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Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study☆

Roger D. Weiss[a,b,*], Jennifer Sharpe Potter[a,b,c], Margaret L. Griffin[a,b], Scott E. Provost[a], Garrett M. Fitzmaurice[a,b,d], Katherine A. McDermott[a], Emily N. Srisarajivakul[a], Dorian R. Dodd[a], Jessica A. Dreifuss[a,b], R. Kathryn McHugh[a,b], Kathleen M. Carroll[e]

[a] McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
[b] Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
[c] University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
[d] Department of Biostatistics, Harvard School of Public Health, 677 Huntington Street, Boston, MA 02115, USA
[e] Department of Psychiatry, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

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ABSTRACT

Background: Despite the growing prevalence of prescription opioid dependence, longitudinal studies have not examined long-term treatment response. The current study examined outcomes over 42 months in the Prescription Opioid Addiction Treatment Study (POATS).
Methods: POATS was a multi-site clinical trial lasting up to 9 months, examining different durations of buprenorphine-naloxone plus standard medical management for prescription opioid dependence, with participants randomized to receive or not receive additional opioid drug counseling. A subset of participants ($N = 375$ of 653) enrolled in a follow-up study. Telephone interviews were administered approximately 18, 30, and 42 months after main-trial enrollment. Comparison of baseline characteristics by follow-up participation suggested few differences.
Results: At Month 42, much improvement was seen: 31.7% were abstinent from opioids and not on agonist therapy; 29.4% were receiving opioid agonist therapy, but met no symptom criteria for current opioid dependence; 7.5% were using illicit opioids while on agonist therapy; and the remaining 31.4% were using opioids without agonist therapy. Participants reporting a lifetime history of heroin use at baseline were more likely to meet DSM-IV criteria for opioid dependence at Month 42 (OR = 4.56, 95% CI = 1.29–16.04, $p < .05$). Engagement in agonist therapy was associated with a greater likelihood of illicit-opioid abstinence. Eight percent ($n = 27/338$) used heroin for the first time during follow-up; 10.1% reported first-time injection heroin use.
Conclusions: Long-term outcomes for those dependent on prescription opioids demonstrated clear improvement from baseline. However, a subset exhibited a worsening course, by initiating heroin use and/or injection opioid use.

1. Introduction

Despite the high rate of prescription opioid abuse and dependence in the U.S. (Substance Abuse and Mental Health Services Administration, 2012), little research has been published on the treatment of patients dependent upon prescription opioids. Moreover, no follow-up studies to date have examined long-term response to treatment and course of illness in this population. Virtually all studies of the long-term course of opioid dependence examine heroin users (Darke et al., 2007; Flynn et al., 2003; Grella and Lovinger, 2011; Hser et al., 2001; Vaillant, 1973). However, as emerging data suggest that outcomes for those dependent upon prescription opioids may differ from those using heroin (Moore et al., 2007; Nielsen et al., 2013; Potter et al., 2010), we cannot assume that results from longer-term studies of heroin dependence apply to those abusing prescription opioids.

Longitudinal follow-up of substance-dependent patients generates important information regarding treatment response and

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* Corresponding author at: Harvard Medical School, Division of Alcohol and Drug Abuse, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.
Tel.: +1 617 855 2242; fax: +1 617 855 2699.
E-mail address: rweiss@mclean.harvard.edu (R.D. Weiss).

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course of illness. In particular, studies have shown that longer-term outcomes and predictors of outcome (Brecht and Herbeck, 2014; Grella et al., 2003; Project MATCH research group, 1998) at 3–5 years can differ from those found at shorter-term follow-up. This is consistent with viewing substance use disorder as a chronic disease with a course that spans years rather than a single episode (McLellan et al., 2000).

The Prescription Opioid Addiction Treatment Study (POATS), conducted by the National Drug Abuse Treatment Clinical Trials Network, is, to date, the only large randomized controlled study examining the treatment of patients dependent upon prescription opioids with a history of minimal or no heroin use (Weiss et al., 2011). POATS compared different combinations of buprenorphine-naloxone (bup-nx) and counseling in this population. As the first large-scale controlled trial for prescription opioid dependence, POATS presented a unique opportunity to follow this patient population beyond the treatment period. Therefore, during the main trial, we decided to extend the assessment period to follow POATS participants 18, 30, and 42 months after randomization in the main trial. We previously reported results from the 18-month follow-up (Potter et al., 2014); the current paper extends this work to present results from the entire 42-month POATS follow-up study. The aim of this exploratory study was to examine the course of opioid use and related outcomes post-treatment and their relationship to baseline characteristics, treatment response in the main POATS trial, and current treatment.

2. Methods

2.1. Description of the main POATS trial and outcomes

POATS was conducted from 2006 to 2009 at 10 sites from the National Drug Abuse Treatment Clinical Trials Network (Weiss et al., 2011). Briefly, individuals age ≥18 who met DSM-IV (American Psychiatric Association, 1994) criteria for current opioid dependence (i.e., not physical dependence alone) were eligible unless they used heroin on >4 of the past 30 days, had a lifetime opioid dependence diagnosis due to heroin alone, had ever injected heroin, required opioids for ongoing pain management, were psychiatrically unstable, required urgent medical treatment for other substance dependence, had liver function tests >5 times normal, or were pregnant or nursing.

Using a two-phase, adaptive treatment design, participants were randomized in each phase to either standard medical management (SMM) or SMM plus individual opioid drug counseling (ODC), to investigate whether adding counseling to bup-nx and SMM led to better opioid use outcomes. Originally, SMM was designed to approximate office-based opioid dependence treatment in primary care (Fiellin et al., 1999). SMM consisted of brief visits with a physician, combining buprenorphine-naloxone administration with medically-focused counseling. This included reviewing substance use and treatment adherence; encouraging abstinence, self-help group participation, and a healthy lifestyle; asking about opioid craving and pain; and offering referrals as needed. ODC (Mercer and Woody, 1999; Pantalon et al., 1999) focused more extensively on relapse prevention issues, skill-building, and lifestyle change, while offering education on addiction and recovery and reinforcing the importance of abstinence and the benefits of self-help groups; these sessions lasted 45–60 min.

