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The Use of Off-Label Medications in Substance Abuse Treatment Programs

Maria Paino, PhD,

Oakland University, Rochester, Michigan, Department of Sociology, Anthropology, Social Work, and Criminal Justice

Lydia Aletraris, PhD,

University of Georgia, Athens, Georgia, Owens Institute for Behavioral Research

Paul M. Roman, PhD

University of Georgia, Athens, Georgia, Owens Institute for Behavioral Research

Abstract

Background: Substance use disorder (SUD) treatment centers serve a population of clients who have diverse needs, and may desire or require access to varied treatments while seeking care for their SUDs. While pharmacotherapies have increased in popularity for the treatment of SUDs, adoption rates do remain quite low. But a wider array of pharmacotherapies has become available in recent years which may shift the trend. This paper helps shed light on how variations in SUD treatment centers develop and persist with regard to the adoption and delivery of off-label medications.

Methods: We use a nationally representative and longitudinal sample of SUD treatment centers in the US (N=196). We use a logistic regression to analyze the relationship between organizational characteristics and offering any medications, off-label. We also use a negative binomial regression to analyze the relationship between organizational characteristics and the number of medications that were used off-label.

Results: Our findings reveal that older centers, accredited centers, and centers that offer mental health screenings are all positively associated with the provision of off-label medication in SUD treatment. We also find a positive relationship between private funding and offering a greater number of off-label medications.

Conclusions: Our results suggest that SUD clients who seek treatment from centers that offer medications off-label, may have access to a greater number of medication-assisted treatment options.

Please direct correspondence to Maria Paino at the Department of Sociology, Anthropology, Social Work, and Criminal Justice, Oakland University, 506 Varner Hall; Rochester, MI 48309; paino@oakland.edu.

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Keywords

Off-Label Medication; Treatment Centers; Medication-Assisted Treatment; Substance Use Disorders

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Introduction

Substance use disorder (SUD) treatment centers serve clients with diverse needs, who may desire or require access to varied treatments while seeking care for their SUDs. While FDA-approved medications for SUD have increased in popularity, adoption rates remain low.^{1–3} An array of pharmacotherapies are not FDA-approved for SUD treatment, but have FDA-approval for other indications. In clinical trials, these pharmacotherapies have shown some success in treating SUDs. Despite the clinical findings on these medications for off-label use, little is known about national trends of offering these medications in SUD treatment centers. This study focuses on the adoption and delivery of off-label medications (i.e. medications that are FDA-approved, but not for the treatment of substance use disorders) in substance abuse treatment centers.

In this paper, we consider organizational characteristics in an effort to better understand which treatment centers adopt off-label medications in their treatment of SUDs. By focusing on the organizational characteristics we shed light on how inequalities in SUD treatment centers develop and persist with regard to the adoption of off-label medication use. We use a nationally representative and longitudinal sample of SUD treatment centers in the United States to assess which treatment centers engage in off-label medication use.

Background on Off-Label Medication Use

We focus our attention on six medications that show promise for SUD treatment but are not currently FDA-approved for SUD treatment – baclofen, clonidine, divalproex, gabapentin, ondansetron, and topiramate. We highlight these medications because these are the off-label medications that were mentioned in face-to-face interviews with the clinical directors from these data. We recognize that other FDA-approved medications are also used to treat substance use disorders (e.g. Zofran), but our data prevents us from including those medications in this study. Below, we briefly discuss recent research and clinical trials dedicated to assessing the effectiveness of these medications in SUD treatment. Due to the lack of FDA-approval, we also note safety concerns.

