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Randomized clinical trial comparing buprenorphine/ naloxone and methadone for the treatment of patients with failed back surgery syndrome and opioid addiction

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Abstract

Opioid analgesic consumption has led to an unprecedented epidemic of overdose death and opioid addiction in the US history. The treatment of chronic pain in patients with opioid addiction who receive prescriptions for opioid medications presents a clinical dilemma. Continuing opioid medication could result in hyperalgesia rendering opioids ineffective and in an iatrogenic therapeutic damage as evidenced by the worsening of addiction. Discontinuing opioid medications could result in severe pain and cravings that often leads the patient to the illicit market. This study compared methadone and buprenorphine/naloxone in patients with failed back surgery syndrome and opioid addiction. Nineteen participants were randomly assigned to methadone or buprenorphine/ naloxone and were followed for 6 months. In an intent-to-treat analysis analgesia, craving, functioning, drug use, depression, and treatment retention were assessed monthly. It was planned to enroll 66 patients with failed back surgery syndrome and opioid addiction; however, enrollment was closed early due to suspected abuse of medications. Patients in both treatment conditions exhibited significantly improved 24-hour pain severity with up to 20% reduction of pain severity at the last follow-up ($p < .05$). However, patients receiving methadone reported significantly reduced current pain severity, whereas patients receiving buprenorphine/naloxone did not. Patients reported significantly improved functioning, fewer cravings, less opioid use, and depression ($p < .05$) across the treatment conditions. When given a choice between methadone and buprenorphine/ naloxone, buprenorphine/ naloxone is recommended due to its superior safety profile. Treatment with either needs to be monitored closely.

Keywords

methadone; buprenorphine; opioid addiction; chronic pain; failed back surgery syndrome

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The study was registered with the Food and Drug Administration (www.ClinicalTrials.gov) and was given the identifier number NCT01559454.

Introduction

Opioid analgesic consumption has led to an unprecedented epidemic of overdose death and opioid addiction in the US history (Kolodny et al., 2015).

For up to 43% of chronic pain patients, long-term treatment with opioids results in the development of tolerance to the analgesic effects of opioids and might be complicated by aberrant medication taking behaviors (e.g., dose escalations, “doctor shopping,”) (Breckenridge & Clark, 2003). Continuation of opioid medications reinforces these behaviors and may not provide adequate pain relief, but increases hyperalgesia instead. In contrast, discontinuation results in hyperalgesia and severe pain, which increases the potential to return to licit or illicit opioids (Garland, Froeliger, Partin, & Howard, 2013; Ling, Mooney, & Hillhouse, 2011).

For chronic pain patients with opioid addiction, the recommendation is discontinuation of the short-acting opioids followed by the use of non-opioid analgesics combined with behavioral addiction treatment to reduce pain and cravings and improve functioning along with consideration of buprenorphine, methadone, or naltrexone for treatment when appropriate (Substance Abuse and Mental Health Services Administration, 2011).

Clinicians need evidence-based guidelines to treat chronic pain patients with opioid addiction in an office-based setting to tackle the epidemic of addiction. We previously showed the effectiveness of buprenorphine taper for detoxification and methadone and buprenorphine treatment in patients with chronic pain and opioid addiction (Blondell et al., 2010; Neumann et al., 2013). This study compared 6-month methadone and buprenorphine/naloxone treatment in patients with failed back surgery syndrome and opioid addiction in a primary care setting on: analgesia, functioning, illicit drug use, treatment retention, depression, and cravings. The new components are the more homogenous pain condition sample and additional and/ or refined outcomes measures.

Methods

This superiority study used a prospective 2-arm open-label randomized clinical trial design comparing methadone and buprenorphine/naloxone in patients with chronic back pain and an addiction to prescription opioids who had been treated with opioids for pain prior to inclusion into the study.

The study protocol was approved by the Institutional Review Board of the University at Buffalo and was conducted between January 2012 and May 2014.

The participants were randomized into one of two groups that were pre-determined by drawing lots using a 3:3 ratio, block randomization procedure. This information was kept concealed and was referred to by the research associate at each enrollment. Participants and treatment providers were not blinded to the conditions. There was no compensation to patients for enrolling to not interfere with the real-world primary care setting.

