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Am J Addict. Author manuscript; available in PMC 2011 March 1.

Published in final edited form as:
Am J Addict. 2010 ; 19(2): 141–146. doi:10.1111/j.1521-0391.2009.00017.x.

Conducting Clinical Research with Prescription Opioid Dependence: Defining the Population

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Abstract

Most treatment studies of opioid-dependent populations have focused predominantly on heroin users, despite a recent increase in those dependent upon prescription opioids. A key methodological challenge involved in studying the latter group involves defining the population. Specifically, researchers must decide whether to include 1) concurrent heroin users and 2) individuals with pain. The multi-site Prescription Opioid Addiction Treatment Study is examining treatments for this population. This paper describes various inclusion criteria considered by the study team related to heroin use and pain. The goal was to recruit a distinct but generalizable population of individuals dependent upon prescription opioids.

Introduction

Prescription opioid misuse has recently become a highly prevalent problem in the United States. In 2007, there were 2.5 million new users of prescription medications for non-medical purposes among individuals aged 12 years or older in the United States; 2.15 million people were new users of prescription opioid drugs.1 Among users of all illicit substances, this group represented the largest number of past-year initiates in 2007.

With the increased prevalence of prescription opioid misuse, studying treatments for those who develop dependence on prescription opioids is critical. Most treatment studies of opioid-dependent populations have heretofore focused either exclusively or predominantly on heroin users.2–5 However, some evidence suggests that traditional treatments for opioid dependence may result in differential outcomes for persons dependent upon heroin versus prescription opioids.6,7 Therefore, studying treatment outcomes in a population of exclusively prescription opioid-dependent individuals is necessary to determine whether specific treatment strategies should be tailored for this population.

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Declaration of Interest

Dr. Weiss has received research support from Eli Lilly & Company and has consulted to Titan Pharmaceuticals. Dr. Potter has received research support from Forest Laboratories and has consulted to Observant LLC. Dr. Ling has served as a consultant to and has received research support from Reckitt Benckiser; he also received an unrestricted grant from Hythiam, Inc., and is on the Scientific Advisory Board of US WorldMeds.

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To this end, the multi-site Prescription Opioid Addiction Treatment Study (POATS) is currently being conducted under the auspices of the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN); the CTN, a partnership between academic research centers and community drug abuse treatment programs, conducts multi-site clinical trials with drug-dependent patients in community treatment programs. POATS was launched in 2006 in response to the epidemiologic trends described above; this study is comparing the efficacy of different durations and intensities of combinations of buprenorphine/naloxone and drug counseling in the treatment of patients with prescription opioid dependence.

In designing this study, one of the key methodological issues that we faced involved defining our study population. When doing so, two specific populations presented the greatest challenge when determining eligibility criteria: 1) those who had used heroin, and 2) individuals with pain. In both instances, a goal was to identify a distinct but generalizable population of treatment-seeking individuals who were dependent upon prescription opioid drugs. We sought to distinguish our population from those who had participated in previous studies (i.e., those who had primarily used heroin). However, because some individuals who are dependent upon prescription opioids have also used heroin,8 we did not want to be so strict in our exclusion criteria regarding heroin use as to end up recruiting a study population that was unrepresentative of patients seeking treatment for prescription opioid dependence in clinical settings. We also recognized that patients who had been prescribed opioids for pain and had become dependent on them could differ substantially from individuals without pain who used prescription opioids illicitly.9 In deciding which of these potential participants to include in our study, then, our goal was to identify a population that was 1) distinct, 2) generalizable to the general population of those dependent on prescription opioid drugs (thus making our results applicable to patients seeking treatment outside of research settings and allowing us to recruit an adequate number of participants to conduct our study successfully), and 3) heterogeneous enough to determine whether different subtypes would respond to treatment differentially. Because other studies of individuals dependent upon prescription opioids will be conducted, this manuscript will review the various methodological issues we faced in defining our population. We will review our decisions and discuss the results of those decisions in relation to 1) our ability to recruit an adequate participant population, and 2) the types of potential participants that we excluded.

