HHS Public Access

Author manuscript

Am J Addict. Author manuscript; available in PMC 2015 July 09.

Published in final edited form as:

Am J Addict. 2015 April ; 24(3): 258–264. doi:10.1111/ajad.12180.

Baseline Characteristics of Patients Predicting Suitability for Rapid Naltrexone Induction

Shanthi Mogali, MD[1], **Nabil A. Khan**[1], **Esther S. Drill, MS**[2], **Martina Pavlicova, MS, PhD**[2], **Maria A. Sullivan, MD, PhD**, **Edward Nunes, MD**[1,3], and **Adam Bisaga, MD**[1,3]

[1]Division of Substance Abuse, New York State Psychiatric Institute, New York, NY

[2]Department of Biostatistics, Columbia University, New York, NY

[3]Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY

Abstract

Background and Objectives—Extended-release (XR) injection naltrexone has proved promising in the treatment of opioid dependence. Induction onto naltrexone is often accomplished with a procedure known as rapid naltrexone induction. The purpose of this study was to evaluate pre-treatment patient characteristics as predictors of successful completion of a rapid naltrexone induction procedure prior to XR naltrexone treatment.

Methods—A chart review of 150 consecutive research participants (N = 84 completers and N = 66 non-completers) undergoing a rapid naltrexone induction with the buprenorphone-clonidine procedure were compared on a number of baseline demographic, clinical and psychosocial factors. Logistic regression was used to identify client characteristics that may predict successful initiation of naltrexone after a rapid induction-detoxification.

Results—Patients who failed to successfully initiate naltrexone were younger (AOR: 1.040, CI: 1.006, 1.075), and using 10 or more bags of heroin (or equivalent) per day (AOR: 0.881, CI: 0.820, 0.946). Drug use other than opioids was also predictive of failure to initiate naltrexone in simple bivariate analyses, but was no longer significant when controlling for age and opioid use level.

Conclusions—Younger age, and indicators of greater substance dependence severity (more current opioid use, other substance use) predict difficulty completing a rapid naltrexone induction procedure. Such patients might require a longer period of stabilization and/or more gradual detoxification prior to initiating naltrexone.

Scientific Significance—Our study findings identify specific characteristics of patients who responded positively to rapid naltrexone induction.

Address Correspondence to Mogali, The New York State Psychiatric Institute and College of Physicians & Surgeons of Columbia University, 1051 Riverside Dr., Unit 120, New York, NY.10032. mogalis@nyspi.columbia.edu.

Dr. Mogali and Mr. Khan conducted literature searches, designed the investigation, and gathered data. Ms. Drill and Ms. Pavlicova undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Declaration of Interest

Dr. Mogali, Mr. Khan, Ms. Drill, Ms. Pavlicova, Dr. Sullivan, and Dr. Bisaga have no conflicts to declare.

INTRODUCTION

Opioid dependence is a serious and major global public health concern.[1] The mainstays of treatment for opioid dependence in the United States and Canada have been detoxification followed by psychosocial treatment, or agonist (methadone or buprenorphine) maintenance therapy.[2] Detoxification followed by psychosocial treatment carries the appeal of getting patients "drug-free" and, while a successful approach for some individuals, is associated with a high relapse rate.[3,4,5] Opioid agonist treatment with buprenorphine or methadone is often effective for treatment seeking patients. However, some patients have difficulty accessing opioid maintenance treatment centers or providers. Many patients fail to achieve abstinence with these treatments and some who are maintained on opioid agonist treatment eventually no longer want to remain physically dependent on buprenorphine or methadone.[6,7] In such cases, detoxification with an opioid antagonist provides a suitable alternative treatment. In the past, antagonist maintenance therapy with naltrexone was thought to be primarily successful for subsets of patients with high motivation (eg, professionals whose employment might prohibit abuse). However, recent developments, including the combination of naltrexone with behavioral incentives,[8,9,10,11,12] and the advent of long-acting injectable naltrexone,[13] have improved long-term adherence levels close to what can be expected for agonist treatment.[14] Thus, naltrexone holds broader promise as an alternative maintenance therapy for opioid dependence.

A critical challenge with the antagonist treatment approach, however, is that a patient needs detoxification from opioids prior to induction onto naltrexone, in order to avoid precipitated withdrawal. It is recommended that 7–10 days of abstinence from opioids are needed to ensure a safe and comfortable induction.[15] However, detoxification followed by such a long delay carries a high risk of relapse if patients are discharged to outpatient care. The cost of longer inpatient stays are often not supported by third-party payors. A rapid detoxification and naltrexone induction procedure was thus developed to minimize the length and discomfort of opioid detoxification,[16] and has been refined over the years.[17,18] Nonetheless, this procedure remains associated with high rates of dropout[19,20,21] and we do not have a good understanding of factors that may contribute to premature treatment termination.

