTS

Subject Characteristics

Of the 33 participants who signed informed consent, 30 participants entered the study and received at least one dose of study medication. Of these 30 participants, five participants did not complete the gabapentin induction, four of which did not proceed beyond week 2. Of these four participants, two were noncompliant with the protocol and one left the study after a pharmacy error in which the buprenorphine taper was started during week 2 instead of week 3. The other participant had difficulty tolerating the gabapentin during induction, necessitating a gabapentin maintenance dose of (800 mg/day). Although the participant did not complete the gabapentin induction, she was allowed to undergo the buprenorphine taper.

Twenty-four of the 26 individuals who started the buprenorphine taper completed this phase, 22 of whom continued on to undergo the gabapentin taper. Data from 2 of the 13 individuals who underwent the buprenorphine taper in the gabapentin group were excluded from the analyses. One participant was noncompliant with buprenorphine dosing procedures and we had evidence of medication diversion during the trial. The other participant was maintained on 800 mg of gabapentin, which was a dose lower than that shown not to differ from placebo (i.e., 900 mg/day) in a prior detoxification trial (Kheirabadi, et al., 2008). This participant was considered dropped from the protocol during week 2 of the study for retention purposes.

Retention rates did not differ between treatment groups (Figure 2; Wilcoxon Rank Sum p=0.40; gabapentin=3.79±1.64 and PLA=4.31±0.94 weeks) with 22 of 28 participants (78.6%) completing the entire buprenorphine taper and 20 of 28 (71.4%) completing the entire protocol.

Baseline characteristics of those 24 subjects who at least started the buprenorphine taper essentially did not differ between medication groups (Table 2). Participants were approximately 30 yrs of age, 87.5% Caucasian and 45.8% Female. The vast majority of participants were prescription drug users (91.7%). The placebo group showed a trend toward greater oral and lesser intravenous routes of drug administration relative to the gabapentin group.

Adverse Events

During week 1, 12 adverse events occurred that were deemed at least possibly related to study participation. All were mild and are common side effects associated with buprenorphine, including nausea/vomiting (N=3), sleep disturbances (N=2), blurred vision (N=2), constipation (N=1), headache (N=1), increased sweating (N=1), tense muscles (N=1) and somnolence (N=1). During week 2, the following adverse events occurred that were at least possibly study related and showed a greater incidence in the gabapentin than placebo group: nausea/vomiting (gabapentin: N=2; placebo: N=1), somnolence (gabapentin: N=2; placebo: N=0), sleep disturbances (gabapentin: N=2; placebo: N=0), loss of motor skills (gabapentin: N=1; placebo: N=0), and lightheadedness (gabapentin: N=1; placebo: N=0). All events were mild and did not require an intervention, except for the lightheadedness, which occurred on day 4 during induction onto gabapentin. Even though vital signs were within the normal range, to be conservative, the induction to the maintenance dose of gabapentin was discontinued for this participant. During buprenorphine taper (weeks 3–4) there were 4 mild, potentially study-related adverse events with only fatigue having a greater prevalence in the gabapentin (N=1) than placebo (N=0) group. During the final week (gabapentin taper), no adverse events were reported.

Outcomes

During the buprenorphine taper (weeks 3–4), no significant treatment group differences in either the subjective (OWSC; F=0.12, *df*=22, p=0.73) or objective (OOWS; F=0.78, *df*=22, p=0.39) measures of opiate withdrawal occurred, although a significant change over time in subjective (F=3.08, *df*=103, p<0.01) but not the objective (F=0.30, *df*=106, p=0.91) measures of opiate withdrawal were observed. Physiological measures did not differ between gabapentin and placebo (data not shown). Systolic blood pressure and heart rate showed a dose x time interaction; however, no significant differences were observed between treatment groups at any given time point (data not shown).

The percentage of participants with positive opiate/opioid UDS during the buprenorphine taper showed a significant drug by time interaction (OR=0.73, p=0.004), such that the

probability of opioid-positive urines decreased by 0.73 for each day during the taper in the gabapentin group relative to placebo group (Figure 4). Urine results did not differ between groups during week 1 or 5.