The study was conducted at an outpatient primary care office that was affiliated with the university and specialized in providing addiction services (medication-assisted treatment). Participants were recruited in 3 ways. (1) The electronic medical records of the affiliated primary care offices were reviewed for eligible patients who received opioid medications for one of the pain conditions specified above. The primary care physicians of 1503 potentially eligible patients were asked for approval for contacting the patient to participate in this study. Patients who were approved to be contacted were called and screened. (2) Patients seeking treatment called the addiction medicine clinic directly where this study was conducted and were screened during their first visit. (3) Information (i.e., brochures) about the study was disseminated to local health professionals (e.g., mental health professionals, orthopedic surgeons, hospitals etc.) who referred patients to the clinic for further screening. Callers were screened for study eligibility. A physician, usually the principal investigator, assessed eligible patients during a face-to-face interview. It was planned to enroll 66 patients. The flowchart is shown in Figure 1.

Participants

Men and women with post-surgical chronic non-malignant back pain and failed back surgery syndrome due to past spinal surgery and an addiction to prescription opioids were eligible for randomization. The inclusion criteria included: (1) medically stable [Clinical Opiate Withdrawal Scale (COWS) score \leq 5, no acute opioid withdrawal], (2) ability to give consent, (3) ability to understand spoken and basic written English, (4) age 18–64 years, inclusive, (5) residence in one of two local counties, (6) presence of a medication monitor, usually a family member that monitors the medication administration, (7) health insurance or other ability to pay for treatment, and (8) the approval from patient's primary care physician. Exclusion criteria were previously published in Neumann et al. (2013). Additionally, individuals were excluded from the study if: (1) they were lacking a "medication monitor, (2) were medically unstable, or (3) were a member of a vulnerable population, including prisoners.

On the first visit, opioid dependence was confirmed with a 7-item checklist based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) for opioid dependence (304.01) (American Psychiatric Association, 2000) and a Drug Abuse Screening Test (DAST) score $>$ 4 (Skinner, 1982). The main opioid of choice had to be a prescription analgesic. Because it is difficult to diagnose addiction in chronic pain patients, addiction was determined by patients self-identifying as being "addicted," meeting DSM-IV criteria for dependence, and having a DAST score $>$ 4. Patients had to have a past surgery with one of the following diagnoses that are consistent with ICD terminology: post-laminectomy syndrome of the lumbar region, mechanical complication of internal orthopedic device, implant or graft or another acquired deformity of the spine. These were associated with one of the following pain syndromes: lumbar spinal stenosis, degenerative spondylolisthesis, or degenerative disc disease. The diagnosis of a failed back surgery syndrome was confirmed by clinical examination and the presence of a surgical scar on the back or by diagnostic imaging (i.e., CT, MRI).

Treatment

Participants were randomly assigned to receive either of the following 6-month treatment protocols: 1) oral methadone tablets 30–60 mg/day; doses were divided 3–4 times daily (active comparator group) or 2) sublingual buprenorphine/naloxone 8/2–16/4 mg, doses were divided 2–4 times daily (experimental group). The dose range of buprenorphine originated from a 2005 study by Malinoff and the dosage range of methadone was chosen according to the recommendation in a 2001 study by Reisine & Pasternak (Malinoff, Barkin, & Wilson, 2005; Reisine & Pasternak, 2001). We showed in our previous study that these doses resulted in significant analgesia (Neumann et al., 2013). The design of this randomized clinical trial was 2×2 factorial: Treatment (buprenorphine/ naloxone, methadone) x Follow-up (baseline, 6 months). The detailed study and clinical procedures associated with induction, monitoring, dosing, and prevention of diversion are described in Neumann et al., 2013 and Blondell et al., 2010 (Blondell et al., 2010; Neumann et al., 2013).

Participants were allowed to crossover to the other study medication upon request, if they thought they had an inadequate response to the initial study medication (i.e., inadequate pain control, severe cravings, intolerable side effects, etc.). Participants were allowed to withdraw from this protocol at any point during the study.

Participants were seen at least monthly during follow-ups and were required to provide urine samples for toxicology screening at every visit. Most participants were required by the physician to be seen biweekly at some point during the treatment, but were only asked to fill out surveys and questionnaires on a monthly basis. The length of the prescription given out varied based on the clinician's assessment of the participant's clinical progress and trustworthiness (e.g., consistent negative toxicology, documented counseling attendance, bringing a lockbox), but was never longer than 1 month. After the 6-month follow-up period, participants were allowed to choose one of the following final treatment plans: 1) taper off the study medication and use only non-opioid analgesics, 2) return to using their previous opioid medications, or 3) remain on buprenorphine or methadone treatment.