Use, Efficacy, and Safety

Baclofen, a muscle relaxer and antispastic agent, is an effective treatment for addictive disorders, especially for reducing alcohol craving and intake in alcohol-dependent clients,^{4–7} and may be preferable to acamprosate for clients with severe alcohol dependence.⁸ Beyond the treatment of alcohol-dependent clients, there is support for the use of baclofen for cocaine-dependent clients.⁹ Studies on the efficacy of baclofen are mixed, and safety remains one of the primary concerns among physicians, with only 37.4% of physicians stating that baclofen's safety was equal to, or higher than, approved treatments.¹⁰

Clonidine, approved for treating high blood pressure, anxiety, and attention-deficit/hyperactivity disorder, is becoming increasingly common in medical practice.¹¹ In addition to these indications, clonidine is often used to support opioid detoxification and withdrawal.¹² Research suggests that buprenorphine-naloxone may be more efficient than clonidine in decreasing symptoms and reducing cravings related to opioid withdrawal and abuse, although this difference is only significant during the first few days of detoxification.¹³

Divalproex, commonly used to treat seizure disorders, has been associated with safe withdrawal and relapse prevention in alcohol-dependent clients.¹⁴ Cocaine-dependent clients may also find divalproex to be a safe and viable treatment,¹⁵ especially when paired with psychosocial treatments.¹⁶ For example, a clinical trial using cocaine-dependent clients found that divalproex decreased craving frequency and intensity as well as reported time using cocaine.¹⁷ Unlike other SUDs, cocaine use disorder does not currently have an FDA-approved pharmacological treatment; thus, clients with cocaine use disorders may be especially likely or willing to find treatment centers that offer medications off-label.

The anticonvulsant gabapentin is typically used for the treatment of seizures,¹¹ and there is not much research on its off-label use in SUD treatment. However, there is some support for its inclusion in SUD treatment. For instance, gabapentin has been shown to be effective in reducing alcohol craving and consumption¹⁸ and improving verbal abilities in chronic alcoholics.¹⁹ The use of gabapentin in higher dosages appears to be especially effective for reducing alcohol cravings and increasing rates of abstinence;²⁰ furthermore, this medication is ideal for clients with liver problems.²¹ The combination of naltrexone and gabapentin is also associated with improved drinking outcomes compared to the use of naltrexone alone.²² With regard to safety, gabapentin shows modest side effects; these include fatigue, insomnia, and headaches.²¹

Ondansetron, used to prevent nausea and vomiting, has been shown to be effective among alcohol-dependent clients who experienced early-onset alcoholism, and somewhat effective in the reduction of cocaine use among cocaine-dependent clients.⁹ Studies show that ondansetron reduces alcohol cravings and reduces the desirable effects of alcohol consumption.²¹ Low doses of ondansetron seem most effective,²³ and side effects include insomnia, headache, reduced appetite, fatigue, and diarrhea.²¹

Topiramate is an anticonvulsant used to treat seizures and migraines. Topiramate is an effective treatment for alcohol, nicotine, and cocaine dependence.⁹ In a meta-analysis, research shows that topiramate is superior to a placebo, and indirect comparisons suggest it is superior to naltrexone, acamprosate, and nalmefene.²⁴ The growing body of evidence that topiramate is effective for treating AUDs has led to research in the use of topiramate for other SUDs.^{25,26} In a series of clinical trials, topiramate (used in conjunction with cognitive behavioral therapy) was found to reduce short-term cocaine-use and increase abstinence.^{27–32} While the efficacy of topiramate is promising, there are many side effects associated with its use (e.g., dizziness, paresthesia, memory impairment).²¹ Much like divalproex, however, the relative effectiveness of topiramate for treating clients with cocaine use disorders may result in treatment centers increasing their use of this medication off-label.

Organizational Characteristics of Treatment Centers

In this study, we assess the relationship between a treatment center's organizational characteristics and the provision of off-label medications. A significant body of research suggests that organizational characteristics play a substantial role in how treatment centers approach the treatment of SUDs.^{1,2,33–37} This study contributes to this important line of inquiry, by increasing our knowledge regarding the availability of off-label medications. In the case of SUD treatment centers, we expect that age and size will be important resources and advantages. Older organizations will be more likely than their younger counterparts to provide these newer forms of treatment. Similarly, we expect that larger organizations will be more likely to offer medications off-label to their clients.