DISCUSSION

The results of this pilot study suggest that gabapentin may improve treatment outcomes in participants undergoing a 10-day detoxification from buprenorphine. During the buprenorphine taper, participants receiving gabapentin had significantly less illicit opioid use over time. The fact that total opioid withdrawal scores did not differ across medication groups is inconsistent with the results of an open-label study of adjunctive gabapentin at 1,600 mg/day during a methadone-assisted detoxification procedure (Salehi, et al., 2011), which showed that gabapentin decreased subjective withdrawal symptom scores relative to those measured in a prior placebo-controlled trial of gabapentin at 900 mg/day during methadone-assisted detoxification (Kheirabadi, et al., 2008). This discrepancy may be due to differences in the time course, if not intensity, of withdrawal symptoms produced by methadone and buprenorphine (L. Gowing, et al., 2009). Nevertheless, the results of these studies are consistent in terms of gabapentin facilitating improvements in treatment outcomes and suggest that larger clinical trials examining the efficacy of gabapentin in the context of opioid-assisted detoxification may be warranted.

Opioid withdrawal appears to be expressed through opioid and non opioid receptors acting on the largest noradrenergic bundle in the brain, the locus coeruleus (e.g., see (Koob, Maldonado, & Stinus, 1992; Nestler, 1992; Redmond, 1984; Williams, et al., 2001); for exception see (MacDonald, Christie, Williams, Bellchambers, & Bellchambers, 1997)), with excitatory amino acid input from the paragigantocellularis (Akaoka & Aston-Jones, 1991; Ennis & Aston-Jones, 1988). One site where excitatory amino acid neurotransmission occurs is the N-methyl-D-aspartic acid (NMDA) receptor. This receptor is part of a receptor/ion channel complex with multiple regulatory sites, including the following: a L-glutamate recognition site for NMDA competitive antagonists, ion channel recognition sites for noncompetitive NMDA antagonists, a strychnine-insensitive glycine modulatory site, a polyamine site for NMDA noncompetitive antagonists, and sites on cationic channels permeable to potassium, sodium and calcium (Mayer & Miller, 1990). As a sodium and calcium channel blocker (Dickenson & Ghandehari, 2007; Landmark, 2007), gabapentin may alleviate the expression of withdrawal, at least in part, through its inhibitory effect on this excitatory input by inhibiting the release of glutamate (see (Olive, Cleva, Kalivas, & Malcolm, 2012)). This finding is consistent with prior research showing that NMDA receptor antagonists decrease tolerance and physical dependence development in opiate-treated animals (Marek, Ben-Eliyahu, Gold, & Liebeskind, 1991; Tiseo & Inturrisi, 1993; Trujillo & Akil, 1991; Trujillo & Akil, 1994), as well as, decrease the severity of naloxone-precipitated withdrawal in opiate dependent rats (Koyuncuoglu, Gunogor, & Sgduyu, 1990; Rasmussen et al., 1991). Thus, gabapentin may be effective in alleviating opioid withdrawal through its interaction with secondary mechanisms underlying this phenomenon.

From a clinical standpoint, the pharmacological profile of gabapentin may support its further evaluation as a potential treatment for opioid withdrawal. For instance, gabapentin has been shown to be generally safe and well tolerated at doses up to at least 1800 mg/day (Bogan, Bornemann, Kushida, Trân, & Barrett, 2010; Ellenbogen et al., 2011; Inoue, Uchimura, Kuroda, Hirata, & Hattori, 2012). Moreover, because gabapentin is excreted unchanged in the urine, has no interactions with hepatic metabolic processes and has low protein binding (Rose & Kim, 2002), it has minimal potential for drug interactions. In addition, like several anticonvulsants, gabapentin has low abuse liability (Ewan & Martin, 2011; Gentry, Hill, & Malcolm, 2002). However, we note that several anecdotal reports of abuse and withdrawal

symptoms associated with abrupt cessation of gabapentin have been reported (Corá-Locatelli G, 1998; Kruszewski, Paczynski, & Kahn, 2009; Tran, Hranicky, Lark, & Jacob, 2005), particularly in individuals with drug or alcohol problems (Hellwig, Hammerquist, & Termaat, 2010; Pittenger & Desan, 2007). These reports suggest that those receiving gabapentin should be observed for signs of abuse or dependence and cessation of gabapentin should not be abrupt but rather occur over the course of at least one week (Pfizer, 2012b). Be that as it may, in the present study gabapentin was generally well tolerated. Although the gabapentin induction of one participant was suspended due to lightheadedness, this was a conservative decision due to the pilot nature of the trial, particularly given that vital signs were with normal limits. Thus, gabapentin possesses several favorable pharmacological characteristics that may support further consideration as an adjunct to opioid-assisted detoxification.

