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After studying this article, you should be able to:

- Consider recommending both opioid agonist treatment and mutual-help group attendance to improve opioid abstinence in patients with opioid use disorder

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Correlates of Opioid Abstinence in a 42-Month Posttreatment Naturalistic Follow-Up Study of Prescription Opioid Dependence

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ABSTRACT

Objective: The natural course of prescription opioid use disorder has not been examined in longitudinal studies. The current study examined correlates of opioid abstinence over time after completion of a treatment trial for prescription opioid dependence.

Methods: The multisite Prescription Opioid Addiction Treatment Study examined different durations of buprenorphine-naloxone treatment and different intensities of counseling to treat prescription opioid dependence, as assessed by *DSM-IV*; following the clinical trial, a longitudinal study was conducted from March 2009–January 2013. At 18, 30, and 42 months after treatment entry, telephone interviews were conducted (N = 375). In this exploratory, naturalistic study, logistic regression analyses examined the association between treatment modality (including formal treatment and mutual help) and opioid abstinence rates at the follow-up assessments.

Results: At the 3 follow-up assessments, approximately half of the participants reported engaging in current substance use disorder treatment (47%–50%). The most common treatments were buprenorphine maintenance (27%–35%) and mutual-help group attendance (27%–30%), followed by outpatient counseling (18%–23%) and methadone maintenance (4%). In adjusted analyses, current opioid agonist treatment showed the strongest association with current opioid abstinence (odds ratios [ORs] = 5.4, 4.6, and 2.8 at the 3 assessments), followed by current mutual-help attendance (ORs = 2.2, 2.7, and 1.9); current outpatient counseling was not significantly associated with abstinence in the adjusted models.

Conclusions: While opioid agonist treatment was most strongly associated with opioid abstinence among patients with prescription opioid dependence over time, mutual-help group attendance was independently associated with opioid abstinence. Clinicians should consider recommending both of these interventions to patients with opioid use disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT00316277

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Clinical Points

- While buprenorphine is clearly a highly effective treatment for opioid use disorder, it is not known what concomitant psychosocial treatment approaches would improve treatment outcomes in patients receiving buprenorphine.
- In patients with opioid use disorder, recommending attendance at mutual-help groups such as Alcoholics Anonymous or Narcotics Anonymous in addition to buprenorphine therapy can be helpful.

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Over 11 million people reported past-year nonmedical use of opioid analgesics in 2016, more than 12 times the number of those using heroin in the same time period.[1] Research suggests that nonmedical prescription opioid use is associated with elevated risk for multiple comorbidities, including additional substance use disorders and other psychiatric disorders.[2,3] However, most studies of opioid use disorder treatment have included primarily those dependent upon heroin; relatively little treatment outcome research has focused on those dependent either exclusively or primarily upon prescription opioids. The Prescription Opioid Addiction Treatment Study (POATS), carried out as part of the National Drug Abuse Treatment Clinical Trials Network, is the largest treatment outcome study yet conducted for those dependent upon prescription opioids.[4] POATS, which included 653 participants at 10 US sites, examined different lengths of buprenorphine-naloxone (bup-nx) treatment and different levels of intensity of counseling in the treatment of patients who were dependent either exclusively or primarily on prescription opioids. The main trial showed far higher rates of "successful" opioid use outcomes (abstinence or near-abstinence from illicit opioids) among study participants while they were stabilized on bup-nx (49%) than they achieved after tapering from bup-nx (7%–9%).