Methods

Study Overview

POATS is a study taking place at 10 treatment programs around the country as part of the NIDA Clinical Trials Network. The primary objective of the study is to determine whether the addition of individual drug counseling to the prescription of buprenorphine/naloxone (along with standard medical management) improves outcomes for participants dependent on prescription opioid drugs during 1) an initial 4-week taper, and 2) a subsequent 12-week stabilization treatment for those who did not respond successfully to the initial taper. This two-phase outpatient study utilizes an adaptive treatment design. In the first phase of the study, participants are inducted onto sublingual buprenorphine/naloxone, are stabilized on this medication at a dose up to 32 mg for two weeks, and are then tapered off of buprenorphine/naloxone over the next two weeks; during this period, they are randomly assigned to Standard Medical Management or Enhanced Medical Management. Standard Medical Management is a manualized intervention consisting of relatively brief (i.e., 15–20 minutes) medically focused visits that combine buprenorphine management with brief counseling methods to help participants abstain from opioid use; the version used in POATS is a slightly modified version of a previous manual.10 Enhanced Medical Management consists of Standard Medical Management plus additional individual drug counseling twice a week; the drug counseling also employs a manualized approach that has been modified for

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POATS from a previous treatment manual.11 Study participants who remain abstinent or nearly abstinent (according to pre-specified criteria) during this 4-week period and the subsequent 8 weeks are deemed "Phase 1 successes," and receive no further study treatment. Those who relapse to opioids during this first phase may be eligible to enter the second phase of the study, consisting of 12 weeks of buprenorphine stabilization, followed by a 4-week taper and 8 additional weeks of follow-up. As in Phase 1, individuals who enter Phase 2 are randomly assigned to weekly Standard Medical Management or Enhanced Medical Management, which consists of an additional twice-weekly individual drug counseling for 6 weeks and weekly drug counseling for the next 6 weeks. The study has recently completed randomization of its target of 653 Phase 1 participants. General inclusion and exclusion criteria are listed in Table 1; specific criteria regarding heroin use and pain are discussed below.

Methodological Considerations: Heroin Use

Many individuals who are dependent on prescription opioids also use heroin concurrently, or have used heroin in the past.12,13 In defining the population for POATS, we considered several options regarding the inclusion of individuals who had used heroin. The decision about the inclusion of heroin users reflected an attempt to balance the benefits of studying a real-world sample (which would permit inclusion of heroin users) with our desire to examine a new population of individuals with primary prescription opioid dependence. We therefore decided that we wanted to study a distinct population, but did not want to completely eliminate those who had ever used heroin, particularly since CTN community treatment programs reported that many patients who presented for treatment of prescription opioid dependence had histories of past heroin use. Indeed, we wanted to include some people who had used heroin in order to determine whether even a minimal history of heroin use affected treatment outcomes in patients dependent on prescription opioid drugs.

With respect to the inclusion of persons having any history of heroin use, the advantages and drawbacks of several design options were considered, including the following extremes: 1) enroll all individuals who had used heroin, regardless of amount, or 2) exclude anyone who had ever used heroin. While inclusion of persons irrespective of their heroin use histories might produce the most generalizable findings, this option would not allow us to study a distinct population of individuals with prescription opioid dependence. Conversely, exclusion of anyone with a lifetime history of any heroin use would yield the purest, most distinct population of individuals dependent upon prescription opioids. However, the population would likely not be generalizable, and we would be unable to determine the degree to which a history of any heroin use affected treatment outcome in this population. To balance these competing considerations, we established the following heroin-related criteria: we excluded anyone who 1) used heroin on 5 or more days in the month prior to intake (to eliminate those without a clear predominance of prescription opioid use), 2) had ever met lifetime diagnostic criteria for opioid dependence attributable to heroin use alone (for the same reason as above), or 3) had ever injected heroin (since their course of addiction appears to develop along a trajectory that differs from non-injectors14,15). Because we believed that a history of heroin use could have prognostic relevance, we decided to stratify our study population according to whether the participant had ever used heroin.

Methodological Considerations: Pain

In addition to the options regarding the eligibility of heroin users, we considered several options regarding potential participants with pain. Many patients with prescription opioid dependence have been prescribed opioids for pain; others may seek to self-medicate their pain with illicitly-obtained opioids, and others initiate and become dependent upon

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prescription opioids for reasons unrelated to the treatment of pain. Moreover, those with pain may have been taking opioids for several weeks or many years.

With respect to inclusion of patients experiencing pain, we again strived to achieve a balance between the desire for a representative sample and a distinct population. To be most inclusive, we could have included participants regardless of pain status. More distinct populations could have included only people with pain or without pain. However, because pain is common but by no means universal among patients with prescription opioid dependence, this would have severely restricted the population in either direction. Safety issues were also a factor in our design considerations, as pain is a signal of a potential medical problem that may require attention before including an individual in a clinical trial. We therefore decided to exclude only participants with 1) a traumatic or major pain event within the past 6 months (to distinguish between acute pain and chronic pain), or 2) pain of sufficient severity to require ongoing future pain management with opioids; participants who were currently receiving prescription opioids for pain had to receive clearance from their prescribing physician to enter the trial and thus discontinue their use of opioid analgesics. We also excluded persons who were physically dependent upon opioids solely as a consequence of taking opioids as prescribed by their physician, since these individuals would not meet DSM-IV criteria for opioid dependence. Otherwise, we accepted individuals with or without chronic pain, which we defined with the Brief Pain Inventory as pain “other than everyday kinds of pain” for at least 3 months.16 Because we did not know what the potential impact of chronic pain would be on treatment outcome, we stratified participants according to the presence or absence of current chronic pain (as defined above) at intake.

