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Initial Response as a Predictor of 12-Week Buprenorphine-Naloxone Treatment Response in a Prescription Opioid–Dependent Population

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ABSTRACT

Objective: Initial medication response has been shown to predict treatment outcome across a variety of substance use disorders, but no studies have examined the predictive power of initial response to buprenorphine-naloxone in the treatment of prescription opioid dependence. We therefore conducted a secondary analysis of data from the Prescription Opioid Addiction Treatment Study to determine whether initial response to buprenorphine-naloxone predicted 12-week treatment outcome in a prescription opioid–dependent population.

Method: Using data from a multisite, randomized controlled trial of buprenorphine-naloxone plus counseling for *DSM-IV* prescription opioid dependence (June 2006–July 2009), we conducted a secondary analysis to investigate the relationship between initial medication response and 12-week treatment outcome to establish how soon the efficacy of buprenorphine-naloxone could be predicted (N = 360). Outcomes were determined from the Substance Use Report, a self-report measure of substance use, and confirmatory urinalysis. Predictive values were calculated to determine the importance of abstinence versus use at various time points within the first month of treatment (week 1, weeks 1–2, 1–3, or 1–4) in predicting successful versus unsuccessful treatment outcome (based on abstinence or near-abstinence from opioids) in the last 4 weeks of buprenorphine-naloxone treatment (weeks 9–12).

Results: Outcome was best predicted by medication response after 2 weeks of treatment. Two weeks of initial abstinence was moderately predictive of treatment success (positive predictive value = 71%), while opioid use in both of the first 2 weeks was strongly predictive of unsuccessful treatment outcome (negative predictive value [NPV] = 84%), especially when successful outcome was defined as total abstinence from opioids in weeks 9–12 (NPV = 94%).

Conclusions: Evaluating prescription opioid–dependent patients after 2 weeks of buprenorphine-naloxone treatment may help determine the likelihood of successful outcome at completion of the current treatment regimen.

Trial Registration: ClinicalTrials.gov identifier: NCT00316277

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A patient's initial response to medication can sometimes indicate the likely course of treatment. If the initial response is strongly associated with later outcome, then early changes can be made (eg, switching or supplementing medications) for patients who exhibit a poor initial response. Clinician guidelines that help predict the probability of medication efficacy can be useful in preventing patient dropout resulting from delayed medication response (eg, with antidepressants).[1] Conversely, knowing that a poor initial treatment response strongly predicts an unfavorable longer-term outcome can help minimize delays in switching or augmenting the initial treatment regimen.[2]

A strong relationship between initial response and later treatment outcome has been demonstrated for a variety of medications, both for psychiatric disorders, such as depression[3–6] and psychosis,[7,8] and for substance use disorders.[9–12] In particular, the ability of initial response to predict outcome has been determined for medications to treat nicotine,[9] cocaine,[10,13] methamphetamine,[11] and heroin[12] dependence. However, no studies have examined the ability of early medication response to predict buprenorphine-naloxone treatment outcome in prescription opioid–dependent patients. It cannot be assumed that the response to different medications in other substance use disorder populations can be extended to prescription opioid–dependent patients taking buprenorphine-naloxone. Furthermore, the increasing prevalence of prescription opioid dependence suggests a need to examine the timeline of medication response in this relatively understudied population.

Nonmedical prescription opioid use has become a serious and widespread problem.[14] Rates of abuse or dependence are now the second highest of any drug class in the United States,[15] and frequency of overdose deaths is higher than that for heroin and cocaine combined.[16] Most studies of opioid–dependent patients to date have focused on heroin users, primarily in methadone maintenance treatment. Since some research has suggested that those dependent on prescription opioids may have different, perhaps better, treatment outcomes than those dependent upon heroin,[17–19] more research is needed that focuses on primary prescription opioid–dependent patients. In a recent study, Weiss et al[20] found that approximately half of prescription opioid–dependent patients achieved ≥ 3 weeks of opioid abstinence in the last 4 weeks of a 12-week trial of buprenorphine-naloxone. However, research on the general timeline of buprenorphine efficacy[21,22] and studies of initial buprenorphine response as part of a predictive model of treatment outcome[23,24] have to date been conducted only in primarily heroin or mixed-opioid–dependent populations. To our knowledge, there has been no research on the predictive value of initial response to buprenorphine among patients with primary dependence on prescription opioids. Furthermore, no study has

Clinical Points

- The optimal time point to evaluate buprenorphine-naloxone for prescription opioid dependence is at the end of the first 2 weeks of treatment.
- Prescription opioid–dependent patients who use opioids in both weeks 1 and 2 of buprenorphine-naloxone treatment will most likely not achieve opioid abstinence at week 12.

examined a variety of time points in defining initial response to buprenorphine to help determine an optimal guideline for deciding when to consider changing or supplementing pharmacotherapy.

