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Review

The Prescription Opioid Addiction Treatment Study: What have we learned

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ABSTRACT

Background: The multi-site Prescription Opioid Addiction Treatment Study (POATS), conducted by the National Drug Abuse Treatment Clinical Trials Network, was the largest clinical trial yet conducted with patients dependent upon prescription opioids (N = 653). In addition to main trial results, the study yielded numerous secondary analyses, and included a 3.5-year follow-up study, the first of its kind with this population. This paper reviews key findings from POATS and its follow-up study.
Methods: The paper summarizes the POATS design, main outcomes, predictors of outcome, subgroup analyses, the predictive power of early treatment response, and the long-term follow-up study.
Results: POATS examined combinations of buprenorphine-naloxone of varying duration and counseling of varying intensity. The primary outcome analysis showed no overall benefit to adding drug counseling to buprenorphine-naloxone and weekly medical management. Only 7% of patients achieved a successful outcome (abstinence or near-abstinence from opioids) during a 4-week taper and 8-week follow-up; by comparison, 49% of patients achieved success while subsequently stabilized on buprenorphine-naloxone. Long-term follow-up results were more encouraging, with higher abstinence rates than in the main trial. Patients receiving opioid agonist treatment at the time of follow-up were more likely to have better outcomes, though a sizeable number of patients succeeded without agonist treatment. Some patients initiated risky use patterns, including heroin use and drug injection. A limitation of the long-term follow-up study was the low follow-up rate.
Conclusions: POATS was the first large-scale study of the treatment of prescription opioid dependence; its findings can influence both treatment guidelines and future studies.

1. Introduction

Non-medical prescription opioid use has emerged as a major public health challenge over the past two decades. In 2014, 4.3 million Americans used prescription opioids for non-medical reasons, making prescription opioids the second most used illicit drug (Center for Behavioral Health Statistics and Quality, 2015). On average, more than 1000 patients per day visited an emergency department because of non-medical use of prescription opioids in 2011 (Crane, 2015). Moreover, overdose deaths from prescription opioids climbed steadily throughout the end of the last decade. Although they declined slightly in 2012, they increased again by 9% in 2014, comprising the majority of all opioid-related deaths (Rudd et al., 2016). Treatment of prescription opioid use disorders has become extremely common; in 2013, 746,000 patients received treatment for prescription opioid use disorders in inpatient locations or mental health centers (Substance Abuse and Mental Health Services Administration, 2014), and 24% of patients who were started on pharmacotherapy for opioid use disorders primarily used prescription opioids.

Since its approval in 2002, buprenorphine-naloxone (bup-nx) has become a mainstay of pharmacotherapy for opioid use disorders. However, because the approval of bup-nx derived from

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large-scale clinical trials conducted predominantly in heroin users (Fudala et al., 2003; Ling et al., 1998), it was unclear the degree to which its use in those dependent upon prescription opioids would yield similar outcomes. Indeed, evidence suggests that prescription opioid users differ in important ways from those who use heroin. Prescription opioid users, on average, use less total opioid per day, have fewer co-occurring substance use disorders, have better family and social functioning, shorter treatment histories, are less likely to administer by injection, and experience fewer legal consequences (Moore et al., 2007; Rosenblum et al., 2007). Overall, prescription opioid users have better treatment outcomes than those who use heroin (Nielsen et al., 2013; Potter et al., 2013). It has even been suggested that the favorable characteristics of prescription opioid users may mean that these patients might not require the same treatments as do heroin users, with some researchers questioning the necessity of long-term agonist therapy for this population (Sigmon, 2006). Empirical evidence can best validate our treatments for prescription opioid use disorder.

One factor that may play an important role in the successful treatment of prescription opioid use disorders is drug counseling. One study of heroin users in methadone maintenance treatment programs showed that adding drug counseling increases opioid-negative urine-screens (McLellan et al., 1993). However, other studies have not found meaningful differences when drug counseling is added (Senay et al., 1973; Gruber et al., 2008; Schwartz et al., 2011). It is unclear, however, the degree to which we can generalize from studies of heroin users receiving methadone maintenance treatment to prescription opioid users receiving office-based bup-nx. Prior to the study we will describe below, only one study, with a modest population size, had examined the role of counseling in patients receiving office-based bup-nx, finding no benefit from more intensive counseling over standard medical management (Fiellin et al., 2006). However, no study had looked specifically at the role of counseling in prescription opioid users.