Screening and Eligibility Procedures

Participants were screened initially using a telephone screening instrument. All potential participants provided verbal consent to be screened in this manner. The screening instrument provided basic indicators of potential eligibility, such as experiencing a traumatic or major pain event in the past 6 months and having a history of heroin injection. Based on their responses, individuals who appeared potentially eligible were invited to attend a face-to-face interview, at which they signed written informed consent after study procedures were explained to them. They then completed the baseline assessment. All study procedures were reviewed and approved by the study site Institutional Reviews Boards and were monitored by an independent Data and Safety Monitoring Board, chosen by NIDA personnel.

Results

Overall Recruitment

A total of 3691 individuals were screened by telephone for the study, of whom 1651 (44.7%) were deemed eligible for an in-person screening; 2040 participants (55.3%) were ineligible. A total of 867 participants came for an in-person screening visit; 214 (24.7%) were ineligible and 653 (75.3%) were randomized. We were able to reach our recruitment target within the study timeline; we initially projected that each site would randomize an average of 3 participants per month. Of the 10 sites that participated in the study, 9 met at least 90 percent of their total randomization target, and 6 exceeded their target.

Reasons for Ineligibility

Heroin—Among those screened by telephone, heroin-related criteria were the most common reasons for exclusion. A history of heroin injection (n=785, 38.5% of those excluded) was by far the most common exclusion criterion, followed by use of heroin on >4 of the past 30 days (n=254, 12.5%), current maintenance treatment with either methadone

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(n=182, 8.9%) or buprenorphine (n=110, 5.4%), or use of opioids for <20 of the last 30 days.

Reasons for heroin-related ineligibility among those undergoing in-person screening included 1) current use of heroin for ≥ 5 days in the previous month (n = 18, 2.1% of those undergoing in-person screening), 2) a lifetime history of opioid dependence attributable to heroin use alone (n = 17, 2.0%), and 3) a history of heroin injection (n = 16, 1.8%). Among the final enrolled study population, 150 of the 653 study participants (23.0%) had a history of heroin use.

Pain—Eighty-six participants (4.2%) were excluded on the telephone because of a traumatic or major pain event in the past 6 months. Pain-related reasons for ineligibility from the in-person screening interview were 1) lack of clearance from the participant's treating physician to enter the trial (n = 22, 2.5%), 2) requirement for ongoing pain management with opioids (n = 10, 1.2 %), and 3) occurrence of a major pain event within the previous 6 months (n = 2, 0.2%). A total of 274 of the 653 randomized participants (42.0%) had current chronic pain at intake.

Discussion

Individuals with prescription opioid dependence represent a heterogeneous population; potentially important subgroups are characterized by their experiences with pain and their histories of heroin use. The results of this study suggest that it is feasible to identify a distinct but generalizable subpopulation of treatment-seeking individuals with prescription opioid dependence for clinical research that includes some level of heterogeneity in these two dimensions. Further, significant numbers of these individuals who want treatment can be recruited readily from multiple sites for a large-scale clinical trial.

Approximately half of those who were screened over the telephone were excluded because of heavy heroin use or a history of heroin injection. However, despite our decision to accept those who had used heroin occasionally, 80% of our enrolled study participants had no history of heroin use. In light of the high proportion of participants who had never used heroin, we would have still successfully recruited a large number of study participants even if we had chosen to exclude people with any history of heroin use. Although this would have resulted in a purer sample of individuals with prescription opioid dependence, the sample would have been less generalizable to the broader population of individuals seeking treatment for prescription opioid dependence.