Due to the nature of pilot studies in general, this study has several limitations. For instance, we did not adequately measure craving in this trial, hampering our ability to characterize the incidence, time course and severity of “craving.” Moreover, we received several unsolicited reports of improved sleep quality, suggesting that this measure might have been important to assess. Because withdrawal symptoms might emerge or continue after the buprenorphine taper, delaying the start of the gabapentin taper may have been useful strategy to determine its longer-term effects on outcomes. In addition, although gabapentin appears to improve short-term treatment response during buprenorphine-assisted detoxification, whether gabapentin improves longer-term treatment outcomes is unclear at this time. More research is necessary to clarify the potential of gabapentin as an effective adjunct to opioid-assisted detoxification.

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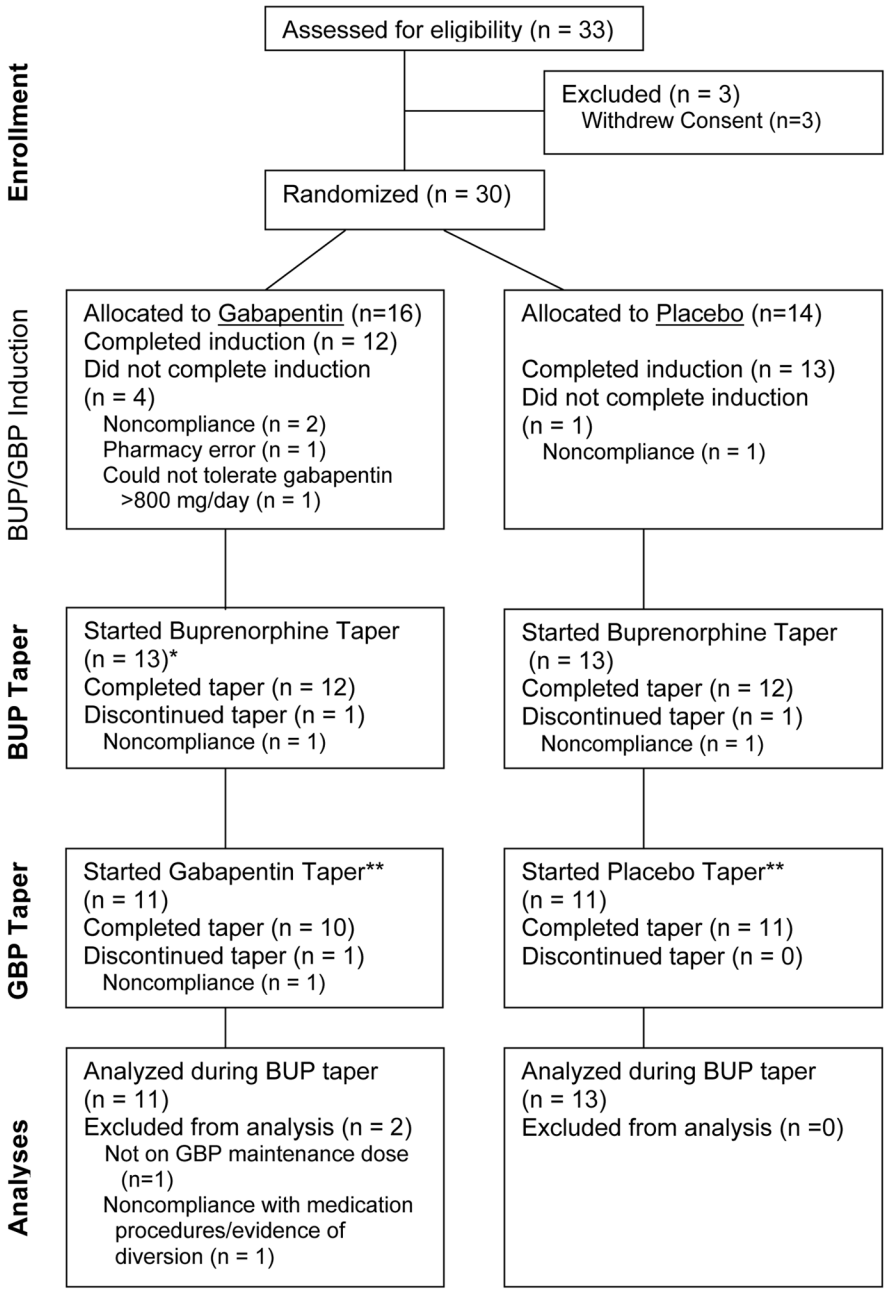

Figure 1.