Funding sources are another way treatment centers may distinguish themselves from their competitors. Private funding sources incentivize centers to be innovative in their use of treatment technologies, as they have to compete for scarce resources. Even after controlling for other organizational characteristics, centers that rely on public funds are less likely to offer any medication-assisted treatment (MAT) innovations for SUD.³⁸ Rogers' ³⁹ concept of a technology cluster in his diffusion of innovations theory suggests that private funding, which has been consistently shown to be a predictor of MAT adoption would facilitate adoption of off-label medications as well. We argue here that treatment centers with greater resources are more likely to adopt and provide medications not yet approved for SUD treatment to their clients, especially since safety remains a primary concern for prescribing medications off-label.¹⁰

We address two specific research questions to help us understand how a treatment center's organizational characteristics contribute to off-label medication use in SUD treatment. First, how are organizational characteristics related to offering *any* medications for off-label use? Second, how are organizational characteristics associated with providing a greater number of medications for off-label use?

Methods

Data for these analyses come from the National Treatment Center Study (NTCS), a family of ongoing, national studies on SUD treatment centers in the US. This is a nationally representative sample of treatment centers, created using the Substance Abuse and Mental Health Services Administration's Substance Abuse Treatment Center Locator to randomly sample treatment centers across the US. Recent data shows there are 15,528 SUD treatment centers in the U.S.,⁴⁰ and in 2013, there were 15,496 SUD treatment centers.⁴¹ This sample was stratified to account for the population size of the county, and centers were required to be open to the public and offer at least one level of care between ASAM Level 1 (structured outpatient treatment) and Level III (residential/inpatient treatment services).⁴² At least 25% of the caseload had to be primarily alcohol-dependent in order to be included in this sample.

Two waves of interviews took place, allowing for longitudinal analysis of treatment centers. The first wave of interviews was conducted between June 2009 and January 2012 in 307 treatment centers, and this represented a 68% response rate among eligible treatment

centers. The second wave of interviews was conducted between 2011 and 2013. This wave of interviews resulted in a sample of 372 centers, which represented an 85% response rate among eligible treatment centers. Both waves are representative samples, but not all centers are the same over time. Due to sample attrition (e.g., closures, refusals, unable to contact), centers that dropped out of wave 1 were replaced with representative centers in wave 2. Despite this attrition, 200 treatment centers were interviewed in both waves. We restricted our analyses to these 200 centers in order to better account for causality between organizational characteristics and the provision of off-label medications within treatment centers. After excluding cases where data was missing on any variable, we were left with a sample of 196 centers.

Interviews took place face-to-face with administrators and clinical directors. Administrators were interviewed on organizational management and structure, while clinical directors provided information on treatment philosophy and medications used in the center. This study was reviewed and approved by the Institutional Review Board at the University of Georgia.

Measures

Dependent Variables

Off-Label Medication Use: We created a dichotomous variable that was coded as 1 if the treatment center used any of the following six medications off-label in wave two: baclofen, clonidine, divalproex, gabapentin, ondansetron, and topiramate. The variable was coded as 0 if the clinical director did not report using any of these medications in wave two.

Count of Off-Label Medications: We created a count variable indicating the number of medications used off-label in the center. This variable ranged from 0 to 6, where a 6 would indicate that the center offered all six medications.

Independent Variables—Each variable is measured in wave one, and used to predict the dependent variables from wave two.

Age: The age of the center, in years.

Size: Size was measured by average daily client census. We logged this variable to adjust for skew.

Private Funding: This variable ranges from 0 to 100, and indicates the percentage of funding from sources other than governmental grants or contracts (e.g., client fees, private insurance, and income sources other than “block” funding such as government contracts or grants). These include Medicare and Medicaid because they are not guaranteed sources of revenue for centers, making them similar to private sources.

Accredited: This is a dichotomous variable where a center was coded as 1 if it received accreditation from the Joint Commission (JC) or Commission on Accreditation of Rehabilitation Facilities (CARF).

12-Step Model: This is a continuous variable that indicates the extent to which a treatment center relied upon a twelve-step model. Clinical directors self-rate their center from 0 to 5, where 0 indicates the center did not rely upon the twelve-step model to any extent, and 5 indicates the center relied on a twelve-step model to a very great extent.

Behavioral Therapies: This is a continuous variable that counts from 0 to 4, indicating the number of behavioral therapies offered by the treatment center.

Profit Status: This is a dichotomous variable that indicates whether or not the center was for-profit (1=for-profit; 0=not-for-profit).