Over 40% of the study participants had current chronic pain. This is consistent with other studies that have similarly shown a high prevalence rate of chronic pain in this population. For example, in a multi-state survey of 5663 opioid dependent persons enrolling in 72 methadone maintenance treatment programs, 52% of primary prescription opioid abusers reported a lifetime history of chronic pain.17 In a retrospective chart review of 75 patients receiving methadone maintenance treatment, 45% of primary prescription opioid users reported a history of at least one pain episode.18

Generalizability of the present findings to the broader population of individuals with primary prescription opioid dependence is strengthened by our large sample size and the high level of regional diversity and population heterogeneity afforded by including 10 community-based clinics nationwide. Our study has some limitations, however. While 22 patients were excluded from the study due to lack of clearance from their treating physician, we did not specify the reasons for lack of clearance; in some instances, it is possible that the treating physician simply did not return the telephone call from the study staff. Although it

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would have been informative to know more about the specific circumstances surrounding these cases, the number of exclusions for this reason was relatively small (2.5% of the participants who had an in-person assessment), and the primary purpose of requiring clearance from the treating physician as an inclusion criterion was to ensure the participants' safety. An additional limitation of the study is the reliance on self-report for assessment of heroin-related exclusion criteria, which may have resulted in misreporting of heroin use. The same can be said for pain-related eligibility criteria. However, in the absence of other reliable indicators, self-report is considered the standard for assessing pain.19

In sum, the methods used in the present study have demonstrated face validity, and may be replicated in future studies seeking a distinct but generalizable subset of persons dependent upon prescription opioids. This would aid in cross-study comparisons of outcomes. Accounting for the unique characteristics of this growing population in the design of clinical research studies may help in developing successful evidence-based treatment approaches for these patients.

Acknowledgments

Supported by Grants U10 DA15831 (Dr. Weiss), K24 DA022288 (Dr. Weiss), K23 DA022297 (Dr. Potter), U10 DA13035 (Dr. Selzer), U10 DA013045 (Dr. Ling), and T32 DA07272 (Dr. Chim) from the National Institute on Drug Abuse, Bethesda, Md.

We thank the staff and participants at the community treatment programs and regional research and training centers of the National Institute on Drug Abuse Clinical Trials Network for their involvement in this project, including Chestnut Ridge Hospital (Appalachian Tri-State Node), San Francisco General Hospital (California/Arizona Node), St. Luke's Roosevelt Hospital and Long Island Jewish Medical Center-Addiction Recovery Services (Long Island Node), Bellevue Hospital Center (New York Node), McLean Hospital (Northern New England Node), East Indiana Treatment Center (Ohio Valley Node), Adapt, Inc. (Oregon/Hawaii Node), Integrated Substance Abuse Programs (Pacific Node), Behavioral Health Service of Pickens County (Southern Consortium Node), and Providence Behavioral Health Services (Washington Node). We also thank the staff of the Clinical Coordinating Center (The EMMES Corporation, Rockville, MD) and the Data and Statistics Center (The Duke Clinical Research Institute, Durham, NC), and the staff of the Center for the Clinical Trials Network at the National Institute on Drug Abuse (Rockville, MD) for their work on this project.

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Table 1

Prescription Opioid Addiction Treatment Study: General Eligibility Criteria

	Eligibility Criteria
Inclusion Criteria	
1	Ability to read, understand, and provide written informed consent
2	Age ≥ 18
3	If female and of childbearing potential, agrees to use an acceptable method of birth control throughout study
4	Ability to meet study requirements (i.e., can attend weekly visits, able to take medications, etc.)
5	Meets DSM-IV criteria for current opioid dependence
6	Current physical dependence on opioids (using prescription opioids ≥20 days/month) and need for medical assistance for opioid withdrawal
7	Good general health or, if requires ongoing medical/psychiatric treatment (whether currently in such treatment or not), participant is under the care of a physician willing to continue participant's medical management and to cooperate with study site investigators
8	Non-psychotic and psychiatrically stable in the opinion of the study investigator
9	Willingness to provide locator information
10	Prior to induction, participant is in opioid withdrawal (COWS scale > 8), or alternatively, participant's dose of methadone (if receiving it for pain; those receiving methadone treatment for opioid dependence are excluded) is ≤40 mg
Exclusion criteria	
1	A medical condition that would make participation medically hazardous
2	A known allergy or sensitivity to buprenorphine or naloxone
3	An acute severe psychiatric condition or is psychosis
4	Participant has been a suicide risk within the past 30 days
5	Dependence on alcohol, sedative-hypnotics or stimulants, and requiring immediate medical attention
6	Participation in another investigational drug study within the last 30 days
7	Participation in methadone or buprenorphine maintenance treatment for opioid dependence within 30 days of study enrollment
8	A current or pending legal status that would make the participant unlikely to remain in the local area for the duration of the study
9	If female, participant is pregnant, lactating, or unwilling to follow study required measures for pregnancy prevention
10	Inability to remain in the local area for the duration of the study
11	Liver function tests > 5 times the upper limit of normal
12	Surgery scheduled within the next 6 months that would preclude participation during the active treatment phase of the study
13	Current participation in formal substance abuse treatment