Flow diagram of subject progress through the phases of the randomized clinical trial. BUP refers to buprenorphine and GBP refers to gabapentin. The * indicates that one participant who did not complete the induction protocol underwent the buprenorphine taper. The ** indicates that a participant who completed the buprenorphine taper dropped out of the study prior to the gabapentin taper.

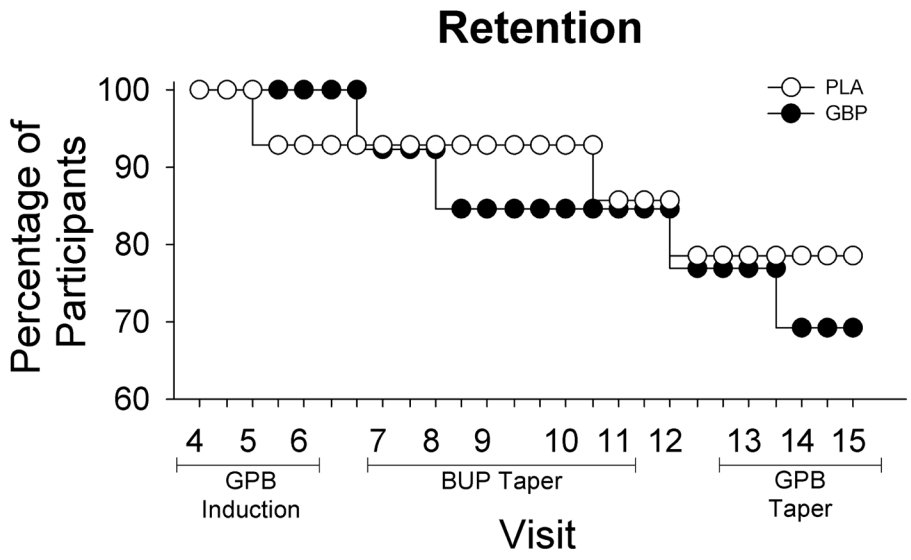

Figure 2.
Percentage of participants retained in each of the two treatment groups during each week of the study. X-axis: visit and phase of study.

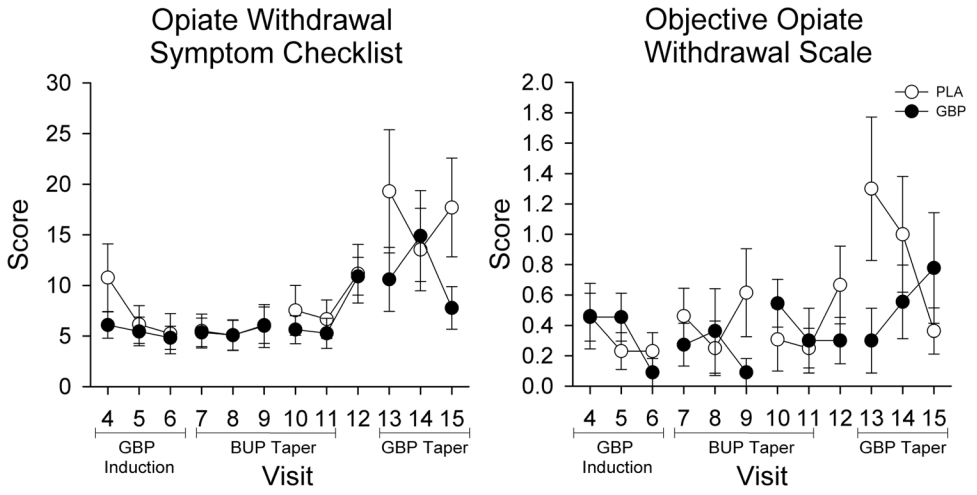

Figure 3.

Scores on the Opioid Withdrawal Symptom Checklist (left panel) and the Objective Opioid Withdrawal Scale (right panel). X-axis: number of visit and phase of study. Each data point represents the mean ± S.E.