Measures of Treatment Outcome

Baseline data for participants that were assessed included medical history, demographic characteristics, and substance use history (Table 1), as well as data for diagnoses (DAST) and withdrawal (COWS). The primary outcome was analgesia. On the first and last visit and at each follow-up, pain severity was assessed using a 0–10 point numerical rating scale, a visual analogue scale (VAS) (Boonstra, Schiphorst Preuper, Reneman, Posthumus, & Stewart, 2008), and the Brief Pain Inventory (BPI) (Cleeland, 2009). Secondary outcomes included treatment retention and retention on study medication. Furthermore, self-reported functioning (Roland Morris disability questionnaire) (Roland & Fairbank, 2000), cravings (VAS), depression (BDI-II) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), self-reported drug use (i.e., marijuana, benzodiazepines, cocaine, opioids) measured as number of days of retrospectively reported drug use at each monthly follow-up (time line follow back), and self-reported alcohol use were assessed.

Urine samples were collected under monitored conditions (i.e., by indirect observation of the urine collection and by checking urine temperature with a heat sensitive strip on the collection container). Direct observation of the urethra while voiding was generally not performed unless requested by the physician. Specimens were submitted to an outside commercial lab determined by the participants' health insurance. The laboratory screened the specimens for opiates (morphine), oxycodone, fentanyl, methadone, buprenorphine, amphetamines, barbiturates, benzodiazepines, cannabis, and cocaine using an immunoassay, and the immunoassay results were confirmed with gas chromatography/mass spectroscopy (GS/MS). Opioid withdrawal symptoms and signs were documented using the COWS at induction after visit 1 (Wesson & Ling, 2003).

Statistical analysis

Research data were converted from paper study forms to electronic medical records (EMR) for research and clinical purposes. When available, missing data were supplemented with clinical information from the EMR that was entered by the physician. Data were extracted from the EMR and were analyzed using SPSS version 25 (SPSS Inc., Chicago, IL) and GraphPad Prism 6 (GraphPad Software, La Joella, CA). An alpha level of 0.05 was selected for our statistical tests. Pearson chi square was used to compare all categorical variables at baseline. A two-tailed, unequal or equal (where appropriate) variance t-test was calculated to assess the differences of continuous variables at baseline. The design of this randomized clinical trial was 2 × 2 factorial: Treatment (buprenorphine/ naloxone, methadone) x Follow-up (baseline, 6 months). A repeated-measures analysis of variance (ANOVA) was used for the continuous outcome variables. Outcome measures were analyzed using an intent-to-treat analysis. The last observation was carried forward to the last follow-up for non-completers. Missing data were replaced by the series mean.

Results

Adverse events

Two participants who received methadone arrived sedated to the last follow-up appointment. They were partners who exhibited urine toxicology positive for opioids at every visit. Both admitted to abusing intravenous heroin and oral benzodiazepine continuously throughout the study. The PI suspected abuse of the study medication and consequently reported a potential adverse event to the IRB, which recommended that enrollment be closed. One of these participants had been assigned to methadone and was started on buprenorphine/naloxone following this incidence with good clinical outcomes. The other participant had been assigned to buprenorphine/naloxone and had switched to methadone after 1 month and was also restarted on buprenorphine/naloxone with good clinical outcomes.

Participant characteristics

Nineteen participants were randomized to receive either buprenorphine/naloxone (10) or methadone (9). All 19 participants (100%) had Medicare or Medicaid as health insurance, 13 (68.4%) possessed an additional private health insurance. Baseline characteristics of completers versus non-completers and medication-switchers versus non-switchers are displayed in Table 1. Significantly more participants in the buprenorphine-assigned group

reported alcohol use at baseline than participants in the methadone-assigned group ($p = .027$).

Outcomes

Completion of treatment—Of the 19 enrolled participants, 10 participants (52.6%) completed the study. Treatment retention did not differ between methadone and buprenorphine/naloxone groups. Four participants switched study medications and completed the study, 3 from methadone to buprenorphine/naloxone and 1 from buprenorphine/naloxone to methadone. Completion of the study was associated with younger age of onset of opioid problem ($p = .011$) and higher severity of depression as measured by the BDI rating ($p = .019$).