Long-term follow-up of drug-dependent participants can generate important data about treatment response and recovery trajectories. Following completion of the POATS trial, we therefore conducted a 42-month naturalistic long-term follow-up study of this population (N = 375); telephone interviews were conducted 18, 30, and 42 months following initial randomization into the treatment trial. The most striking finding in the follow-up study was the high rates of self-reported opioid abstinence, both among participants receiving opioid agonist treatment (80%) and, even more surprising, among those not receiving agonist treatment (50%) at month 42.[5] Neither baseline sociodemographic or clinical characteristics nor response to treatment in the main trial were associated with opioid abstinence at month 42[5]; the only outcome predictor was the use of heroin prior to trial entry; participants with a history of any heroin use (regular users were excluded) were more likely to have opioid dependence at month 42. We found in the follow-up study that opioid agonist treatment was associated with a higher rate of opioid abstinence[5,6]; this finding was also reported by Hser et al[7] in a long-term follow- up of a comparative trial of buprenorphine and methadone. However, the association between opioid abstinence and psychosocial treatment received during the follow-up period was not investigated. The aim of the current exploratory study was to examine the natural history of treatment for prescription opioid use disorder and its association with opioid abstinence after completion of the randomized controlled treatment trial. Specifically, we examined the roles of agonist treatment, formal behavioral treatment, and mutual-help (sometimes called self-help) meeting attendance on opioid abstinence in the POATS long-term follow-up study. Understanding the association between ongoing treatment and long-term outcomes can provide critical information on the optimal long-term management of opioid use disorder.

METHODS

Description of the POATS Treatment Trial and Outcomes

The main POATS trial was conducted from 2006 to 2009 at 10 sites in the United States as part of the National Drug Abuse Treatment Clinical Trials Network. Study participants were individuals aged at least 18 years who met *DSM-IV*[8] criteria for current opioid dependence based either entirely or primarily on opioid analgesics. Those who reported heroin use on > 4 of the previous 30 days, those with a lifetime history of opioid dependence due to heroin alone, and those who had ever injected heroin were excluded, as were those who required ongoing opioid use for pain management. For complete details, see Weiss and colleagues.[4]

POATS employed a 2-phase, adaptive treatment research design; in the first phase, participants received a 4-week bup-nx taper and 8 weeks of follow-up and were randomized to either standard medical management (SMM) or SMM plus individual opioid drug counseling (ODC). In the second phase, for those who relapsed to opioid use during Phase 1, participants received 12 weeks of bup-nx stabilization, another 4-week taper, and 8 weeks of post-taper follow-up. Again, they were randomized to SMM alone or SMM plus ODC, to investigate whether the addition of counseling to bup-nx and SMM improved opioid use outcomes. In Phase 1, only 7% of participants had successful opioid use outcomes (abstinence or near-abstinence). In Phase 2, 49% of participants had successful outcomes during their last 4 weeks on bup-nx stabilization.[4] When participants

Table 1. Associations Between Treatment Modalities for Opioid Use Disorder

	Opioid Agonist Treatment	
Mutual-help	Yes, % (n)[a]	No, % (n)[a]
Month 18, N = 252**	43.8 (35)	23.3 (40)
Month 30, N = 312*	37.0 (44)	21.2 (41)
Month 42, N = 306*	38.1 (43)	23.8 (46)
	Outpatient Counseling	
Mutual-help	Yes, % (n)[a]	No, % (n)[a]
Month 18, N = 252**	64.9 (37)	19.5 (38)
Month 30, N = 312**	50.0 (34)	20.9 (51)
Month 42, N = 306**	60.0 (33)	22.3 (56)
	Opioid Agonist Treatment	
Outpatient counseling	Yes, % (n)[a]	No, % (n)[a]
Month 18, N = 252**	42.5 (34)	13.4 (23)
Month 30, N = 312	40.3 (48)	10.4 (20)
Month 42, N = 306*	36.3 (41)	7.3 (14)

[a]Ns represent numerators of reported percentages.
*$P < .01$.
**$P < .001$.

were tapered after 12 weeks of bup-nx stabilization and followed for 8 weeks post-taper, the success rate dropped to 9%. Adding individual counseling to bup-nx and medical management meetings did not improve outcomes.