It is important for addiction specialists to understand the complex psychological, behavioral and social factors that contribute to attrition in any treatment program. It is especially important in the context of strengthening a promising but underutilized approach such as opioid antagonist treatment. If there are characteristics of patients that predict which patients are more versus less likely to successfully initiate naltrexone treatment using rapid induction method, this could prove important to efforts to improve naltrexone induction procedures and reduce dropout. Such characteristics could be valuable in tailoring treatment to the patient, for instance by delaying naltrexone induction for patients who likely need a slower detoxification. Patient characteristics associated with dropout may also offer clinicians insight into the mechanisms underlying difficulties with naltrexone induction. We therefore examined demographic and clinical characteristics of opioid dependent patients at baseline as predictors of successful and unsuccessful induction onto naltrexone in a series of patients entering clinical trials of naltrexone maintenance.

METHODS

Participant Selection and Study Procedures

A retrospective clinical chart review of 150 opioid-dependent patients seeking detoxification and treatment within the context of three clinical trials (Trial Identification Numbers: NCT00476242, NCT00332228, NCT00577408) at the Substance Treatment and Research Services (STARS) clinic, housed at the New York State Psychiatric Institute (NYSPI), was conducted. This sample was selected from consecutive research study admissions of treatment-seeking opioid-dependent adults (aged 18–60) between January 2007 and December 2009. Patients were recruited through word of mouth and advertisements in local media, and if deemed eligible, gave written informed consent to one of three opioid-dependence treatment studies, each offering injection naltrexone after a successful detoxification and oral naltrexone induction. The trials each shared identical screening processes, and nearly identical inpatient and outpatient procedures. The most salient points of difference were as follows. The longest-running study of 24 weeks ("Trial A") had a four-cell treatment design with arms involving random assignment to either oral or injection naltrexone (Depotrex™), and arms also involving random assignment to either the treatment-as-usual of Compliance Enhancement therapy (CE) versus a newer, more comprehensive behavioral therapy, Behavioral Naltrexone Therapy (BNT). Trials B and C were simpler standard two-cell protocols. Trial B was a 24-week trial and was designed as a follow-up to Trial A, using the more comprehensive BNT instead of CE and including random assignment to either oral or injection naltrexone (now the more well-known formulation of Vivitrol™ instead of Depotrex™). Trial B involved no other medications under research, and like Trial A provided for a standardized schedule for ancillary meds.[22] In Trial C was a 12-week study in which all patients received extended-release naltrexone; the main study drug was the NMDA glutamate receptor antagonist memantine which was started on day 5 of study participation.[21] This third study also allowed participants more flexibility in receiving ancillary pharmaceutical treatment than the former two trials did. Research inclusion and exclusion criteria for these studies were similar, as each of the trials sought treatment-seeking opioid-dependent individuals. Participants presenting with unstable medical or psychiatric conditions that might have interfered with naltrexone induction and treatment were excluded from all studies. Those prospective patients on methadone or buprenorphine maintenance were excluded, as were those taking more than 30 mg per day of illicit methadone, as methadone usage was previously associated with poor success rate on naltrexone[23], presumably due to its long half-life and increased likelihood of precipitated withdrawal during a rapid naltrexone induction. Those with a history of opioid overdose were also excluded as a riskminimizing measure for post study participation. These studies were approved by the New York State Psychiatric Institute IRB.

Screening Procedures

At the baseline screening assessment, each prospective participant met with a masters level therapist for a comprehensive diagnostic interview (SCID). At this time, demographic information and data on opioid dependence was collected (eg, longest period of abstinence, duration and route of drug use, quantity of current drug use-translated into equivalent number of heroin bags). Since some of the participants were oral (PO) users (opioid

analgesics, as opposed to heroin), the opioid of choice (i.e. hydrocodone, oxycodone, etc.) as reported by the participant was converted to oral morphine equivalents. We estimated that 20 mg of oral morphine was equivalent to one bag of heroin. For oral preparations 30 mg of morphine was equivalent to 40 mg of hydrocodone or 20 mg of oxycodone. Cross-tolerance was not accounted for in the conversion of prescription narcotics to bags of heroin. Information regarding concurrent and past drug use, past attempts at detoxification and rehabilitation, family drug use, presence of legal troubles, and Hamilton Depression Scale was also collected. Additionally, a full medical and psychiatric evaluation was conducted by a physician.