We therefore conducted a secondary analysis of data from the Prescription Opioid Addiction Treatment Study (POATS)[20] to determine whether initial response to buprenorphine-naloxone predicted 12-week treatment outcome in a prescription opioid–dependent population. In particular, we wanted to know how soon 12-week outcome could be predicted based on abstinence or use at various time periods within the first 4 weeks of initiating buprenorphine-naloxone treatment.

METHOD

Main Study Overview

This secondary analysis used data from POATS (ClinicalTrials.gov identifier: NCT00316277), a multisite randomized controlled trial of buprenorphine-naloxone plus adjunctive counseling, conducted from June 2006 until July 2009 under the auspices of the National Drug Abuse Treatment Clinical Trials Network.[20] The study employed a 2-phase, adaptive treatment research design. In the first phase, hereafter known as the "brief treatment phase," participants received 2 weeks of buprenorphine-naloxone stabilization, a 2-week taper, and 8 weeks of follow-up. Participants who were "successful" in this phase, ie, abstinent or nearly abstinent from opioids, were finished with the study. Those who relapsed to opioids were offered the second, "extended treatment phase": 12 weeks of buprenorphine-naloxone stabilization, a 4-week taper, and 8 weeks of follow-up.

Participants in the first (brief treatment) phase of POATS received 4–12 mg of buprenorphine-naloxone on the day of their induction and could receive 8–32 mg/d during stabilization. In the second (extended treatment) phase, most participants who had returned to opioid use in the first phase (n = 328 of 360 participants) received the same induction regimen as those in the first phase of the trial; those who returned to opioid use in the first phase but were not physically dependent could alternatively be inducted with an initial dose of 2 mg (n = 32). In both phases, physicians could adjust the medication dose by up to 8 mg at weekly Standard Medical Management (SMM) visits (see next paragraph), based on withdrawal symptoms, use of opioids, craving, and side effects.

In both phases, participants were randomized to receive (in addition to buprenorphine-naloxone) either SMM alone or SMM plus individual opioid dependence counseling (ODC). Standard Medical Management, which was originally designed to approximate office-based treatment in a primary care setting,[25] was administered to all participants; SMM involved brief physician visits that combined the administration and dose adjustment (as needed) of buprenorphine-naloxone with medically-oriented counseling, including reviewing substance use; addressing treatment adherence issues when needed; encouraging abstinence; asking about lifestyle choices, pain, opioid craving, and participation in self-help groups; and offering referrals. Opioid dependence counseling[26,27] focused on developing relapse prevention skills, advocating abstinence and lifestyle change, recommending self-help groups, and offering education about addiction and recovery. The 45–60 minute ODC sessions were administered by a separate person in addition to the 15–20 minute SMM sessions for participants in the SMM + ODC condition. The present study used data from the 12 weeks of buprenorphine-naloxone treatment in the extended treatment phase. An extensive review of study design and procedures can be found elsewhere.[28]

Study Population

Participants who were 18 years of age or older were recruited at 10 sites across the United States. All met *DSM-IV-TR*[29] criteria for opioid dependence. Because most opioid dependence treatment research has been conducted with heroin-dependent populations, the target population in POATS was those with primary prescription opioid dependence. Thus, exclusion criteria included use of heroin on more than 4 days in the past month, lifetime injection of heroin, and lifetime opioid dependence based on heroin alone. Some heroin use was allowed due to the high prevalence of occasional heroin use among those who primarily abuse prescription opioids[30] and the desire to study a generalizable sample. Potential participants were not aware of any exclusion criteria, including heroin use, to increase the likelihood of reliable self-reporting. Confirmation of heroin history was provided by 2 interviews, the Addiction Severity Index[31] and the Composite International Diagnostic Interview (CIDI).[32] Other exclusion criteria included a major pain event in the last 6 months, the need for ongoing opioid medications for pain management, participation in another medication study within the past month, and current participation in formal substance use disorder treatment. For participants who were being prescribed opioids for pain at screening, permission from the prescribing physician was required for study participation. POATS was approved by the Institutional Review Boards at each participating institution. All participants gave written informed consent.