Longitudinal Follow-Up Study Procedures

Institutional review boards at each site approved the longitudinal follow-up study, which was registered at ClinicalTrials.gov (identifier: NCT00316277). Written informed consent was obtained after the procedures had been fully explained. Trained research assistants conducted telephone interviews at the lead site (McLean Hospital) from March 2009 to January 2013. Assessments were targeted for 18, 30, and 42 months after participants' initial entry into the treatment study. Assessments (45–60 minutes) covered the past 12 months; $75 was awarded for each assessment, similar to other substance use treatment studies.[5,9] For more detail, see Weiss and colleagues.[5]

Longitudinal Follow-Up Study Measures

Follow-up interviews included a selection of questionnaires used in the POATS trial; additional items assessed participants' substance use and treatments received since completion of the treatment study. For the current exploratory study, a subset of the longitudinal measures was analyzed, including only those described below. *DSM-IV* diagnoses of opioid dependence used the Composite International Diagnostic Interview (CIDI) Section L.[10] Items from the Addiction Severity Index[11] assessed days using opioids over the past 30 days. A questionnaire designed specifically for this follow-up study assessed current utilization of pharmacotherapy, formal behavioral treatment, and mutual-help group attendance for SUD. For the analyses reported, "outpatient counseling" refers to outpatient counseling and/or intensive outpatient/day hospital treatment; the term "agonist treatment" refers to both full agonist (ie, methadone) and partial agonist (ie, buprenorphine) treatment.

Statistical Analysis

For this exploratory analysis, we analyzed the associations between current treatment utilization (dichotomous measures of opioid agonist treatment, mutual-help attendance, and outpatient counseling) and opioid use at the 18-, 30-, and 42-month follow-up assessments in a longitudinal study conducted after participation in the POATS treatment trial. Bivariate associations for categorical variables were assessed with χ^2 tests. To examine the adjusted associations between the most common treatments and the binary outcome of opioid abstinence in the past 30 days, generalized linear models (eg, logistic regression) were estimated, while also adjusting for site and initial treatment condition (since not all follow-up participants entered the second phase of the main trial, we adjusted for initial treatment condition only). SPSS v.20[12] was used for all analyses.

RESULTS

The follow-up study enrolled 375 (57%) of the 653 original POATS participants, with 338 providing data.[5] Follow-up study retention was strong: 94% of the month 18 participants continued to month 30, and 93% of month 30 participants continued to month 42. Overall, follow-up participants and nonparticipants had similar sociodemographic and clinical characteristics at baseline, as well as similar rates of successful treatment outcomes in the main trial. The best predictor of participation in the follow-up study was length of time elapsed since completion of the treatment study: nonparticipants had been out of contact with study staff for twice as many months on average as participants.[13]

Natural Course of SUD Treatment Utilization

At the 3 follow-up assessments, most participants reported engaging in some form of SUD treatment at some time during the past year (61%–66%); fewer reported current treatment involvement (47%–50%). Because study treatment was limited to the main trial, treatments occurring during follow-up were self-initiated. Buprenorphine maintenance was the most common current treatment (27%–35%). Current use of other SUD medications during follow-up was less common: 4% received methadone maintenance and < 1% used other SUD medications. Other common current treatments were mutual-help group attendance (27%–30%) and outpatient counseling (18%–23%).

We examined the associations between the most common treatments and found that current utilization of one was associated with current utilization of the others (Table 1). Participants reporting current opioid agonist treatment were more likely to report mutual-help attendance at each follow-up time, when compared to those not currently receiving agonist treatment. For example, at month 18, patients receiving opioid agonist treatment were significantly more likely to be receiving mutual-help treatment than those not receiving opioid agonist treatment (43.8% vs 23.3%). Similarly, current opioid agonist treatment was associated with current outpatient counseling at each follow-up

Table 2. Bivariate Associations Between Current Opioid Abstinence and Current Treatment

	Agonist Treatment		Mutual-Help		Outpatient Counseling	
Abstinence	Yes, %	No, %	Yes, %	No, %	Yes, %	No, %
Month 18, N = 252	80.0**	36.6	69.3**	42.4	73.7**	43.6
Month 30, N = 312	84.0**	50.8	78.8**	57.7	73.5	60.7
Month 42, N = 306	79.6**	50.8	74.2*	56.2	83.6**	56.6

*$P < .01$.
**$P < .001$.