All participants received bup-nx and weekly SMM. In the first phase ("brief treatment"), participants received a 4-week bup-nx taper and were followed for 8 additional weeks; only 7% of participants had successful opioid use outcomes (abstinence or near-abstinence) in this phase. In the second phase ("extended treatment"), offered to participants who relapsed to opioid use during or soon after the initial taper, participants were stabilized on bup-nx for 12 weeks; the primary study outcome measure was "success:" self-reported, urine-confirmed opioid abstinence in week 12 of bup-nx stabilization and at least 2 of the previous 3 weeks (weeks 9–11). Forty-nine percent of participants had successful outcomes in extended treatment. Adding ODC (twice weekly in brief treatment; twice weekly for six weeks, then once a week for six weeks in extended treatment) to bup-nx and SMM did not improve outcomes. Secondary analyses suggested that outcomes did not vary by chronic pain, whereas even minimal lifetime heroin use (heavy heroin users were excluded) was associated with poorer outcomes. Participants were tapered off bup-nx over the next four weeks and were then followed for 8 weeks, with no more study contact until December 2008 (when the follow-up study was approved), when they were offered the opportunity to participate in the follow-up study.

2.2. Follow-up study procedures

Although not part of the original POATS protocol, long-term follow-up was added due to the unique nature of the study sample. Institutional Review Board approval was obtained for the follow-up extension from each site. Participants provided written informed consent at their local site, and additional telephone oral consent with a lead team staff member. Telephone interviews were conducted by trained research assistants at the lead site (McLean Hospital) between March, 2009 and January, 2013. Targets for assessment dates were 18, 30, and 42 months after participants entered the first phase of the study. To maximize the opportunity to obtain data, assessments could occur from one month prior to the target assessment date until one month prior to the following assessment date. Assessments covered the past 12 months and lasted 45–60 min. Participants received $75 for each assessment, similar to other SUD treatment studies (Festinger et al., 2005); participants also received $5 per quarterly contact update, and $10 to keep the first scheduled assessment. A $25 bonus was offered as an additional incentive for participants at risk to miss their target date.

2.3. Follow-up study measures

Follow-up interviews consisted of a subset of questionnaires from the main POATS trial (Weiss et al., 2011 for details), supplemented by items to assess the participants' subsequent course of substance use and treatments received. The following measures were administered at all three follow-up points.

The Composite International Diagnostic Interview (CIDI) Section L (World Health Organization, 1997) was used to diagnose opioid dependence. In this report, we distinguish between those with "current opioid dependence" (meeting current DSM-IV criteria for the disorder) and those with "opioid dependence on agonist therapy." The latter category, according to DSM-IV, describes individuals on agonist therapy, with no DSM-IV symptoms of current opioid dependence (other than tolerance and withdrawal). Unless specified otherwise, "current opioid dependence" refers to participants' meeting current symptomatic criteria.

Substance use at follow-up was assessed with drug and alcohol use items from the Addiction Severity Index (McLellan et al., 1992). Four items assessing overall health and pain were retained from the Medical Outcome Study Short Form-36 (Ware and Sherbourne, 1992). The Fagerström Test for Nicotine Dependence measured severity of dependence among smokers (Heatherton et al., 1991). Substance use and treatment for SUD, pain, and mental health problems during the past year were assessed with questionnaires designed for the follow-up study. A subset of items from the Pain and Opiate Analgesic Use History (Weiss et al., 2010b) was retained.

In the absence of a generally accepted method to reliably distinguish opioid use as prescribed from illicit use, and our reliance on self-report, we did not attempt to distinguish these types of opioid use from each other (the only exception occurred when participants reported being prescribed buprenorphine or methadone to treat opioid dependence itself). This decision rule was consistent with our inclusion criteria and procedures during the main trial; patients who had been prescribed opioids for pain prior to the main trial had to receive permission from their prescribing physician to discontinue opioids and enter the study. Thus, the study sample reflected a group for which opioid management of pain was not considered the indicated treatment, at least at study entry.

2.4. Statistical analysis

In this exploratory analysis, we examined changes over time in opioid use, related clinical outcomes, and treatment utilization, as well as predictors of outcomes at 42-month follow-up. Bivariate associations were assessed with chi-square tests for categorical variables and two-tailed independent *t*-tests for continuous variables. For analyses examining longitudinal change in binary outcomes, marginal regression models were estimated using the generalized estimating equations (GEE) approach. These models are a natural extension of generalized linear models (e.g., logistic regression) to the longitudinal setting; GEE allows all available repeated measures per subject to be incorporated in the analysis while appropriately accounting for the positive correlation among repeated assessments. Mixed effects models were used in analysis of longitudinal change in continuous outcomes. All longitudinal models were adjusted for initial treatment condition; to account for potential clustering of data within study sites, these models also included site as fixed effects via inclusion of an indicator, or dummy variable, for each site. Models examining methadone maintenance and inpatient treatment as binary dependent variables did not adjust for site due to low prevalence of these outcomes. Adjusting the longitudinal models for gender and race did not alter the results. Multivariable models examined predictors of 42-month status, including the sociodemographic, clinical, and treatment study characteristics shown in Table 1 (only redundant characteristics were excluded); these models were adjusted for initial treatment condition and site. All analyses used SPSS v.20 (IBM Corporation, 2011).