Measures

Daily substance use was assessed using the Substance Use Report, a self-report questionnaire modeled on the Timeline Followback, which uses a calendar method to assist recall[28,33] (available from the authors upon request). Urine samples were

screened for methadone, oxycodone, propoxyphene, and the Opiate 300 analytes group (morphine, heroin, and codeine), as well as other standard drugs of abuse (eg, cocaine). Both the Substance Use Report and urine samples were obtained weekly. At baseline, co-occurring psychiatric diagnoses were assessed using the CIDI[32] for 2 disorders of particular interest in this population: major depressive disorder (MDD) and posttraumatic stress disorder (PTSD).[34,35]

Success in the brief treatment phase was defined as (1) completing all 12 weeks of treatment and follow-up with self-reported opioid use on no greater than 4 days per month, (2) no consecutive weeks of opioid-positive urine drug screen results, (3) no more than 1 missing urine sample throughout the 12 weeks, and (4) no other substance use disorder treatment (besides self-help groups such as Narcotics Anonymous). Participants who were unsuccessful in the brief treatment phase (eg, by providing opioid-positive urine tests for 2 consecutive weeks) were eligible to enter the extended treatment phase. Success in the extended treatment phase was defined as abstinence in week 12 (the final week of buprenorphine-naloxone stabilization) and in at least 2 of the 3 previous weeks. Participants were considered to have an opioid-abstinent week if they attended the scheduled research visit, reported no opioid use in the past week, and had a urine test that was negative for opioids. Missed visits or urine tests were considered nonabstinent weeks.

Main Study Results

Of the 653 participants in the brief treatment phase, 43 (6.6%) had successful outcomes and were finished with the study. Of the 360 participants who subsequently enrolled in the extended treatment phase, 177 (49.2%) achieved success at completion of buprenorphine-naloxone stabilization. Among the 183 participants who were unsuccessful, 38 (19 in each treatment condition) dropped out of the study. There was no difference in outcome between counseling conditions (SMM + ODC vs SMM alone) in either the brief or the extended treatment phase. At the end of the extended phase taper (week 16), the rate of successful outcome (abstinence in week 16 and 2 of the 3 previous weeks) dropped to 26.1% (94 of 360 participants). At week 24 (8 weeks after taper completion), only 31 (8.6%) of the extended-phase participants achieved successful outcome, defined as abstinence in week 24 and at least 2 of the 3 previous weeks.

Statistical Analyses

Because 610 (93.4%) of the original 653 study participants were unsuccessful in the brief treatment phase, the present study used data only from the extended treatment phase; 360 of these 610 participants (59.0%) entered the extended treatment phase. To determine initial response to treatment, we examined 4 time periods within the first 4 weeks of the extended treatment phase: week 1, weeks 1–2, weeks 1–3, and weeks 1–4. *Initial response to treatment* was defined as either abstinence or use during every week in a time period. For example, initial response to treatment was defined as "use" in weeks 1–2 if a participant used opioids both in week 1 and again in week 2. *Final response to treatment* was defined in 2 different ways: (1) *success* refers to POATS criteria for a successful outcome, abstinence in week 12 (the final week of buprenorphine-naloxone stabilization) and at least 2 of the 3 previous weeks; and (2) *abstinence* refers to complete abstinence from opioids in weeks 9–12. We included the latter outcome in this report because it is considered by some to be the gold standard for a positive treatment response in studies of drug use disorders.[36] *Positive predictive value* was defined as the degree to which initial abstinence predicted final treatment success (alternatively, abstinence). Positive predictive value (PPV) = 100 × (number of participants who were initially abstinent in a given period and had a successful outcome/number of all participants who were abstinent in that initial period); sample calculation for week 1 PPV = 100 × (131/208) = 63% (see Table 1A). *Negative predictive value* was defined as the degree to which opioid use in every week during the early treatment period predicted unsuccessful outcome or inability to achieve abstinence at the end of buprenorphine-naloxone stabilization. Negative predictive value (NPV) = 100 × (number of participants who used opioids in a given initial period and had an unsuccessful outcome/number of all participants who used opioids in that initial period); sample calculation for week 1 NPV = 100 × (106/152) = 70% (see Table 2A).