Given the lack of guidance on pharmacologic and psychosocial treatments for prescription opioid dependence, the National Drug Abuse Treatment Clinical Trials Network sponsored the Prescription Opioid Addiction Treatment Study (POATS) to address these issues (Weiss et al., 2011). The Clinical Trials Network, under the auspices of the National Institute on Drug Abuse, is a partnership between addiction researchers, community treatment program directors, and the National Institute on Drug Abuse itself to design and conduct multi-site clinical trials in community substance use disorder treatment programs and general medical settings.

This article will discuss the design and findings of the POATS trial, including a 3.5-year follow-up study, and will comment on some of its implications and current perspectives. POATS was intended *a priori* to answer the following questions: (1) Does adding opioid drug counseling to buprenorphine-naloxone plus medical management improve opioid use outcomes? (2) How many patients dependent upon prescription opioids can achieve successful opioid use outcomes with a brief taper of bup-nx, as opposed to bup-nx stabilization? (3) Which patient characteristics predict successful outcomes? (4) Which patient characteristics predict successful response to counseling? Questions later raised included: (1) Can initial response to treatment predict outcomes at the end of treatment? and (2) What are the long-term (up to 42 months) outcomes of study participants?

2. Methods

2.1. POATS design considerations

Designing POATS presented several challenges. The investigators had to weigh the relative importance of studying a new population (those dependent upon prescription opioids rather than heroin) vs. choosing a population that was generalizable to treatment-seeking patients (many of whom have experimented with heroin). To resolve this, study investigators included those who had used heroin unless they (1) had ever injected heroin, (2) had ever met criteria for opioid dependence based on heroin use alone, or (3) had used heroin on >4 days in the month before study entry (Weiss et al., 2010).

The other design issue relevant to this population was related to chronic pain, which is common in these patients (Barry et al., 2009; Potter et al., 2008; Rosenblum et al., 2003). The investigators chose to include those with chronic non-cancer pain if they had not experienced a major pain event in the previous 6 months. Moreover, for those being prescribed opioids for pain, the prescriber had to agree that it was safe and medically appropriate for the patient to stop opioid use.

2.2. Overall study design

POATS employed a two-phase adaptive treatment research design, which is intended to approximate clinical practice by beginning with a non-intensive treatment approach and utilizing a more intensive treatment strategy for patients who fail to respond to the initial treatment. In this study, Phase 1 consisted of a 4-week bup-nx taper, with participants randomized to receive either standard medical management (SMM) alone or SMM plus individual opioid drug counseling (ODC). Patients who were successful in this first phase, i.e., they were abstinent or nearly abstinent from opioids during both the taper and an 8-week follow-up period, were deemed to have successfully finished the study. Those who returned to opioid use during Phase 1 were offered the second phase, consisting of 12 weeks of bup-nx stabilization followed by a 4-week taper and 8 weeks of follow-up; again, participants were randomized to receive either SMM alone or SMM + ODC. The statistical analysis included the intention-to-treat population (i.e., all randomized participants) to compare outcomes between the two counseling conditions; generalized estimating equation models were employed to account for the potential correlation of outcomes among participants at each of the 10 study sites. To be considered to have had an abstinent week, a participant had to self-report no opioid use and have an opioid-negative urine test; a missing urine sample was considered positive for opioids. Planned secondary analyses included examination of the role of pain and heroin use; predictors of outcome; and predictors of response to counseling. The study was powered for the main outcome, not the secondary analyses. A long-term follow-up study (see below for details) was proposed and approved during the main trial.

2.3. Study population

The POATS population consisted of 653 participants age >18, at 10 U.S. sites. Participants were 60% male, 91% Caucasian, half never-married, and 63% employed full-time; mean age was 33. Participants were near-daily users of opioid analgesics, but had relatively little other substance use; cannabis was the most frequently used non-opioid, with an average of 5 days a month. Interestingly, two-thirds of the population had never sought opioid use disorder treatment before. Twenty-three per cent of patients had a lifetime history of heroin use, and 42% reported current chronic pain at study entry, defined by self-report as pain (excluding pain from withdrawal) beyond everyday kinds of pain, for >3 months.