Pain—Repeated-measures ANOVA for current pain severity measured with the VAS showed a significant interaction of Follow-up and Treatment [$F(1,16) = 6.87, p = .019$]. Participants receiving methadone reported significantly less severe pain at 6 months ($M = 41.31 \pm 7.14$) than they did at baseline ($M = 76.89 \pm 2.96, p = .05$). Participants assigned to buprenorphine reported significantly less pain ($M = 59.78 \pm 7.5$) than did those assigned to the methadone group ($M = 76.89 \pm 2.96, p = .05$) at baseline.

Repeated-measures ANOVA for 24-hour pain severity assessed with the VAS showed a significant main effect of Follow-up [$F(1,17) = 12.89, p = .002$]. Across both treatment conditions, participants reported less 24-hour pain at 6 months ($M = 63.49 \pm 4.51$) than they did at baseline ($M = 78.82 \pm 2.8$), which corresponds to a pain reduction of 20%.

Repeated-measures ANOVA for pain severity measured by the BPI resulted in an interaction of Treatment and Follow-up [$F(1,17) = 7.14, p = .016$]. Participants randomized to buprenorphine/naloxone showed significantly lower pain severity at baseline ($M = 5.95 \pm 0.32$) than did participants assigned to methadone ($M = 7.01 \pm 0.26, p < .05$). The explanation is that participants assigned to buprenorphine/naloxone had significantly less least pain ($p = .01$). Participants assigned to methadone reported significantly less severe pain at 6 months ($M = 5.27 \pm 0.5$) than they did at baseline ($M = 7.01 \pm 0.26, p < .05$), which corresponds to a reduction of pain severity by 25%.

Cravings—The repeated-measures ANOVA for current cravings measured using a VAS showed a main effect of Follow-up [$F(1,17) = 24.62, p < .001$]. Participants of both treatment conditions reported significantly fewer cravings at 6 months ($M = 18.74 \pm 4.89$) than they did at baseline ($M = 64.15 \pm 8.04$), which is a 91.8% reduction in cravings.

Functioning—The repeated-measures ANOVA for functioning assessed by the Roland-Morris Disability Test showed a significant main effect of Follow-up [$F(1,17) = 13.5, p = .002$]. Participants assigned to either treatment reported significantly lower scores, and therefore better functioning at 6 months ($M = 14.29 \pm 1.14$) than they did at baseline ($M = 18.15 \pm 1.07$), which corresponds to 21.4% increase in functioning.

Depression—The repeated-measures ANOVA for depression assessed by the Beck Depression Inventory showed a significant main effect of Follow-up [$F(1,17) = 8.41, p$

= .01]. Participants assigned to either treatment reported significantly less severe depression at 6 months ($M = 16.24 \pm 2.57$) than they did at baseline ($M = 21.17 \pm 2.7$), changing from moderate depression at the beginning of the study to mild depression at the end of the study.

Drug use—The repeated-measures ANOVA for number of days taking opioids in the past month resulted in a significant main effect of Follow-up [$F(1,17) = 79.75, p < .001$]. Participants assigned to either treatment condition reported to have used less opioids during the past 30 days at the last visit ($M = 3.58 \pm 0.97$ days) compared to baseline ($M = 23.85 \pm 2.14$ days). Of the 10 participants completing the study, 1 participant in each condition had a urine toxicology positive for opioids at the end of the study compared to 3 in the buprenorphine group and 4 in the methadone group at baseline. Two participants in the buprenorphine group and 1 participant in the methadone group reported to have used opioids in the last month compared to 3 in the buprenorphine group and 5 in the methadone group at baseline.

Side effects—At 6 months, 2 participants reported nausea/vomiting, 2 sedation/sleepiness/cloudy thinking, 4 constipation, 1 cravings for old drugs, 3 insomnia/sleeping problems/using dreams, and 3 headaches.

1-year follow-up—Search of the electronic records 1 year after completion of study showed that of the 19 who were enrolled, 7 (36.8%) participants remained in treatment with the study medication, 7 (36.8%) had returned to full-agonist opioid treatment prescribed by a pain management physician, 3 (15.8%) had received addiction treatment (inpatient detoxification or outpatient methadone maintenance), and no information was available for the remaining 2 (10.5%). The two participants associated with the potential adverse event were receiving outpatient methadone maintenance.