RESULTS

Participant Characteristics

Participants ranged in age from 18 to 64 years old, with a mean age of 32.5 years (SD = 9.7). Just over half (58.1%, n = 209) were male, and most (90.6%, n = 326) were white. The mean education was 12.9 years (SD = 2.2). Half were never married, and 60.3% (n = 217) were employed full-time in the last 3 years. Lifetime PTSD was reported by 18.3% (n = 66), while past-year PTSD was reported by 12.8% of participants (n = 46). About one-third (34.2%, n = 123) had lifetime MDD, and 20.0% (n = 72) had past-year MDD.

Lifetime heroin use was reported by 27.8% of participants (n = 100), and 41.4% (n = 149) reported chronic pain. Nearly one-third (27.8%, n = 100) met criteria for lifetime alcohol dependence. The most common past-year nonopioid substance use disorders were cannabis dependence (6.7%, n = 24), sedative-hypnotic dependence (6.7%, n = 24), and cocaine dependence (4.7%, n = 17). Most participants (81.4%, n = 293) did not have any past-year nonopioid substance dependence diagnoses. As previously reported,[37] nonopioid substance dependence was not associated with treatment outcome.

Early Response as a Predictor of 12-Week Treatment Outcome

Early abstinence as a predictor of positive treatment response in weeks 9–12. Positive predictive values (PPVs) are presented in Tables 1A and 1B for the 2 different ways in which 12-week treatment response was defined. Abstinence in both weeks 1 and 2 was moderately predictive of *success* at week 12 (as defined in POATS: abstinence in ≥ 3 of the

Table 1. Positive Predictive Values

A. Predicting Successful Treatment, Defined as Abstinence From Opioids in Week 12 and at Least 2 of the 3 Previous Weeks (N = 360)

	Initial Abstinence and Final Success, n	Initial Abstinence and Final Lack of Success, n	**Positive Predictive Value, %**	95% Confidence Interval
Week 1	131	77	**63**	56–70
Weeks 1–2	112	46	**71**	64–78
Weeks 1–3	93	34	**73**	66–81
Weeks 1–4	86	27	**76**	68–84

B. Predicting Complete Abstinence From Opioids in Weeks 9–12 (N = 360)

	Initial Abstinence and Final Abstinence, n	Initial Abstinence and Final Lack of Abstinence, n	**Positive Predictive Value, %**	95% Confidence Interval
Week 1	101	107	**49**	42–55
Weeks 1–2	88	70	**56**	48–63
Weeks 1–3	73	54	**57**	49–66
Weeks 1–4	68	45	**60**	51–69

Table 2. Negative Predictive Values

A. Predicting Unsuccessful Treatment, Defined as Inability to Achieve Opioid Abstinence in Week 12 and at Least 2 of the 3 Previous Weeks (N = 360)

	Initial Use and Final Lack of Success, n	Initial Use and Final Success, n	**Negative Predictive Value, %**	95% Confidence Interval
Week 1	106	46	**70**	62–77
Weeks 1–2	80	15	**84**	77–92
Weeks 1–3	65	10	**87**	79–94
Weeks 1–4	53	7	**88**	80–96

B. Predicting Inability to Achieve Complete Opioid Abstinence in Weeks 9–12 (N = 360)

	Initial Use and Final Lack of Abstinence, n	Initial Use and Final Abstinence, n	**Negative Predictive Value, %**	95% Confidence Interval
Week 1	122	30	**80**	74–87
Weeks 1–2	89	6	**94**	89–99
Weeks 1–3	72	3	**96**	92–100
Weeks 1–4	58	2	**97**	92–100

last 4 weeks, including week 12), with PPV = 71%, whereas abstinence in week 1 alone was less predictive. Abstinence in weeks 1–3 and 1–4 was only marginally better at predicting successful outcome than abstinence in weeks 1–2 (Table 1A). The ability of initial abstinence to predict opioid *abstinence* in weeks 9–12 was no better than chance at week 1 and did not rise appreciably for longer periods of initial abstinence (Table 1B).