Rapid Naltrexone Induction Procedure

Eligible participants gave informed consent and were admitted to an inpatient research unit for an approximately 7-day duration of the detoxification and naltrexone induction procedure. The Rapid Induction Protocol[18] followed the guideline outlined in Table 1. Thus, on the day of admission (day 1), non-opioid medications (clonidine, clonazepam, ranitidine, ibuprofen, and zolpidem and trazodone) were started and continued throughout the inpatient period. On day 2, 16–24 h after the patient ceased opioid use, and as withdrawal signs and symptoms escalate, low-dose buprenorphine was administered (4 mg in the morning and 4 mg in the evening). After a one day of wash-out (Day 3) oral naltrexone was initiated slowly with 3 mg on day 4, and incrementally increased to 6 mg on day 5 and 25 mg on day 6. Naltrexone precipitated withdrawal symptoms were managed with additional doses of non-opioid medications (mostly clonidine and clonazepam). Patients who completed this Rapid Naltrexone Induction protocol successfully were then randomly inducted onto either oral or injectable naltrexone. On day 7, patients received either two consecutive 50 mg doses of maintenance oral naltrexone ($N = 47$) or a single dose of the extended-release naltrexone intramuscular (IM) injection (Depotrex™ or Vivitrol™) ($N = 37$), and subsequently discharged for outpatient treatment (Table 1). Patients who completed the inpatient naltrexone induction procedure, received the target dose of naltrexone and were discharged to outpatient treatment and were considered to have completed the detoxification-induction procedure; all others were considered non-completers.

Data Analysis

The primary outcome measure for this analysis was binary categorical completion status during the inpatient detoxification phase (ie, completers vs. non-completers). To test for simple associations between completion status and the panel of baseline demographic and clinical predictor variables, we used independent *t*-tests for continuous variables and Chi square tests for categorical variables (or Fisher's exact test for categories with $n < 5$). All tests were two-tailed and set at $\alpha = 0.05$ for this exploratory analysis. We then performed a logistic regression (SAS® PROC LOGISTIC) with completion status as the outcome, building a preliminary main-effects model by including all predictor variables significant at $p < .25$, and conducting a backward elimination procedure to arrive at a final model including only those predictor variables significant at *p*-values <.05. The purpose of this step-wise procedure was to determine which predictors were most important, remaining significant after control for other predictors.

RESULTS

Of the 150 opioid-dependent patients included in the analysis, 84 (56%) completed the inpatient Rapid Naltrexone Induction procedure, and 66 were identified as non-completers. Table 2 summarizes the comparisons of demographic and clinical characteristics between the completers and noncompleters. Completers were significantly older, used less opioid at baseline, were more likely using exclusively opioids versus those who also used other substances, and were less likely to be using cannabis. Completers had a later age-at-onset of opioid dependence (but more years of regular opioid use, quantified as the difference between age at first use and current age), more educational attainment, less history of legal problems, less current nicotine use, and less history of prior inpatient rehabilitation program participation. Notably, there were no apparent differences between completers and non-completers in the prevalence of current mood or anxiety disorders, nor mood symptoms as measured by the Hamilton Depression Scale. There was also no evidence of association between completers and non-completers in the type of opioid used (heroin compared to prescription opioid users). A multivariate regression analysis was conducted to determine an interaction between number of bags and type of opioid use, eg. to see whether the effect of number of bags changes depending on opioid type. The interaction terms was not significant ($p = 0.356$). Failure to complete appeared slightly more likely among intravenous users, but this did not approach significance.

The final logistic regression analysis (Table 3) yielded two statistically significant baseline characteristics that were associated with completion of the Rapid Naltrexone Induction protocol: the pre-admission level of opioid use and age. Older patients, and those using less opioid at baseline, were found to be more likely to complete the naltrexone induction. Figure 1 shows box-plots of the distribution of these two variables comparing completers vs non-completers. The distribution for baseline daily opioid use is particularly interesting, showing that about 75% of completers were using less than 10 bags per day at baseline, while around 50% of non-completers were using more than 10 bags per day, and the distribution for the non-completers had a longer upper tail—ie, patients with the highest level of daily opioid were in the early-dropout category.