Discussion

Participants assigned to both treatment conditions (methadone and buprenorphine/naloxone) showed a reduction of 24hr pain severity by 20% assessed with the VAS at 6 months compared to baseline. However, only participants assigned to methadone reported a reduction of current pain severity measured by the VAS and BPI, but participants receiving buprenorphine/naloxone did not. Participants in both treatment conditions reported less cravings, less depression, less drug use, and improved functioning at the 6-month follow-up compared to the initial visit. The treatment conditions did not differ in treatment retention, drug use, depression, functioning, and side effects at 6 months.

The reduction in pain confirms the finding of our pilot study that both treatments reduced pain in participants with chronic pain and opioid addiction (Neumann et al., 2013). A new finding is that while participants in both conditions reported an improvement of 24-hour pain, only the methadone group reported an improvement of current pain. These results are clinically relevant because participants also reported an improvement of functioning, depression, and cravings and reduced opioid use.

Fifty-two percent completed the study. This treatment retention resembles our previous study, in which 48% of the participants completed the treatment (Neumann et al., 2013).

The potential adverse event of the suspicion of misuse of the study medication methadone resulted in the closure of enrollment. The two participants in question had used heroin intravenously at least once a month throughout the study and appeared intoxicated at the last follow-up appointment. As a full opioid agonist methadone has the side effect of sedation. However, this is not to be expected at the small doses that were prescribed to these participants who were tolerant to opioids. Therefore, we recommend that strict guidelines need to be followed when prescribing methadone for chronic pain and opioid addiction, which includes education and counseling of participants on methadone's safety and careful dose initiation and titration of methadone (Chou et al., 2014; Rosenblum et al., 2012; Streltzer, Ziegler, & Johnson, 2009).

The effectiveness and efficacy of methadone in treating opioid addiction has previously been shown (Amato, Minozzi, Davoli, & Vecchi, 2011). As a μ receptor agonist it has analgesic properties (Carpenter, Chapman, & Dickenson, 2000). In addition, NMDA receptor antagonists also appear to have analgesic properties (Reisine & Pasternak, 2001). Buprenorphine is a partial μ -opioid receptor agonist and κ -opioid receptor antagonist. The analgesic effect is hypothesized to be the result of its μ -opioid agonist effect (Gordon et al., 2010). Conversely, κ -opioid receptor antagonists have been shown to reduce withdrawal symptoms (Spanagel, Almeida, Bartl, & Shippenberg, 1994). They have antidepressant and anti-anxiolytic effects (Knoll, Meloni, Thomas, Carroll, & Carlezon, 2007).

Pain, cravings, depression, and function measures were based on self-report and potentially reflect a therapeutic alliance effect. Because this effectiveness trial was open-label and not blinded, researchers' and physicians' expectations and hypotheses of outcomes might have affected patient outcomes. The study had a small sample size. Despite the small sample size, there were some statistically significant results. However, smaller effects might have not been detected due to the low power. Consequently, generalization of the study results might be limited.

Patients with chronic pain and opioid addiction are a clinical dilemma, which can be targeted with buprenorphine or methadone treatment. In this original clinical trial both 6-month buprenorphine and methadone treatment improved pain, function, and reduced cravings in these participants in a real-world primary care clinic. Most participants were still in treatment 1 year after completion of the study. When a primary care physician is confronted with a patient who has postsurgical chronic back pain and an addiction, either buprenorphine or methadone may be advisable compared to continuation of full-agonist opioid medications. Buprenorphine is recommended over methadone due to its superior safety profile. When buprenorphine is not effective, methadone may be used in highly reliable patients; however, we suggest that methadone should be used only by physicians who are familiar with the use of this medication and that patients be closely monitored for adverse events (every 1–2 weeks).