Table 3. Logistic Regression Model of Current Opioid Treatments Associated With Current Prescription Opioid Abstinence Over Time (N = 338)[a]

Abstinence	Estimate	Adjusted Odds Ratio	*P* Value
Month 18 treatment (N = 252)			
Opioid agonist (n = 80 yes)	1.68	5.38	< .001
Mutual-help (n = 75)	0.81	2.25	.022
Outpatient counseling (n = 57)	0.42	1.53	.30
Month 30 treatment (N = 312)			
Opioid agonist (n = 119)	1.53	4.63	< .001
Mutual-help (n = 85)	1.00	2.71	.005
Outpatient counseling (n = 68)	−0.32	0.72	.40
Month 42 treatment (N = 306)			
Opioid agonist (n = 113)	1.02	2.76	< .001
Mutual-help (n = 89)	0.66	1.93	.037
Outpatient counseling (n = 55)	0.85	2.34	.053

[a]The overall treatment effect was significant at each time (adjusted for site and initial treatment condition): at month 18, $\chi^2_3 = 47.65$, $P < .001$; at month 30, $\chi^2_3 = 38.64$, $P < .001$; and at month 42, $\chi^2_3 = 34.05$, $P < .001$.

assessment. Finally, participants reporting mutual-help attendance were more likely to report outpatient counseling as well.

Which Patient-Initiated Treatments Were Correlated With Opioid Abstinence?

Current abstinence from opioids was associated with receiving current treatment in bivariate analysis (Table 2). At months 18, 30, and 42, agonist treatment was associated with abstinence; mutual-help attendance was also associated with abstinence at each follow-up time. However, in bivariate analyses, participants receiving outpatient counseling were more likely to be abstinent at months 18 and 42 only.

Multivariable logistic regression models examined the association among the 3 most commonly utilized treatments and opioid abstinence at months 18, 30, and 42 (Table 3). Overall, opioid agonist treatment showed the strongest association with opioid abstinence, with odds ratios over time of 5.4, 4.6, and 2.8 at months 18, 30, and 42, respectively. This association was statistically significant at each follow-up time point, even after controlling for the effects of the other 2 treatment types, mutual-help attendance and outpatient counseling. That is, participants in opioid agonist treatment at month 18 had more than 5 times the odds of being opioid abstinent than those not receiving this treatment, and they had almost 3 times the odds of being abstinent at month 42.

The association between opioid abstinence and mutual-help group attendance was also significant. Participants who attended mutual-help groups had more than 2 times the odds of being opioid abstinent at month 18, almost 3 times the odds at month 30, and almost twice the odds at month 42 compared to those not attending mutual-help groups, even after controlling for the effects of opioid agonist treatment and outpatient counseling. Outpatient treatment, however, was not associated with opioid abstinence at any follow-up time in the models controlling for opioid agonist treatment and mutual-help attendance. Interactions among the 3 treatments were examined, but none were significant at any follow-up time.

DISCUSSION

In the Prescription Opioid Addiction Treatment Study, participants receiving opioid agonist treatment in the 3.5-year naturalistic follow-up phase of the trial reported significantly higher rates of abstinence from opioids than those not receiving agonist treatment.[5] In the current study, bivariate analysis showed that not only was agonist treatment associated with opioid abstinence, but mutual-help attendance and outpatient counseling were also associated with abstinence. Multivariable logistic regression models confirmed the association between opioid abstinence and both agonist treatment and mutual-help attendance at months 18, 30, and 42. However, outpatient counseling was not associated with opioid abstinence in the adjusted models at any of the follow-up time points. Overall, these findings suggest that continued receipt of treatment, optimally opioid agonist treatment plus mutual help, is robustly associated with abstinence from illicit opioids.

The strong association between opioid agonist treatment and opioid abstinence over time contributes further to the literature supporting the efficacy of pharmacotherapy for opioid use disorder. Across timepoints, participants currently receiving opioid agonist treatment had between 2.8 and 5.4 times higher odds of being abstinent from opioids. This benefit underscores the critical importance of access to opioid agonist therapies, particularly against the backdrop of the continued rise of opioid overdose deaths.[14]

The lack of a significant interaction effect between receipt of agonist treatment and mutual-help attendance on opioid use in our follow-up study suggests that while receipt of agonist treatment and attendance at mutual-help meetings were both helpful, neither detracted from nor enhanced the abstinence benefit of the other. Rather, the benefits were independent and additive.