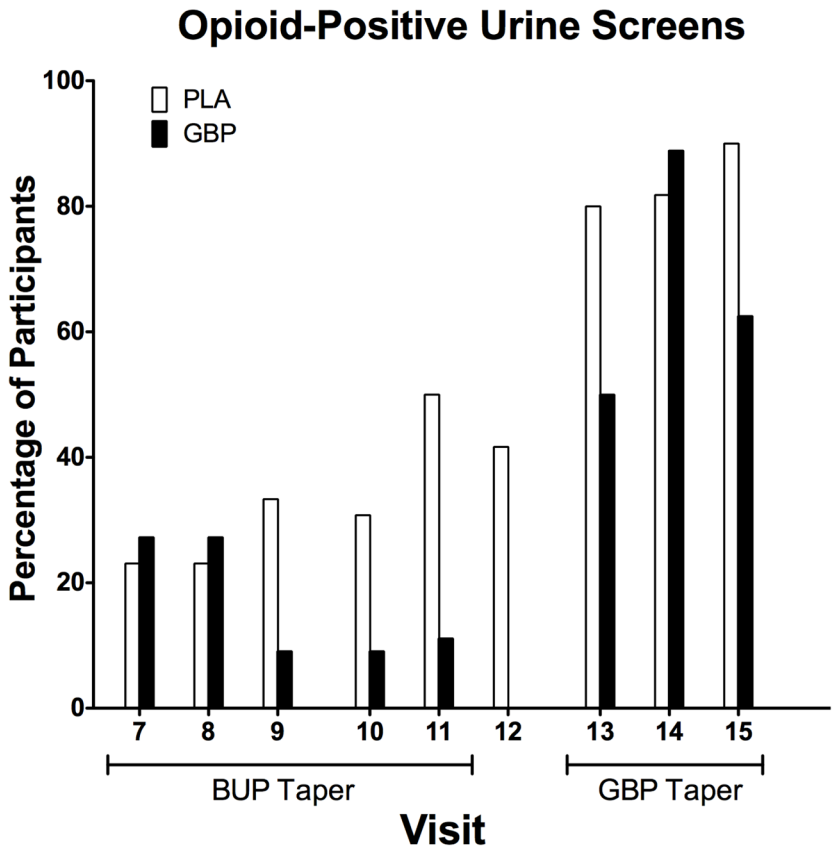

Figure 4.
Percentage of participants with urine drug screens positive for opioids/opiates at each time point during the BUP taper (weeks 3–4) and the gabapentin taper (week 5). X-axis: visit and phase of study.

Table 1

Experimental Design

	Days						
Phase	**1 (M)**	**2 (T)**	**3 (W)**	**4 (Th)**	**5 (F)**	**6 (Sa)**	**7 (Su)**
Week 1: BUP Induction (mg)	4	8	12	12	12	24	
(No GBP or placebo)							
Week 2: BUP Maintenance (mg)	12	12	12	12	12	24	
GBP Induction (mg)	*200*	*400*	*800*	*1200*	*1600*	*1600*	*1600*
Week 3: BUP Taper (mg)	10	10	8	8	6	12	
GBP Maintenance (mg)	*1600*	*1600*	*1600*	*1600*	*1600*	*1600*	*1600*
Week 4: BUP Taper Ends (mg)	4	4	2				
GBP Maintenance (mg)	*1600*	*1600*	*1600*	*1600*	*1600*	*1600*	*1600*
Week 5: *GBP Taper (mg)*	*1200*	*800*	*400*	*200*	Last Visit		

Assessments, vitals and UDS are collected Days 1, 3, and/or 5. BUP refers to buprenorphine; GBP refers to gabapentin.

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Table 2

Summary of group characteristics

Measure	**Placebo (SD)**	**Gabapentin (SD)**			
n	***13***	***11***	***Test Statistic***	***df***	***p***
Age (years)	30.31±4.43	29.00±3.33	t=−0.30	22	0.77
Race (non-AA/AA)	12/1	9/2	χ^2=0.57	1	0.45
Gender (% female)	46.15	45.45	χ^2=0.97	1	0.97
Education (% HS or less)	69.23	81.82	χ^2=0.48	1	0.49
Employment (% not working)	53.85	54.55	χ^2=0.001	1	0.97
Cohabitation (% living alone)	46.14	45.45	χ^2=0.001	1	0.97
Primary Opiate of Choice (MOR/H/MTD/OXY/other)	3/1/2/5/2	1/1/2/4/3	z=0.78		0.78
Route (PO/IV/IN)	7/5/1	3/4/4	*z=1.65*		*0.10*

Race: SD=standard deviation; AA=African American; HS= high school diploma or equivalent; H=heroin; MTD=methadone; MOR=morphine; OXY=oxycodone or oxymorphone; other=hydrocodone, dilaudid, etc; IV=intravenous; IN=intranasal; PO=oral; THC=marijuana; UDS=urine drug screen.