Early opioid use as a predictor of poor treatment response in weeks 9–12. Negative predictive values are presented in Tables 2A and 2B. Opioid use in both weeks 1 and 2 was strongly predictive of unsuccessful outcome in weeks 9–12, with NPV = 84%, whereas opioid use in week 1 alone was only moderately predictive of outcome. Predictive values for opioid use in weeks 1–3 and 1–4 were marginally higher than values for weeks 1–2 (Table 2A). Negative predictive values were strongest when complete *abstinence* from opioids in weeks 9–12 was used to define treatment outcome. Once again, the greatest increase in predictive value occurred between week 1 and weeks 1–2; there were only modest gains in the predictive power of initial opioid use beyond the first 2 weeks (Table 2B).

Counseling. Because we considered the idea that participants who received additional counseling might be more likely to overcome a poor initial response and be successful by the end of treatment, we examined whether treatment condition (ie, SMM + ODC vs SMM alone) influenced the predictive values of the early treatment response. Positive and negative predictive values did not vary by treatment condition.

Dosing. The flexible dosing schedule employed in POATS allowed for variation in dose among study participants. We thus examined the relationship between buprenorphine-naloxone dose and treatment response at both week 2 (early response) and week 12 (end of treatment). Week 2 dose did not significantly differ between those who were abstinent and those who used opioids in the first 2 weeks (mean = 17.9 mg vs 18.3 mg, $t_{229} = 0.47$, $P = .65$). Week 12 dose did not differ significantly between those who achieved *success* and those who did not (mean = 17.1 mg vs 18.1 mg, $t_{285} = 1.19$, $P = .24$). However, week 12 dose was significantly higher among those who did not achieve *abstinence* compared to those who were abstinent in the last 4 weeks of treatment (mean = 16.3 mg vs 18.5 mg, $t_{285} = 2.68$, $P < .01$).

DISCUSSION

To assess the importance of early treatment response to buprenorphine-naloxone stabilization, we used predictive values to examine the degree to which initial response to buprenorphine-naloxone treatment could predict 12-week outcome in a large prescription opioid–dependent sample. We found that an eventual poor treatment outcome could be identified with a high degree of accuracy after just 2 weeks of buprenorphine-naloxone treatment: participants who used opioids in both weeks 1 and 2 were unlikely to have successful outcomes. This was especially true if the outcome to be predicted was complete abstinence from opioids in weeks 9–12: only 6 of the 95 participants who used opioids in the 2 initial weeks achieved opioid abstinence in the last 4 weeks of treatment. Indeed, even opioid use in week 1 was a fairly poor prognostic sign, as it predicted an 80% likelihood that a participant would be unable to abstain from opioids in weeks 9–12 (see Table 2B); this points out the importance of very early response to treatment in this population.

Those participants who achieved abstinence in the first 2 weeks had a reasonably good chance (71%) of a successful outcome, defined (as in our main study) as abstinence in week 12 and ≥ 2 of the 3 previous weeks. However, the

predictive value dropped to little better than chance when the outcome to be predicted was complete opioid abstinence in the last 4 weeks of treatment. Thus, early abstinence, although a promising sign, is not as powerful a predictor of good outcome as early opioid use is as a predictor of ongoing use.

A review of dosing found that our results were not attributable to inadequate dosing at weeks 2 or 12. The only difference in dose was between those who were abstinent and those who used opioids in the last 4 weeks of treatment: buprenorphine-naloxone dose was higher for participants who were unable to attain abstinence, as one would expect in a flexible dosing study in which physicians could increase the dose for those who were not responding to treatment.