Hospital Setting: A center was coded as 1 if it offered treatment in a hospital setting and 0 if it did not offer treatment in a hospital setting.

Outpatient Services: Centers that only offered outpatient services were coded as 1, and centers were coded as 0 if they offered any inpatient/residential services.

Inpatient Services: Centers that only offered inpatient services were coded as 1, and centers were coded as 0 if they offered any outpatient services.

Mental Health: This is a dichotomous variable that was coded as 1 if the center offered mental health screening and 0 if it did not offer mental health screening.

Analytic Strategy

Our analyses proceeded in three steps. First, we analyzed descriptive characteristics of all variables. In addition, we separately analyzed descriptive data for each of the six medications. Second, we used a logistic regression to assess the relationship between organizational characteristics and the off-label use of *any* of the six medications. Finally, we used a negative binomial regression to model the relationship between organizational characteristics and the count of medications that were used off-label.

Results

We provide descriptive statistics in Table 1 and Table 2. Of the 196 centers in our sample, we found 26.02% of treatment centers used at least one of the medications off-label. We also analyzed descriptive statistics for each of the six medications. We found that 3.57% of centers offered baclofen, 13.78% offered clonidine, 14.80% offered divalproex, 15.82% offered gabapentin, 6.12% offered ondansetron, and 10.71% offered topiramate in wave 2. We also analyzed the extent to which treatment centers used the medications in wave 1, in order to get a sense of the general trends of use over time (Figure 1). Centers were not questioned about their use of gabapentin and ondansetron in wave 1, but open-ended questions in wave 1 revealed that gabapentin and ondansetron were utilized off-label in treatment centers. Thus, we added questions about the off-label use of gabapentin and ondansetron to our survey for wave 2. We found 2.55% of centers offered baclofen, 12.76% of centers offered clonidine, 6.63% offered divalproex, and 7.14% offered topiramate in wave 1. These percentages indicate a general increase in off-label medication use among our

longitudinal sample of 196 treatment centers. We graph these trends in Figure 1, and include gabapentin and ondansetron, although they do not have data in wave 1. The graph depicts the large increases for divalproex and topiramate (to a lesser extent), although gabapentin is the most utilized of these medications in wave 2.

In Table 3, we used a logistic regression and tested the relationship between organizational characteristics and offering any off-label medication for SUD. We found that age was significantly associated with off-label medication use. Older treatment centers were significantly more likely to use medications that were not FDA-approved for SUD treatment. Centers that were accredited by JC or CARF were also significantly more likely to engage in off-label medication use. If a treatment center was accredited, then the odds that the center used any of the six medications was 2.72 times higher than if the center was not accredited. Finally, treatment centers that provided mental health screening were significantly more likely to use medications off-label, although this did not reach the standard level of significance ($p=.054$).

Table 4 uses a negative binomial regression to model the relationship between organizational characteristics and the number of medications that a center used off-label for SUD. Older treatment centers were significantly more likely to offer a greater number of medications. Privately-funded centers were also more likely to have a greater number of medications that were used off-label. A 35% increase in private funding was related to a 44% increase in the expected number of such medications used by the treatment center. Accredited centers were positively related to offering a greater number of medications off-label in treatment. In fact, the expected number of these medications increased by 69% for accredited centers, compared to non-accredited centers. Finally, centers with mental health screening were positively and significantly associated with offering a greater number of off-label medication use. The expected number of medications increased by 67% for centers that offered mental health screening, compared to those that did not offer screening.

Discussion

The purpose of this paper was twofold. First, we hoped to understand how organizational characteristics contributed to off-label use of medications in SUD treatment centers. Second, we sought to uncover how organizational characteristics played a role in which centers offered a greater number of off-label medications. Our findings suggest that a small percentage of treatment centers offer medications that have not been approved by the FDA for the treatment of SUDs, although our data show that these numbers have been increasing in recent years. Moreover, organizational characteristics such as age, private funding, accreditation, and offering mental health screenings were consistently important predictors of off-label medication use in SUD treatment centers.