DISCUSSION

The results indicate that older patients and those with lower daily opioid use are more likely to complete an inpatient rapid naltrexone induction procedure, while those older with greater levels of baseline opioid use were less likely to successfully induct onto naltrexone. The finding on baseline level of opioid use is consistent with studies from previous cohorts of patients at our clinic that examined predictors of retention in naltrexone-based treatment.[11,14,23,24] To our knowledge our group has been the first to examine the predictive factors of successful naltrexone induction. There have been some studies from other groups that support our findings of less opioid use and older age as predictors for positive outcomes in short term buprenorphine detoxification.[25,26] Similar studies evaluating treatment outcome in flexible dose-duration methadone detoxification programs have found higher baseline levels of methadone use (measured as average amount used per day), younger age, and longer duration of opioid use as predictors of poor treatment retention.[27] It is important

to note that although Trial C studied the use of memantine, there was no effect observed in the completion status of the rapid naltrexone induction procedures of memantine compared to placebo conditions.[21] The previous clinical trials examined retention which varied between 44 and 70% for all three studies with 3-month naltrexone maintenance and varied between 17 and 46% in the two studies with 6-month naltrexone maintenance.[21,22] Retention was measured across the entire treatment episode which included both inpatient naltrexone induction and outpatient naltrexone maintenance. These findings corroborate previous literature which suggests that a substantial number of patients treated with naltrexone are able to remain in treatment and in abstinence.[28,29] These rates are comparable to retention rates for patients treated with buprenorphine.[30,31,32] The present study, however, focuses specifically on completion of the initial inpatient detoxification.

The goal of the rapid naltrexone induction procedure is to provide a rapid but tolerable transition onto the platform of naltrexone.[18,16] It uses non-opioid medications, clonidine and clonazepam, and others, from the outset to attenuate both spontaneous and any precipitated withdrawal that occurs as naltrexone is introduced. A modest dose of buprenorphine is given only for one day (generally late in Day 1, or Day 2) to treat the worst of the withdrawal. Since the severity of withdrawal is related to the level of physiological dependence, it makes physiological sense that patients with higher baseline levels of opioid use are likely to experience greater withdrawal discomfort during this rapid detoxification-naltrexone induction procedure. Individuals who use higher amount of opioids at baseline might also be less able to tolerate withdrawal symptoms (lower distress tolerance).

The clinical implication would be that for patients with higher levels of opioid use at baseline, a slower induction procedure, allowing for further time before initiating naltrexone, and higher doses of adjunctive medications, including higher dose and/or longer duration of buprenorphine administration, should be considered. For example, instead of beginning naltrexone on the 4th day of admission, as was the target for patients in the present study, naltrexone could be started on the 6th or 7th day, or later, or the starting naltrexone dose could be lower than 3 mg. Buprenorphine might be given for 2 or 3 days, if needed, rather than just one. Guidelines to this effect have recently been published.[18] An alternative procedure, such as an extended cross-taper from buprenorphine to naltrexone could also be utilized to minimize the severity of discomfort emerging during the induction onto naltrexone.[33,34] It is also important to note that ultra-rapid naltrexone induction under general anesthesia has been attempted and proposed for individuals who are unable to tolerate standard detoxification procedures. However, evidence suggests that anesthesia-based detoxification is no more effective at reducing withdrawal symptoms than more gradual detoxification-naltrexone induction methods, and is potentially dangerous in that serious medical complications have been observed.[18,19]

Older age has been associated with better retention in treatment for other substance problems and treatment settings.[35,36] This might reflect the “aging out” phenomenon, or greater maturity or motivation for treatment. Clinically, a recommendation might be to consider a more gradual detoxification-induction for younger patients.

It is also important to note that baseline opioid use and age only explain a fraction of the variance in naltrexone induction completion. Inspection of the relevant box plots (Fig. 1) suggests that while patients with more than 15 bags per day of heroin use at baseline almost invariably failed to complete, a number of patients in the heavy-use range of 7 to 15 bags per day did succeed. Conversely, a number of patients taking less than 7 bags per day at baseline failed to complete. For the "age" variable, the distributions for completers and non-completers substantially overlap. Thus, there are likely unmeasured individual factors contributing to completion status, such as impulsivity, distress tolerance or susceptibility to withdrawal symptoms. During inpatient detoxification all participants received standing and as needed doses of ancillary medications. The use of these medications was only restricted due to safety concerns (eg, standing doses of clonidine were held if blood pressure was below cut-off). The majority of patients took all doses of available adjunctive medications and even with that there remains a significant level of withdrawal. It is possible that more severe withdrawal results in treatment drop-out but we do not have readily available data to assess that in the present manuscript. One recommendation based on this analysis would be to closely monitor withdrawal discomfort during the first 24 h of the rapid induction procedure. Patients with continued high levels of discomfort should be considered for more aggressive withdrawal treatment with more buprenorphine, or even methadone, and a longer, more gradual detoxification with greater delay to naltrexone induction.