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References

- Amato L, Minozzi S, Davoli M, & Vecchi S. (2011). Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database of Systematic Reviews*, 9, CD005031. 10.1002/14651858.CD005031.pub4
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Publishing.
- Beck AT, Ward CH, Mendelson M, Mock J, & Erbaugh J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561–571. 10.1001/archpsyc.1961.01710120031004 [PubMed: 13688369]
- Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, & Salcedo DM (2010). A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and coexistent opioid addiction. *Journal of Addiction Medicine*, 4(3), 140–146. 10.1097/ADM.0b013e3181ba895d [PubMed: 20959867]
- Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, & Stewart RE (2008). Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *International Journal of Rehabilitation Research*, 31(2), 165–169. 10.1097/MRR.0b013e3282fc0f93 [PubMed: 18467932]
- Breckenridge J, & Clark JD (2003). Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *The Journal of Pain*, 4, 344–350. 10.1016/S1526-5900(03)00638-2 [PubMed: 14622692]
- Carpenter KJ, Chapman V, Dickenson AH. (2000). Neuronal inhibitory effects of mehtadone are predominantly opioid receptor mediated in the rat spinal cord in vivo. *European Journal of Pain*, 4, 19–26. 10.1053/eujp.1999.0147 [PubMed: 10833552]
- Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, ... Zeltzer L. (2014). Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *The Journal of Pain*, 15(4), 321–337. doi:10.1016/j.jpain.2014.01.494. [PubMed: 24685458]
- Cleeland CS. (2009). *The Brief Pain Inventory user guide*. Houston, TX: The University of Texas.
- Garland EL, Froeliger B, Partin K, & Howard MO (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways. *Neuroscience and Biobehavioral Reviews*, 37(10 Pt2), 2597–2607. 10.1016/j.neubiorev.2013.08.006 [PubMed: 23988582]
- Gordon A, Rashiq S, Moulin DE, Clark AJ, Beaulieu AD, Eisenhoffer J, ... Darke AC (2010). Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain Research & Management*, 15(3), 169–178. [PubMed: 20577660]
- Knoll a. T., Meloni EG, Thomas JB, Carroll FI & Carlezon W. a. (2007). Anxiolytic-Like Effects of κ -Opioid Receptor Antagonists in Models of Unlearned and Learned Fear in Rats. *Journal of Pharmacology and Experimental Therapeutics*, 323(3), 838–845. 10.1124/jpet.107.127415 [PubMed: 17823306]
- Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, & Alexander GC (2015). The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *The Annual Review of Public Health*, 36, 559–574. 10.1146/annurev-publhealth-031914-122957

- Ling W, Mooney L, & Hillhouse M. (2011). Prescription opioid abuse, pain and addiction: Clinical issues and implications. *Drug and Alcohol Review*, 30(3), 300–305. 10.1111/j.1465-3362.2010.00271.x [PubMed: 21545561]
- Malinoff HL, Barkin RL, Wilson G. (2005). Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *Am J Ther*, 12, 379–384. [PubMed: 16148422]
- Neumann AM, Blondell RD, Jaanimägi U, Giambrone AK, Homish GG, Lozano JR, ... Azadfard M. (2013). A preliminary study comparing methadone and buprenorphine in patients with chronic pain and co-existent opioid addiction. *Journal of Addictive Diseases*, 32, 68–78. 10.1080/10550887.2012.759872 [PubMed: 23480249]
- Reisine T, & Pasternak G (2001). Opioid analgesics and antagonists In Hardman JG & Limbird LE (Eds.), *The pharmacological basis of therapeutics* (10th ed., pp. 251–255). New York: McGraw-Hill.
- Roland M, & Fairbank J. (2000). The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine*, 25(24), 3115–3124. 10.1097/00007632-200012150-00006 [PubMed: 11124727]
- Rosenblum A, Cruciani RA, Strain EC, Cleland CM, Joseph H, Magura S, ... Portenoy RK (2012). Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: Development and pilot test of a clinical protocol. *Journal of Opioid Management*, 8(6), 369–382. 10.5055/jom.2012.0137 [PubMed: 23264315]
- Skinner HA (1982). The drug abuse screening test. *Addictive Behaviors*, 7(4), 363–371. 10.1016/0306-4603(82)90005-3 [PubMed: 7183189]
- Spanagel R, Almeida O, Bartl C, & Shippenberg TS (1994). Endogenous kappa-opioid systems in opiate withdrawal: role in aversion and accompanying changes in mesolimbic dopamine release. *Psychopharmacology*, 115(1–2), 121–127. 10.1007/BF02244761 [PubMed: 7862883]
- Streltzer J, Ziegler P, & Johnson B. (2009). Cautionary guidelines for the use of opioids in chronic pain. *The American Journal on Addictions*, 18(1), 1–4. 10.1080/10550490802544508 [PubMed: 19219659]
- Substance Abuse and Mental Health Services Administration. (2011). *Managing chronic pain in adults with or in recovery from substance use disorders Treatment Improvement Protocol(TIP) 54*. Rockville, MD: Substance Abuse and Mental Health Administration.
- Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). *J Psychoactive Drugs*. 2003;35:253–259. [PubMed: 12924748]