Although predictive values for buprenorphine-naloxone have not previously been established, the present findings are consistent with a wealth of literature demonstrating that early response predicts substance use outcome. One of the first studies to examine the predictive power of initial response to treatment found that treatment response in week 1 or 2 of nicotine dependence treatment predicted treatment outcome at 8 weeks and at 6-month follow-up.[9] A more recent study[38] also found that abstinence in the first 2 weeks of smoking cessation treatment was strongly predictive of outcome at 6 months. Furthermore, initial abstinence was a better predictor than abstinence at any other time point in treatment. Similar results have been found in studies of methadone maintenance treatment[12] and bupropion for methamphetamine dependence,[11] both of which found that early use was a better predictor of poor outcome than early abstinence was of successful outcome. Finally, in cocaine treatment research, both a single initial urine drug screen[13] and 2 weeks of initial abstinence[10] have been shown to be predictive of later abstinence. The present study is the first report on the predictive ability of early treatment response in buprenorphine-naloxone treatment of prescription opioid dependence. Our finding adds to the breadth of literature identifying the first 2 weeks as a key time point for early evaluation across a variety of substance use disorder treatments. Future research should build on the present finding to determine if initial response to buprenorphine-naloxone predicts even longer-term outcome, as has been shown for other substance use disorder treatments.

The present study is both strengthened and limited by the nature of the study population and the design of the main trial. Inclusion criteria were chosen to represent both those who used prescription opioids exclusively and those who used heroin occasionally. Thus, the sample was neither restricted to those who had never used heroin nor open to participants with more severe heroin use. Although such exclusion criteria limit generalizability to an extent, they also increase external validity by focusing on a new population, ie, primary prescription opioid users. The population was 91% white and had, on average, 13 years of education; samples with different sociodemographic characteristics may respond somewhat differently.

A limitation of the study is the fact that the buprenorphine-naloxone stabilization period in the extended treatment phase ended at 12 weeks. Because some patients improve more slowly than others, it is possible that some who were still using opioids at week 12 may have abstained at a later date. The aim of POATS was to examine whether adjunctive counseling improved outcomes for prescription opioid–dependent patients after 12 weeks of buprenorphine-naloxone stabilization, but 12 weeks was not necessarily chosen as an optimal length of pharmacotherapy; the finding that most participants with successful outcomes at the end of 12 weeks were already unsuccessful at 8 weeks post-taper suggests that 12 weeks is likely too short a treatment period to be effective long-term for many patients. The need for longer-term treatment is heightened by the risk of mortality associated with prescription opioid dependence, which has increased in recent years.[39] Another potential limitation is the exclusive focus on participants in the extended treatment phase. While they were similar clinically to those who received brief treatment only,[20] they may have been more motivated to succeed than nonparticipants, given their willingness to participate in further treatment. Using opioids in the first 2 weeks of this "second-chance" extended treatment may have been particularly discouraging, thus leading to continued opioid use.

Finally, it should be pointed out that positive and negative predictive values are dependent on the population being studied and are influenced by the rates of successful treatment outcome; therefore, they should not be applied to populations in which the rates of successful treatment outcome are discernibly different.

This study provides potentially clinically useful information on the predictive ability of initial response to buprenorphine-naloxone in a prescription opioid–dependent population. A benefit of the present study was the comparison of multiple initial response time periods to establish a simple clinical rule for predicting treatment outcome. Rather than wait 4–8 weeks to determine if treatment will likely be effective, clinicians can gain valuable information by evaluating buprenorphine-naloxone efficacy after 2 weeks. It is possible that some adjustment of the treatment regimen at that time (eg, adding intensive outpatient or partial hospital treatment) may improve later treatment outcome; whether this is in fact true is unclear and would be an interesting topic of study. The sooner we can identify likely eventual outcomes based on initial experience with buprenorphine-naloxone, the sooner treatment can be tailored more specifically to patients' individual needs. Additionally, early identification of patients who are likely to do poorly may make treatment more efficient and thus cost-effective, an important aim in light of the economic burden of prescription opioid dependence.

Drug names: buprenorphine-naloxone (Suboxone), bupropion (Wellbutrin, Aplenzin, and others), methadone (Methadose and others), oxycodone (OxyContin, Roxicodone, and others).

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Potential conflicts of interest: **Dr Fiellin** serves as a consultant to Pinney Associates, serving on an external advisory board to monitor the abuse and diversion of buprenorphine. **Dr Weiss** is a consultant for Reckitt Benckiser. **Drs Griffin, Connery**, and **Fitzmaurice** and **Mss McDermott** and **Hilario** report no conflicts of interest.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Addiction section. Please contact Daniel D. Langleben, MD, at dlangleben@psychiatrist.com.