Our results suggest that treatment centers are like other types of organizations, and specific organizational characteristics play an important role in the adoption and off-label use of medications. The use of medications for an unapproved use in SUD treatment has been increasing, and we expect that trend to continue. In general, people want medications that are “safe, evidence-based, and affordable,”⁴³ but one of the primary obstacles for treating

SUDs with medications is the diversity of SUDs. Thus, having more pharmacological options should help meet the varying needs of clients with SUDs.²¹

Treatment centers that adopt off-label medications may be better poised to succeed in a future market where these become more commonplace and receive FDA-approval, especially if they are more cost efficient than more traditional SUD medications. Hence, some treatment centers may exponentially gain advantages over their competitors. Importantly, the treatment centers that are on the forefront of offering these medications are also the centers that may already enjoy greater resources and advantages, thus deepening inequalities between treatment centers. Older treatment centers may gain advantages by including off-label medications in their menu of treatment options. Accredited centers are significantly more likely to adopt off-label medications. Regardless of whether or not treatment centers *should* prescribe medications off-label, it is clear that some centers do and an increasing number of treatment centers are following this trend. If some clients are specifically seeking these particular treatment options, especially if they suffer from a SUD that does not currently have an FDA-approved treatment (e.g., cocaine use disorder), then the centers that offer medications off-label are better poised to attract and retain SUD clients in the long-term.

While off-label use of medications is both legal and common, prescribing a medication for an indication that has not yet been FDA-approved usually occurs with little empirical evidence.⁴³ Furthermore, pharmaceutical companies are prohibited from promoting a medication that is not FDA-approved; therefore, the public may be less aware that the medication can be used off-label. Nonetheless, practitioners should be aware of these medications, especially since they may reduce harm due to substance abuse and addiction if other treatments prove to be less successful for certain clients. Treatment centers that offer medications off-label may be in a position to offer education and training regarding efficacy and safety for the use of these medications. We recommend that SUD treatment centers offer their own lectures, or put seminar systems in place, to discuss the new possibilities in off-label medication use.

Resources are an important factor when considering the number of options a center can provide, however, and privately-funded centers are more likely to offer a greater number of medications that have yet to receive FDA-approval for SUD treatment. Thus, centers that may already enjoy a financial advantage may also gain a competitive edge in the institutional environment. Moreover, the availability of mental health screenings is significantly related to offering a greater number of the six medications examined in this study, and that may indicate their high desirability in clients who exhibit co-occurring problems upon intake.

We want to note several limitations to this study. First, not all of the medications were included in the first wave, thus making an analysis that considers change within an organization impossible. Second, this sample is representative of treatment centers, but we are unable to generalize to all types of treatment centers (e.g., correctional facilities, VA facilities). Finally, data are based on self-reports (from clinical directors and administrators), which may result in social desirability and/or recall bias. This could be especially relevant since these questions asked about the use of off-label prescriptions. Despite these

limitations, we hope this study is a significant step for understanding how organizational characteristics contribute to the adoption and use of off-label medications in treatment centers.

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Figure 1:
Trends in Medications Used Off-Label (N=196)

Table 1:

Descriptive Statistics of Dependent Variables

Variable	Description	Mean (or %)	Standard Deviation (or n)
Off-Label Medications	Dichotomous variable that indicates whether or not the treatment center offers any of the medications, off-label: baclofen, clonidine, divalproex, gabapentin, ondansetron, topiramate. Coded as 1 if it did offer any of the medications, and 0 if it did not.	26.0%	51
Count of Medications Used Off-Label	Count variable that indicates the number of medications that were offered off-label by the treatment center. This variable ranges from 0 to 6.	64.8%	1.33
Baclofen	The center offered baclofen.	3.6%	7
Clonidine	The center offered clonidine.	13.8%	27
Divalproex	The center offered divalproex.	14.8%	29
Gabapentin	The center offered gabapentin.	15.8%	31
Ondansetron	The center offered ondansetron.	6.1%	12
Topiramate	The center offered topiramate.	10.7%	21