The literature supports mutual help, especially Alcoholics Anonymous (AA), as a useful treatment adjunct for those with alcohol use disorder,[15] but the literature on the impact of mutual help for patients with opioid use disorder is less robust, especially beyond 6-month follow-up.[16,17] We are aware of 1 longitudinal study examining mutual help in patients with opioid use disorder,[18] which found greater abstinence among those attending mutual-help meetings at year 4 follow-up. However, most participants were heroin users (77%), and agonist medication status was not reported.

Short-term cohort studies of patients receiving outpatient buprenorphine therapy have noted an association between mutual-help attendance and improved abstinence,[19,20] treatment retention,[21,22] or both.[23] Our findings are consistent with these studies and replicate the results for the first time in a longitudinal follow-up of prescription opioid users. These findings suggest that mutual-help attendance is associated with higher odds of abstinence, independent of opioid agonist treatment.

Many patients have encountered the traditional view held by some members in 12-step mutual-help organizations, especially NA, that opioid-agonist treatment is at odds with true abstinence.[23,24] Indeed, this view is codified in NA official documents[25]: participants receiving agonist treatment are barred from holding service positions and are not recognized for continuous sober periods. In contrast, the official stance of AA differs significantly and indeed provides affirmation that medication choices are between patient and physician.[26] Understanding these nuances is important for treatment professionals. A survey of patients receiving bup-nx found that a considerable percentage (30%) were worried about encountering negative attitudes toward their buprenorphine use; only 33% of participants reported that their providers had discussed disclosing their buprenorphine use.[27] Monico and colleagues[23] found that NA members receiving buprenorphine used various strategies to deal with this issue, including limiting disclosure of their buprenorphine prescriptions and avoiding particular meetings. Patients in these studies achieved some success in managing contradictory viewpoints, an important reminder for clinicians who would categorically avoid referring their patients to NA meetings due to such concerns. Indeed, in our follow-up study, participants receiving opioid agonist treatment were significantly more likely than their counterparts not receiving opioid agonist treatment to report attending mutual-help meetings at all 3 follow-up periods, although data on specific meeting type (eg, AA vs NA vs non–12-step meetings) were not collected. Notably, some evidence suggests that those with a primary drug use disorder report similarly strong abstinence rates whether they attend AA or NA.[28]

While many patients manage to reconcile the dissonant viewpoints between NA and opioid agonist treatment, another approach that has received positive reviews from patients and professional treatment staff has been the development of 12-step–based mutual-help recovery groups specifically catering to patients on opioid agonist treatment, such as Methadone Anonymous.[29–31] Data from these qualitative studies indicate that patients engaged in such groups have reported improved abstinence from co-occurring cocaine, alcohol, and cannabis use.[29]

Although we did not solicit information from participants about their reasons for attending mutual-help meetings during follow-up, it is noteworthy that the standard medical management (MM) in the main trial of POATS consistently included a recommendation to attend mutual-help meetings.[4] Similarly, in the multisite NIAAA COMBINE trial,[32] the study physicians' recommendation at every visit that participants with alcohol dependence attend AA was thought to increase AA attendance among those who received MM; significantly more patients randomized to placebo plus MM attended AA than did those receiving behavioral therapy alone.[33] Based on our POATS follow-up findings, it is possible that regular recommendation of mutual-help attendance by a clinician may have a beneficial effect in opioid use disorder treatment as well, whereas *requiring* mutual-help attendance as a condition of treatment may not be beneficial.[23] Our finding regarding the beneficial effect of mutual-help meetings, coupled with the caveats and special considerations for patients taking buprenorphine who attend NA meetings, suggests that the development and testing of a Twelve Step Facilitation treatment[34] for those taking opioid use disorder medications could be timely.