Younger age at first opioid use, years of continuous opioid use, history of legal problems, and non-opioid drug abuse, showed non-significant associations with failure to complete naltrexone induction. While no firm conclusions can be drawn given the sample size used, it is noteworthy that these findings are suggestive of greater overall severity, and bear further investigation.

Depression was predictive of worse retention in treatment in an earlier study,[23] however, depression diagnosis, depression severity, and anxiety disorder diagnosis was not predictive of naltrexone induction completion status in the present study. Patients with depression were eligible for the studies that made up the present cohort, as long as they were not acutely suicidal or otherwise in need of emergent treatment. There has been a concern that naltrexone may worsen depression, although we have found that depressive symptoms generally improve gradually in the weeks after induction onto naltrexone[37], and that persistent depression can be treated with routine antidepressants.

Limitations of the present study include the lack of measurement of potentially relevant factors, as noted above eg. distress tolerance, impulsivity, chronic pain, and environmental factors (ie, milieu environment). We also do not have a systematic record of patients' stated reasons for premature termination from detoxification, thus missing an important subjective component from our analysis. The generalizability of our results is limited by the nature of our sample which was recruited and treated within a research service in federally-supported clinical trials, rather than community-based treatment programs. More studies are required on this topic to further support the findings from this secondary analysis and to determine whether the results from our use of statistical algorithms are consistent beyond just our specific sample. And several segments of the general opioid-misusing population, eg.

patients with severe medical or psychiatric disorders, pain requiring opioid management, and past history of overdoses, were excluded.

In summary, lower level of opioid use and older age were associated with greater likelihood of completing a rapid naltrexone induction procedure that uses buprenorphine, clonidine and other non-opioid medications to manage withdrawal symptoms. The findings focus on the importance of evaluating severity of opioid dependence when planning to induce an actively using opioid-dependent patient onto naltrexone. Patients with higher levels of opioid use may require more aggressive treatment of withdrawal and a longer delay before initiating naltrexone. The rapid naltrexone induction procedure studied here was implemented in an effort to make naltrexone induction fit within the confines of brief hospitalizations for detoxification typically covered by third party payors, which are attempting to contain costs. With the advent of the long-acting injectable formulation, naltrexone has become an increasingly viable alternative for the longterm management of opioid dependence. However, its successful implementation will require more attention to optimizing procedures for initiating naltrexone among actively using opioid-dependent patients.

Acknowledgment

Funding for this study was provided by NIDA Grant R01-15822-1 (PI: Adam Bisaga, Columbia University Medical Center, New York, NY), NIDA Grant R01 DA010746 (PI: Maria Sullivan, Columbia University Medical Center, New York, NY) and NIDA Grant K24 DA022412 (PI: Edward Nunes, Columbia University Medical Center, New York, NY). NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Dr. Nunes has received medication for research studies from Alkermes/Cephalon, Inc., Reckitt-Benckiser, and Duramed Pharmaceuticals; has received web-based behavioral intervention for research study from HealthSim, LLC; and has received from Brainsway devices under investigation and reimbursement for travel expenses for investigators' meeting. He was paid an honorarium and received reimbursement for travel expenses for attendance at a Lilly Advisory Board Meeting in January 2012 and received educational materials from Otsuka America Pharmaceutical, Inc. in 2013. He plans to serve on Advisory Board for Alkermes in October 2014. The authors alone are responsible for the content and writing of this paper.

REFERENCES

1. Nosyk B, Anglin MD, Brissette S, et al. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. Health Aff (Millwood). 2013; 32:1462–1469. [PubMed: 23918492]
2. Veilleux JC, Colvin PJ, Anderson J, et al. A review of opioid dependence treatment: Pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev. 2010; 30:155–166. [PubMed: 19926374]
3. Day E, Ison J, Strang J. Inpatient versus other settings for detoxification for opioid dependence. Cochrane Database Syst Rev. 2005; 18 CD004580.
4. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011; 68:1238–1246. [PubMed: 22065255]
5. Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: A randomized trial. JAMA. 2008; 5:2003–2011. [PubMed: 18984887]
6. Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008; 2 Art No.: CD002207.
7. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009; 3 Art No.: CD002025.