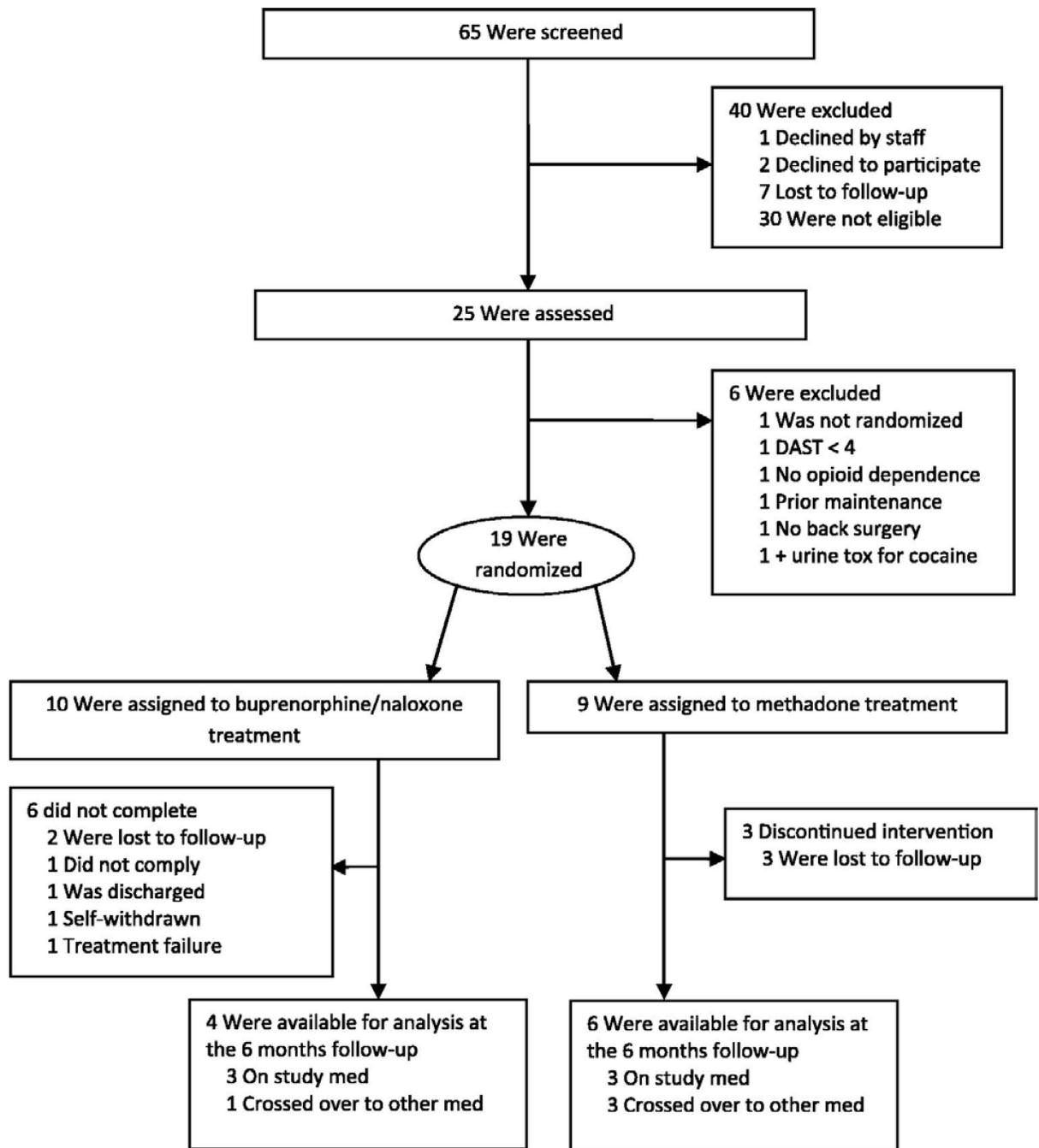


Figure 1:
Participant flow chart

Table 1.