The association between outpatient counseling and abstinence that we found at some follow-up time points, in bivariate analysis, was no longer statistically significant in models adjusted for agonist treatment and mutual-help attendance. Much has been written about the limited empirical data supporting efficacy of behavioral treatment (other than contingency management) offered concomitantly with opioid agonist treatment to improve overall treatment outcomes,[35] with the main POATS trial itself underscoring this challenge.[4] There have been exceptions to this finding in studies of subsets of opioid use disorder patients.[36,37] The fact that increased psychosocial services have generally been considered to enhance the efficacy of methadone maintenance treatment[38] suggests that perhaps we have yet to design studies of bup-nx treatment that accurately pair specific at-risk patients with optimal behavioral treatments. For example, patients with high levels of psychiatric symptoms in methadone maintenance treatment have been found to benefit from psychotherapy,[39] but no comparable study has focused on those receiving bup-nx.

The POATS follow-up study has several limitations (for details, see Weiss and colleagues[5]) including participation by only 57% of the original randomized sample and telephone-based contact with main-trial participants precluding the opportunity for collection of urine toxicology data. Other limitations include lack of data regarding participants' extent of involvement in mutual help, type of mutual-help meetings attended, the temporal association between mutual-help initiation and abstinence, reasons for self-selection in and out of various treatments (eg, agonist treatment, outpatient counseling, and mutual-help groups), dosing of opioid agonist treatment, and frequency of attendance or perceived quality of outpatient counseling services. It is also possible that the associations between treatment participation and outcome may not be causal, but may instead reflect increased motivation and thus inherently better prognosis.

In future studies of opioid use disorder, it would be useful to collect the data on mutual help that has emerged over the past 25 years for alcohol use disorder, including mediators of any positive effects and the degree to which these elements

may augment professional services (ie, peer support services integrated within professional treatment systems). Experimental trials might formally assess the impact of referral to mutual-help meetings for those with opioid use disorder, ensuring that the active referral condition excluded the compulsory element that has not been previously effective. Finally, additional longitudinal data about the experiences of patients with opioid use disorder in mutual-help meetings, including the role of 12-step alternatives such as SMART Recovery, could be informative.

This study, using long-term follow-up data from the largest randomized trial of treatment for prescription opioid dependence to date, found that ongoing treatment was strongly associated with odds of opioid abstinence up to 42 months following the trial. Although current opioid agonist treatment had the strongest association with abstinence, mutual-help attendance was also significantly associated with abstinence. Critically, mutual-help attendance was associated with an additive benefit among those receiving opioid agonist treatment and was also associated with abstinence in those not receiving agonist treatment. Adults with prescription opioid dependence appear to benefit from continued medication and mutual-help participation as part of long-term, ongoing care.

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POSTTEST

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1. **Which of the following statements is supported by the results of the study?**
   a. Mutual help was associated with the greatest odds ratio for current abstinence compared with medication or psychosocial intervention.
   b. Mutual help was associated with a positive odds ratio for current abstinence at all time points.
   c. Outpatient counseling had a higher odds ratio for current abstinence than mutual help at all time points.
   d. No evidence supports a benefit of mutual help in current abstinence outcomes.

2. **Zachary presents to your clinic describing a 5-year history of prescription opioid misuse with recent transition to intranasal use and 1 prior overdose. You initiate treatment with buprenorphine-naloxone. What would be most useful to tell him about attending a 12-step mutual-help meeting?**
   a. Narcotics Anonymous (NA) supports the use of opioid agonist treatment (buprenorphine-naloxone and methadone), and Zachary may benefit from NA recognition of continuous sobriety.
   b. The official stance of NA is to oppose the use of opioid agonist treatment by its members, and therefore attendance cannot be helpful to Zachary.
   c. The official stance of NA is that opioid agonist treatment is inconsistent with true abstinence, but some members on opioid agonist treatment nevertheless find NA helpful.
   d. Nothing. Studies show patients do not want information from their physicians about mutual-help organizations.

3. **Even in the absence of counseling or mutual-help participation, opioid agonist treatment is associated with significantly improved abstinence at long-term follow-up.**
   a. True
   b. False