8. Preston KL, Silverman K, Umbricht A, et al. Improvement in naltrexone treatment compliance with contingency management. Drug Alcohol Depend. 1999; 54:127–135. [PubMed: 10217552]
9. Carroll KM, Sinha R, Nich C, et al. Contingency management to enhance naltrexone treatment of opioid dependence: A randomized clinical trial of reinforcement magnitude. Exp Clin Psychopharmacol. 2002; 10:54–63. [PubMed: 11866252]
10. Carroll KM, Ball SA, Nich C, et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. Arch Gen Psychiatry. 2001; 58:755–761. [PubMed: 11483141]
11. Nunes EV, Rothenberg JL, Sullivan MA, et al. Behavioral therapy to augment oral naltrexone for opioid dependence: A ceiling on effectiveness. Am J Drug Alcohol Abuse. 2006; 32:503–517. [PubMed: 17127538]
12. Silverman K, DeFulio A, Sigurdsson SO. Maintenance of reinforcement to address the chronic nature of drug addiction. Prev Med. 2012; 55:S46–S53. [PubMed: 22668883]
13. Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomized trial. Lancet. 2011; 377:1506–1513. [PubMed: 21529928]
14. Brooks AC, Comer SD, Sullivan MA, et al. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: A quasi-experiement. J Clin Psychiatry. 2010; 71:1371–1378. [PubMed: 20673549]
15. Vivitrol® [package insert]. Waltham, MA: Alkermes, Inc.; 2013.
16. Kosten TR, Morgan CH, Kleber HD. Phase II Clinical trials of buprenorphine: Detoxification and induction onto naltrexone. NIDA research monograph. 1992; 121:101–119. [PubMed: 1406906]
17. Dijkstra BA, De Jong CA, Wensing M, et al. Opioid detoxification from controlled clinical trial to clinical practice. Am J Addict. 2010; 19:283–290. [PubMed: 20525037]
18. Sigmon SC, Bisaga A, Nunes EV, et al. Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. Am J Drug Alcohol Abuse. 2012; 38:187–199. [PubMed: 22404717]
19. Collins ED, Kleber HD, Whittington RA, et al. Anesthesia- assisted, vs buprenorphine-, or clonidine-, assisted heroin, detoxification naltrexone, induction: A, randomized trial. JAMA. 2005; 294:903–913. [PubMed: 16118380]
20. Bisaga A, Sullivan MA, Cheng WY, et al. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend. 2011; 119:23–29.
21. Bisaga A, Sullivan MA, Glass A, et al. A placebo-controlled trial of memantine as an adjunct to injectable extended-release naltrexone for opioid dependence. J Subst Abuse Treat. 2014; 46:546–552. [PubMed: 24560438]
22. Sullivan, MA.; Carpenter, KM.; Elkus, Y., et al. Behavioral naltrexone therapy for heroin dependence: A randomized controlled trial. Drug and Alcohol Dependence 70; College on Problems of Drug Dependence 2008: Abstracts for the 70th Annual Scientific Meeting; June 14–19; San Juan. Puerto Rico.
23. Sullivan MA, Rothenberg JL, Vosburg SK, et al. Predictors of retention in naltrexone maintenance for opioid dependence: Analysis of a stage I trial. Am J Addict. 2006; 15:150–159. [PubMed: 16595353]
24. Carpenter KM, Jiang H, Sullivan MA, et al. Betting on change: Modeling transitional probabilities to guide therapy development for opioid dependence. Psychol Addict Behav. 2009; 23:47–55. [PubMed: 19290689]
25. Hillhouse M, Canamar CP, Ling W. Predictors of outcome after short-term stabilization with buprenorphine. J Subst Abuse Treat. 2013; 44:336–342. [PubMed: 23021099]
26. Hillhouse MP, Marinelli-Casey R, Gonzales, et al. Predicting in-treatment performance and post-treatment outcomes in methamphetamine users. Addiction. 2007; 102:84–95. [PubMed: 17493057]
27. Ekhtiari H, Dezfouli A, Zamanian B, et al. Treatment outcome predictors in flexible dose-duration methadone detoxification program. Arch Iran Med. 2013; 16:599–601. [PubMed: 24093142]

28. Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: Long-term safety and effectiveness. Addiction. 2013; 108:1628–1637. [PubMed: 23701526]
29. Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled multicenter randomized trial. Lancet. 2011; 377:1506–1513. [PubMed: 21529928]
30. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. Health Technol Assess. 2007; 11:1–171. [PubMed: 17313907]
31. Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008; 16 -CD002207.
32. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: Results from a randomized study. Int J Neuropsychopharmacol. 2008; 11:641–653. [PubMed: 18205978]
33. Sigmon SC, Dunn KE, Badger GJ, et al. Brief buprenorphine detoxification for the treatment of prescription opioid dependence: A pilot study. Addict Behav. 2009; 34:304–311. [PubMed: 19081679]
34. Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. JAMA Psychiatry. 2013; 70:1347–1354. [PubMed: 24153411]
35. Dreifuss JA, Griffin ML, Frost K, et al. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. Drug Alcohol Depend. 2013; 131:112–118. [PubMed: 23333292]
36. Agosti V, Nunes EV, Ocepeck-Welikson K. Patient factors related to early attrition from an outpatient cocaine research clinic. Am J Drug Alcohol Abuse. 1996; 22:29–39. [PubMed: 8651143]
37. Mysels DJ, Cheng WY, Nunes EV, et al. The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. Am J Drug Alcohol Abuse. 2011; 37:22–26. [PubMed: 21192125]