N=196

Table 2:**Descriptive Statistics of Independent Variables**

Variable	Description	Mean (or %)	Standard Deviation (or n)
Age	The age of the treatment center, in years.	28.43	14.27
Size	The size of the treatment center was measured using the daily client census. This variable was logged in order to adjust for skew. A mean of 4.04 converts to approximately 58 clients.	4.04	1.07
Private Funding	Continuous variable, ranging from 0 to 100, indicating the percent of funding that came from private sources.	52.05	35.52
Accredited	The center was accredited by either Joint Commission or the Commission on Accreditation of Rehabilitation Facilities.	36.2%	71
12-Step Model	This is a continuous variable, ranging from 0 to 5, indicating the extent to which the treatment center used a twelve-step model. Clinical directors were asked, "On a scale of 0-5, (0= "no extent," 5="a very great extent"), to what extent is this center's treatment of AUD clients based on a 12-step model?"	3.24	1.70
Behavioral Therapies	This is a continuous variable, ranging from 0 to 4, indicating the number of behavioral therapies the center offered (e.g., cognitive behavioral therapy, motivational interviewing, contingency management, and motivational enhancement therapy). Clinical directors were asked about each of the behavioral therapies, and whether or not they are used in the treatment center (e.g., "Is motivational enhancement therapy currently used by any of the counselors in this center?")	2.58	0.94
Profit Status	Dichotomous variable that indicates whether or not the treatment center was for-profit.	20.9%	41
Hospital Setting	The center was located in a hospital.	11.7%	23
Outpatient Services	Dichotomous variable that indicates whether or not the treatment center was outpatient-only. Coded as 1 if the center offered only outpatient services, and 0 if the center offered inpatient services or any combination of inpatient/outpatient services.	49.5%	97
Inpatient Services	Dichotomous variable that indicates whether or not the treatment center was inpatient-only. Coded as 1 if the center offered only inpatient services, and 0 if the center offered outpatient services or any combination of inpatient/outpatient services.	11.7%	23
Mental Health	The center offered mental health screening. Clinical directors were asked "Which of the following best describes this center's standard practice in assessing patients with AUDs for co-occurring psychiatric disorders at intake/admission?" Responses: No AUD patients are screened for co-occurring psychiatric disorders at intake. All AUD patients are screened for co-occurring psychiatric disorders at intake. Some AUD patients are screened for co-occurring psychiatric disorders at intake. The center was given a value of 1 if they selected that either some or all patients were screened.	75.5%	148

N=196

Table 3:

Logistic Regression of Medication Offered Off-Label Regressed on Organizational Characteristics (Odds Ratios)

Variable	Odds Ratios
Age	1.039 *
Size	0.781
Private Funding	1.008
Accredited	2.719 **
12-Step Model	1.015
Behavioral Therapies	1.221
Profit Status	1.574
Hospital Setting	2.225
Outpatient Services	0.735
Inpatient Services	1.603
Mental Health	2.700 †

N=196

† p<.10

* p<.05

** p<.01

*** p<.001

Table 4:

Negative Binomial Regression of Medications Offered Off-Label on Organizational Characteristics (Incidence Rate Ratios)

Variables	Incidence Rate Ratios	Std. Error	e^{b^a}	e^{bStdX^b}	$SDofX^c$
Age	1.030 *	0.014	1.030	1.519	14.271
Size	0.770	0.176	0.771	0.757	1.067
Private Funding	1.010 *	0.005	1.010	1.443	35.516
Accredited	2.979 **	0.343	2.979	1.692	0.482
12-Step Model	1.011	0.108	1.011	1.018	1.701
Behavioral Therapies	1.037	0.198	1.037	1.035	0.939
Profit Status	1.125	0.465	1.125	1.049	0.408
Hospital Setting	2.223	0.507	2.223	1.294	0.323
Outpatient Services	0.835	0.389	0.835	0.914	0.501
Inpatient Services	1.467	0.544	1.467	1.132	0.323
Mental Health	3.279 *	0.489	3.279	1.669	0.431

N=196

t
p<.10

*
p<.05

**
p<.01

***
p<.001

Notes:

a : $e^b = \exp(b) =$ factor change in expected count for unit increase in X

b : $e^{bStdX} = \exp(b \cdot SD \text{ of } X) =$ change in expected count for SD increase in X

c : $SDofX =$ standard deviation of X