Participant characteristics at baseline by completion of study and study med.

Characteristic	Completion of study			Completion on study med		p-value
	Completers (n = 10)	Non-comp. (n = 9)	Non-comp. (n = 9)	Switchers (n = 4)	Non-switchers (n = 15)	
Retention on study med or in study, No. (% yes)	4 (40)	0 (0)	0 (0)	4 (100)	6 (40)	.033*
Days in treatment, mean (SD)	180 (0)	63.8 (45.9)	63.8 (45.9)	180 (0)	110.3 (68.4)	.001*
Age, mean (SD)	41.0 (12.4)	41.3 (9.2)	41.3 (9.2)	41.8 (8.4)	41.0 (11.5)	.905
Gender, No. (% male)	3 (30)	3 (33.3)	3 (33.3)	2 (50)	4 (26.7)	.372
Race, No. (% white)	7 (70)	8 (88.9)	8 (88.9)	2 (50)	13 (86.7)	.396
Marital Status, No. (% never married)	4 (40)	5 (55.5)	5 (55.5)	1 (25)	8 (53.3)	1.000
Education, No. (% attended college)	5 (50)	4 (44.4)	4 (44.4)	2 (50)	7 (46.7)	.572
Employment, No. (% unemployed)	2 (22.2)	0 (0)	0 (0)	1 (25)	1 (6.7)	.093
No. (% disabled)	5 (50)	8 (88.9)	8 (88.9)	1 (25)	12 (80)	
Drug and Alcohol History						
Age of onset of opioid use, mean (SD)	25.1 (9.7)	31.8 (8.3)	31.8 (8.3)	26.0 (8.2)	29.0 (9.9)	.643
Age of onset of opioid problem, mean (SD)	27.6 (5.9)	38.4 (8.2)	38.4 (8.2)	32.0 (4.4)	34.1 (9.9)	.732
Family History, No. (% pos alcohol or drug hx)	6 (60)	2 (22.2)	2 (22.2)	1 (25)	7 (46.7)	.671
Treatment History						
Prior outpatient treatment, No. (% yes)	1 (10)	0 (0)	0 (0)	0 (0)	1 (6.7)	.798
Prior inpatient treatment, No. (% yes)	3 (30)	0 (0)	0 (0)	1 (25)	3 (46.9)	.798
Prior treatment for mental illness, No. (% yes)	5 (50)	2 (22.2)	2 (22.2)	1 (25)	6 (40)	1.000
Criminal History						
Number of arrests, mean (SD)	1.56 (3.3)	1.75 (3.5)	1.75 (3.5)	3.67 (5.5)	1.2 (2.7)	.249
Ever arrested, No. (%yes)	4 (40)	3 (33.3)	3 (33.3)	2 (50)	5 (33.3)	.323
Ever served prison time, No. (%yes)	1 (10)	1 (11.1)	1 (11.1)	1 (25)	1 (6.7)	.180
Baseline levels						
Current pain level, mean (SD)	7.8 (1.1)	7.0 (1.8)	7.0 (1.8)	7.8 (0.7)	7.4 (1.6)	.646
Average pain level, mean (SD)	6.2 (1.4)	5.1 (1.6)	5.1 (1.6)	6.1 (1.6)	5.6 (1.6)	.539
Level of functioning, mean (SD)	55.6 (12.6)	59.6 (19.4)	59.6 (19.4)	54.8 (19.1)	58.1 (15.2)	.714
Urine positive for opiates, No. (% yes)	7 (70)	5 (55.6)	5 (55.6)	4 (100)	8 (53.3)	.109
Urine positive for cocaine, No. (% yes)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	
Urine positive for benzodiazepines, No. (% yes)	2 (20)	0 (0)	0 (0)	2 (50)	0 (0)	.005*
Urine positive for any other drugs, No. (% yes)	3 (30)	0 (0)	0 (0)	2 (50)	1 (6.7)	.043*
Reported use of opiates, No. (% yes)	8 (80)	9 (100)	9 (100)	4 (100)	13 (86.7)	.440
Reported use of alcohol, No. (% yes)	2 (20)	4 (44.4)	4 (44.4)	0 (0)	6 (40)	.159
Reported use of benzodiazepines, No. (% yes)	5 (50)	3 (33.3)	3 (33.3)	3 (75)	5 (33.3)	.043*

*p-value < .05.