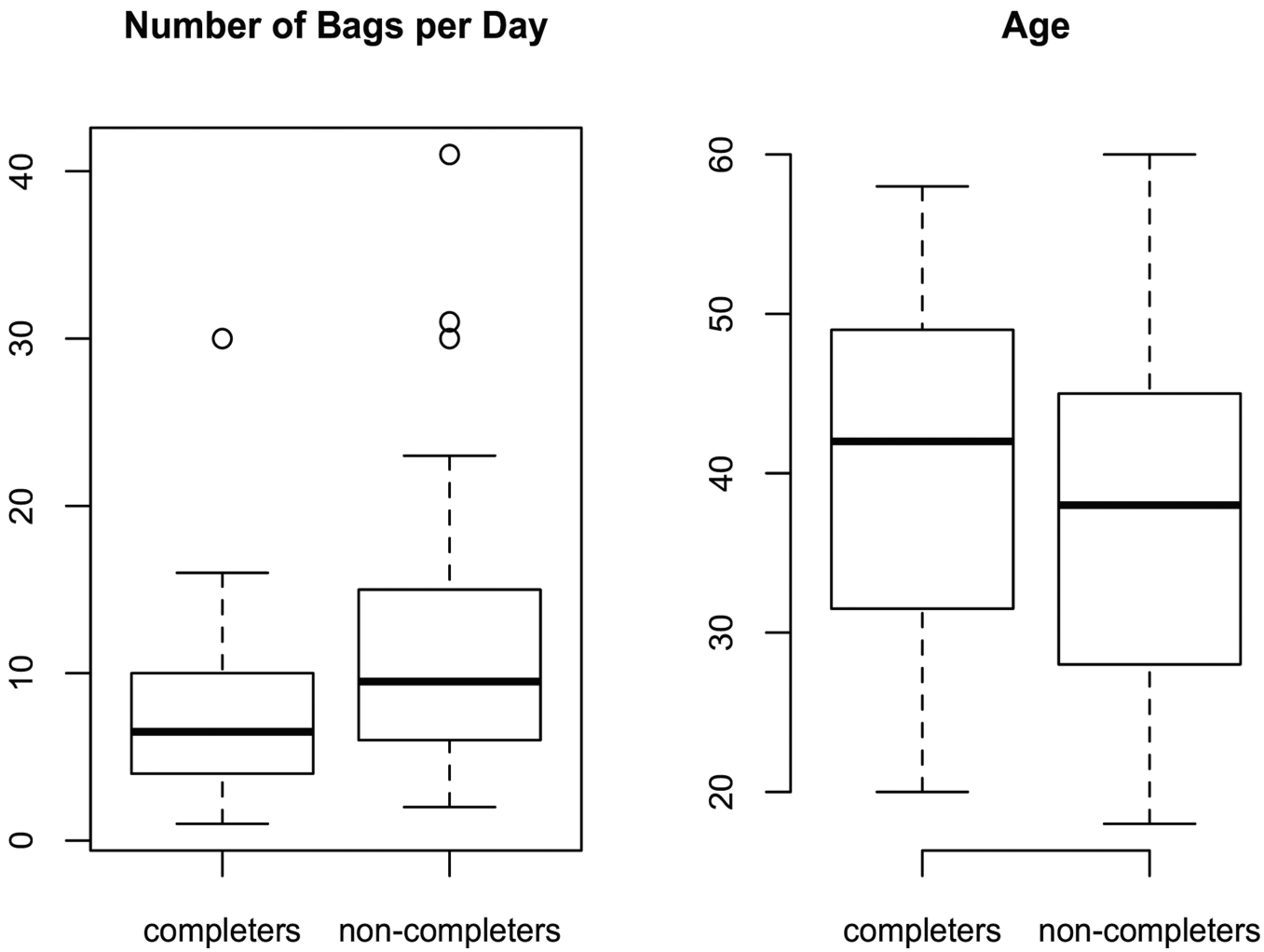

FIGURE 1.

A comparison of the distribution of bags/bag-equivalents of heroin used per day and age (years) between opioid- dependent patients who completed (N = 84), and those who failed to complete (N = 66), an inpatient rapid naltexone induction procedure.

TABLE 1

Protocol guideline for rapid naltrexone induction used in a clinical research unit at the New York State Psychiatric Institute (New York City) for antagonist treatment of opioid-dependence following controlled detoxification

	Day 1, Admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7, discharge
Buprenorphine	—	4 mg BID	—	—	—	—	—
Naltrexone	—	—	—	3 mg	6 mg	25 mg	50 mg PO OR 380 mg IM
Supportive medications	Beginning Day 1, and continuing throughout: Clonidine 0.1–0.2 mg QID, Clonazepam 0.5–1 mg QID, Ibuprofen, Ranitidine, Zolpidem and/or Trazodone at bedtime for sleep						

TABLE 2

Comparison of baseline demographic, clinical and psychosocial characteristics between opioid-dependent patients who completed (*N* = 84), and those who failed to complete (*N* = 66), an inpatient rapid naltrexone induction procedure

Independent Variable	Completers (n = 84)	Noncompleters (n = 66)	
Demographic	**Mean (SD) or n, (%)**	**Mean (SD) or n (%)**	***p*-value**
Age (years)	40.6, (10.4)	36.5, (10.8)	.018
Age at first use (years)	25.6, (8.5)	23.8, (7.2)	.179
Gender (male)	68, (81)	49, (74)	.325
Race (Caucasian)	47, (56)	41, (62)	.483
Psychosocial			
Current significant other	40, (48)	38, (58)	.226
Family history of substance abuse (1 degree)	46, (55)	38, (58)	.742
Level of education			.158
<12 y	17, (20)	22, (33)	
12 y	19, (23)	15, (23)	
>12 y	48, (57)	29, (44)	
Current employment (%)*	43, (51)	29, (45)	.426
Legal history (% affirmative)	38, (46)	39, (59)	.106
Substance use			
Years of regular opioid use	15.0, (11.8)	12.7, (10.3)	.214
Route of use**			.614
PO route	15, (18)	9, (14)	
IV route	28, (34)	27, (41)	
IN route	39, (48)	30, (46)	
Type of opioid***			0.61
Heroin	65, (80)	56, (85)	
Rx opioids	16, (20)	10, (15)	
Bags of heroin use per day	6.9, (4.2)	11.1, (7.8)	<.001
Mean longest period of abstinence (months)	24.4, (58.4)	20, (32.7)	.584
Current substance use			
Opioid only	32, (38)	14, (21)	.026
Marijuana	6, (07)	13, (20)	.022
Alcohol	3, (04)	1, (2)	.631*****
Cocaine/stimulant	9, (11)	6, (9)	.742
Sedative	2, (2)	0, (0)	.504*****
Nicotine	44, (52)	43, (65)	.116
Prior treatment experience			
Prior Detoxification	51, (61)	39, (59)	.840
Outpatient	32, (38)	19, (29)	.232
Opioid agonist maintenance	30, (36)	24, (36)	.978

Independent Variable	**Completers (n = 84)**	**Noncompleters (n = 66)**	
Demographic	**Mean (SD) or n, (%)**	**Mean (SD) or n (%)**	***p*-value**
Therapeutic community	9, (11)	10, (15)	.417
Rehabilitation center	19, (23)	23, (35)	.098
AA/NA	13, (16)	11, (17)	.844
Psychiatric			
Comorbid mood d/o (%)	29, (35)	21, (32)	.727
Comorbid anxiety d/o (%)	15, (18)	15, (23)	.459
Hamilton-D (21) score****	10.3, (6.7)	10.6, (6.1)	.871

* Due to missing data point, *n* = 84 (completers), *n* = 65 (noncompleters);;

** Due to missing data point, *n* = 82 (completers), *n* = 66 (noncompleters);;

*** Due to missing data point and two users who used both kinds of opioids, *n* = 81 (completers), *n* = 66 (noncompleters);;

**** Due to missing data point, *n* =81 (completers), *n* =63 (noncompleters);;

***** Due to missing data point, *n* = 81 (completers), *n* = 63 (noncompleters);;

TABLE 3

Logistic regression model assessing impact of age and degree of opioid dependence, as indicated by mean self-reported bag-equivalents used daily, on completion status in the detoxification-rapid naltrexone induction phase of two clinical trials studying the effectiveness of naltrexone as a treatment for opioid dependence

Variable	β	Wald's c^2	df	*p*	AOR (CI)
Intercept	− 0.0614	0.0072	1	0.9323	
Age	0.0366	4.7702	1	0.0290	1.037 (1.004, 1.072)
Number of Bags	− 0.1283	12.3752	1	0.0004	0.880 (0.819, 0.945)